THE ASSESSMENT AND FUNDING PROCESSES OF DRUGS IN SPAIN AND OTHER OECD COUNTRIES:

WHERE ARE WE AND WHERE ARE WE GOING?

ES-ABBV-230098 (Feb2023)

abbvie

Fundación Weber

THE ASSESSMENT AND FUNDING PROCESSES OF DRUGS IN SPAIN AND OTHER OECD COUNTRIES:

WHERE ARE WE AND WHERE ARE WE GOING?

February 2023

Carried out by:

weber

Sponsored by:

abbvie

Authors

Néboa Zozaya
Director. Area of health economics. Weber

Javier Villaseca
Consultant. Area of health economics. Weber

Fernando Abdalla
Consultant. Area of health economics. Weber

Irene Fernández
Consultant. Area of health economics. Weber

Álvaro Hidalgo-Vega
Professor at the UCLM and President of the Weber Foundation

Expert committee

Miguel Ángel Calleja Hernández
Head of the Pharmacy Service, Virgen Macarena University Hospital, Seville

Pedro Gómez Pajuelo
Former Secretary General of the National Transplant Organisation. Civil servant of the Ministry of Health on leave of absence

Jorge Mestre Ferrándiz
Consultant and researcher in the field of health economics. Associate Professor at the Carlos III University of Madrid

Juan Oliva Moreno
Professor, Department of Economic Analysis, Castilla-La Mancha University

José Luis Trillo Mata
Head of the Pharmacy Service of the Health Area of the Malvarrosa Clinical Department, Valencia

Edited by:

C/ Moreto 17, 5º Dcha.
28014, Madrid

Editorial coordination:
weber@weber.org.es

ISBN: 978-84-126632-0-4
DL: M-5232-2023
DOI: https://doi.org/10.37666/I16-2023

Madrid, February 2023

INDEX

Context and objectives

In these times of constant change, new pharmaceutical innovations and challenges for healthcare systems, it is particularly important the task of getting medicines to patients, promoting innovation and without losing sight of the efficiency and sustainability of the healthcare system in the long term. In recent years there have been significant changes in the process of assessing and pricing medicines in Spain, so that it is now appropriate to analyse the main strengths and weaknesses of the process in order to continue to improve and thus face the future with greater guarantees of success.

The aim of this report is to analyse in depth the process of assessing and funding medicines in Spain and in other countries of the Organisation for Economic Co-operation and Development (OECD) and to get the views of the main agents of the Spanish health system on the functioning of the system, in order to offer ideas for improvement, either on the basis of international best practices or stakeholders' opinions.

Methodology

This project has been carried out in several stages.

1) **Definition of the project by the Advisory Committee.** First, the strategy and scope of the project was defined, with the help of an Advisory Committee made up of **5** experts in medicine assessment and pricing (Table 1). The committee provided guidance on the points on which to focus the search for information and the countries to be analysed, validating the evidence found.

Table 1. Composition of the advisory committee

NAME	POSITION
Miguel Ángel Calleja Hernández	Head of the Pharmacy Service, Virgen Macarena University Hospital, Seville
Pedro Gómez Pajuelo	Former Secretary General of the National Transplant Organisation. Civil servant of the Ministry of Health on leave of absence
Jorge Mestre Ferrándiz	Consultant and researcher in the field of health economics. Associate Professor at the Carlos III University of Madrid
Juan Oliva Moreno	Professor, Department of Economic Analysis, Castilla-La Mancha University
José Luis Trillo Mata	Head of the Pharmacy Service of the Health Area of the Malvarrosa Clinical Department, Valencia

2) **Analysis of the process in other countries: literature review.** Scientific publications, reports, websites and press releases were reviewed, using PubMed, Google, grey literature sources and websites of the various drug assessment agencies, scientific societies and research institutes as search engines. The overall review was conducted between July and December 2021, although some items were subsequently updated. The main items to be searched for, based on the committee's recommendations, were the following: agents and processes; required documentation; characteristics of the clinical and economic evaluation performed; involvement of patients and scientific societies; elements of price and reimbursement decisions; and financial agreements and their monitoring. In addition to **Spain**, the **13** countries selected for analysis were **Germany, Australia, Austria, Canada, South Korea, Scotland, France, England, Italy, Japan, the Netherlands, Portugal** and **Sweden**. The committee reviewed each country's information in depth, and contributed to the final version of the report.

3) **Analysis of the vision of the different national actors: questionnaire.** With the help of the advisory committee, a questionnaire was designed to gather the opinion of different actors in the Spanish healthcare system on the process of assessing and financing medicines in Spain. The questionnaire included a total of **50** questions to diagnose the current situation and potential actions for improvement. Although the sample was not representative and did not include all types of actors in the system, a total of **49** people responded to the survey, representing **32** different actors, with the largest subgroup of respondents (**45%**) being representatives of scientific societies and professional associations (Table 2).

Table 2. Distribution of the agents and persons participating in the survey, by subgroup

SUB-GROUPS	Nº AGENTS	%	Nº OF PERSONS	%
Health authorities	7	22%	7	14%
Scientific societies and professional associations	11	34%	22	45%
Pharmaceutical industry associations	5	16%	7	14%
HTA agencies and health economists	4	13%	7	14%
Patient associations	5	16%	6	12%
TOTAL	**32**	**100%**	**49**	**100%**

The assessment and funding process in Spain

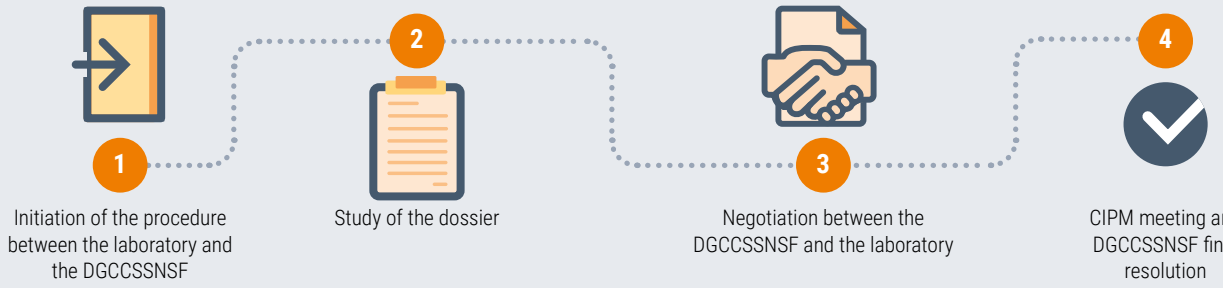
The assessment and funding of new medicines is a complex process, which requires a whole organisational framework and cooperation between different actors. This section outlines the main characteristics and stages in this process in our country.

Agents and process

A feature of the Spanish model is the division of responsibilities. The Spanish Agency of Medicines and Medical Devices (AEMPS) is in charge of marketing authorisation and the Directorate-General of the Basic Portfolio of National Health System and Pharmacy Services (DGCCSSNSF), together with other agents, evaluates and participates in the procedure to determine their inclusion in the set of medicines that can be funded by the NHS.

Based on the documentation provided by the marketing laboratory and the assessments made, the DGCCSSNSF and the laboratory enter into a negotiation process, the outcome of which, sometimes agreed and sometimes not, is referred to the Interministerial Committee on Pricing of Medicines and Healthcare Products (CIPM), which takes the decision on the funding (and, if so, sets the maximum authorised price) of the medicine. Finally, the DGCCSSNSF, by means of a resolution, notifies to the interested party of the CIPM's decision (Figure 1).

Figure 1. The pricing and funding process for medicines in Spain



Source: AIReF (2019)[5]

Note: CIPM: "*Comisión Interministerial de Precios de los Medicamentos*" (Interministerial Committee on Pricing of Medicines and Healthcare Products); **DGCCSSNSF:** "*Dirección General de Cartera Común de Servicios del Sistema Nacional de Salud y Farmacia*" (Directorate-General of the Basic Portfolio of National Health System and Pharmacy Services)

The assessment of medicines is based on the Therapeutic Positioning Report (TPR), a document prepared by REvalMed, an evaluation network formed by the DGCCSSNSF and evaluation experts from the AEMPS and the AACC. The TPRs offer a comparative therapeutic and economic evaluation of medicines, with the aim of providing relevant information, based on scientific evidence, on the positioning of the new medicine, or its new indication, compared to existing pharmacological or non-pharmacological therapeutic alternatives. In 2020, a reform of the TPRs was proposed to prioritise the most urgent TPRs, incorporate economic evaluation and reduce evaluation times. In May 2022, the Ministry of Health published a document specifying that the evaluations are carried out by **143** experts from **18** different specialties (**66%** pharmacists and **7%** haematologists). According to the origin of the professionals, Castilla-La Mancha (**13%**) and Catalonia (**11%**) are the AACC that contribute with the most experts to REvalMed.

Clinical assessment

For the clinical assessment of the medicinal product, the characteristics of the drug and other relevant aspects of administration, duration of treatment and authorisation are presented. The value of its therapeutic benefit or its relevance for clinical practice compared to available treatments is assessed, based on clinical endpoints of trials that have studied them (morbidity or mortality), or on surrogate and/or intermediate clinical variables as well as other variables that may be important. Quality Adjusted Life Years (QALYs) also need to be considered.

Economic evaluation

The latest reform of the TPRs incorporates economic evaluation as one of the pillars on which the positioning of medicines is based. This section is carried out by REvalMed's pharmaco-economic assessment team, following the methodology established by the GENESIS Group. The type of economic evaluation is chosen according to the available evidence, whether it is cost-utility analysis, cost-effectiveness or cost minimisation analysis.

It should be noted that in Spain there is not an officially defined cost-effectiveness threshold, although there are several studies that have analysed funding decisions, extracting implicit willingness-to-pay thresholds of between €**4,585** and €**171,476** per QALY gained. One of the most widely referenced studies places the threshold between €**22,000** and €**25,000**. In addition to the economic evaluation, a budget impact analysis should be presented based on the estimation of the target population.

Patient participation

In Spain, the patients participate in the drug assessment process by providing their comments and allegations to the first draft of the TPR. These comments are sent to the relevant assessment team, either the therapeutic assessment team or the pharmaco-economic assessment team, for updating the TPR, before proceeding to the next phase of the process. No information is available on the extent of the impact of these comments, as the final text is adopted by the Coordination Group.

Elements of pricing and funding decisions

In Spain, the price and funding decision is based on several elements, which help to make a final decision. According to the current regulations (article 92 of the RLD 1/2015), the inclusion of medicines in the NHS funding is carried out taking into account the following six criteria:

a) Severity, duration and sequelae of the different pathologies for which they are indicated.

b) Specific needs of certain groups.

c) Therapeutic and social value of the medicine and its incremental clinical benefit considering its cost-effectiveness.

d) Rationalisation of public spending on pharmaceutical benefits and budget impact on the National Health System.

e) Existence of medicines or other therapeutic alternatives for the same conditions at a lower price or lower cost of treatment.

f) Degree of innovation of the medicine.

The prices of alternative therapies are taken into account in the pricing and funding of medicines.

Financial agreements and their monitoring

The price and funding negotiation process may be conditioned by different financial arrangements, such as cost ceilings, maximum cost per patient, risk-sharing agreements, payment by results or variable prices depending on the volume of purchase, in order to provide greater access to the medicine.

Since 2019, Spain has had a system called Valtermed, which aims to provide optimal information for appropriate decision-making in the macro, meso and micro management of the pharmaceutical benefits of certain high-impact medicines, determining their therapeutic value in real clinical practice. Similarly, some of the agreements reached at the CIPM establish a control of the expenditure on the analysed drug through the monitoring platform for the supply of medicines in the national market (Seguimed).

The assessment and funding process in other countries

This section summarises the main characteristics of each of the countries analysed in order to extract international best practices.

Germany

- **Patient participation:** *Gemeinsame Bundesausschuss (G-BA), Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (IQWiG)* and *Spitzenverband Bund der Krankenkassen (GKV-SV)*
- **Separation of processes:** Clinical and economic evaluation separate from pricing
- **Total process time:** Almost immediate availability during the first year, after which the medicinal product is evaluated if more than 1 million euros of budget impact is budgeted (360 days)
- **Patient participation:** As support in evaluation committees
- **Clinical assessment:** Clinical Benefit Measurement Scale
- **Type of economic evaluations:** Economic evaluation is not used, instead efficient frontier is used
  - **Comparator:** Treatment used in standard practice
  - **Permitted perspectives:** Funder (main) and social (main)
- **Elements of P&R setting:** Reference pricing system, therapeutic value, budget impact and efficient frontier

HIGHLIGHTS

- ✔ **Initial automatic marketing of the medicinal product without prior assessment during the first year**
- ✔ **Use of the efficient frontier to make the price and reimbursement decision**
- ✔ **Orphan drugs are not required to demonstrate additional therapeutic benefit if they do not exceed an annual expenditure of EUR 50 million**

Australia

- **Participating agents:** *Pharmaceutical Benefits Advisory Committee (PBAC)*
- **Separation of processes:** No
- **Total process time:** 140-154 days
- **Patient participation:** Represented and as support in the Committees
- **Clinical assessment:** Use of multi-attribute systems based on patient-reported outcomes and anchored to QALYs
- **Type of economic evaluations:** Cost-effectiveness, cost-utility and cost minimisation
  - **Comparator:** Therapy that it replaces
  - **Permitted perspectives:** Funder (main) and social (additional)
- **Elements of P&R setting:** In-country alternatives, value-based pricing, equity of access, pathology severity, therapeutic value, budget impact, cost-effectiveness, public health issues, patient affordability in the absence of public funding, and ability to target therapy to patients who will benefit most

HIGHLIGHTS

- ✔ **Pioneer country in conducting economic evaluation**
- ✔ **Allows to start the assessment without a marketing approval**
- ✔ **Differentiated process for ODs**
- ✔ **Incorporation of PROMs in the assessment process**
- ✔ **Public availability of the detailed assessment reports of the medicinal product and the reasons for its inclusion in the PBS**

Austria

- **Participating agents:** *Heilmittel-Evaluierungs-Kommission (HEK)* and *Preiskommission*
- **Separation of processes:** Clinical and economic evaluation separate from pricing
- **Total process time:** Not available
- **Patient participation:** No
- **Clinical assessment:** Pharmacological assessment divided into 8 grades of innovation. Classification of the clinical/therapeutic assessment into 6 levels
- **Type of economic evaluations:** Cost-benefit and cost minimisation
  - **Comparator:** Treatment used in standard practice
  - **Permitted perspectives:** Not available
- **Elements of P&R setting:** External reference pricing, in-country alternatives, value-based pricing and therapeutic value

HIGHLIGHTS

- ✔ **Box' system for the reimbursement of medicinal products**
- ✔ **Rapid entry of therapies awaiting funding (red box)**
- ✔ **Use of databases to contain hospital and pharmaceutical health expenditure**

Canada

- **Participating agents:** *Canadian Agency for Drugs and Technologies in Health (CADTH), Patented Medicine Prices Review Board (PMPRB)* and *pan-Canadian Pharmaceutical Alliance (pCPA)*
- **Separation of processes:** Clinical and economic evaluation separate from pricing
- **Total process time:** 186-201 days
- **Patient participation:** Represented and as support in the Committees
- **Type of economic evaluations:** Cost-effectiveness, cost-utility and cost minimisation
  - **Comparator:** Treatment used in standard practice
  - **Permitted perspectives:** Funder (main) and social (additional)
- **Elements of P&R setting:** External reference pricing, in-country alternatives and value-based pricing, budget impact and cost-effectiveness

HIGHLIGHTS

- ✔ **One of the pioneer countries in using economic evaluation**
- ✔ **Use of an algorithm to differentiate assessments of oncology drugs from non-oncology drugs, and single drug innovations from other drugs**
- ✔ **Publication of technical evaluation reports on the CADTH website**

South Korea

- **Participating agents:** *National Health Insurance Service (NHIS), Health Insurance Review and Assessment Service (HIRA)* and *Drug Benefit Coverage Assessment Committee (DBCAC)*
- **Separation of processes:** Clinical and economic evaluation separate from pricing
- **Total process time:** 240-360 days
- **Patient participation:** Represented and as support in the Committees
- **Type of economic evaluations:** Cost-effectiveness, cost-utility and cost minimisation
  - **Comparator:** Not available
  - **Permitted perspectives:** Funder
- **Elements of P&R setting:** External reference pricing, in-country alternatives, value-based pricing, pathology severity, therapeutic value, unmet needs, budget impact, cost-effectiveness and public health issues

HIGHLIGHTS

- ✔ **Allows to start the evaluation without a marketing approval**
- ✔ **Certain oncological and orphan drugs are exempted from requiring an economic evaluation process**
- ✔ **Real-time outpatient prescription and dispensing monitoring system, which prevents inappropriate use of medicines and reduces costs to the system**

Scotland

- **Participating agents:** *Scottish Medicines Consortium (SMC)*
- **Separation of processes:** No
- **Total process time:** 126 days
- **Patient participation:** As support in committees and more actively in the PACE process
- **Type of economic evaluations:** Cost-utility and cost minimisation
  - **Comparator:** Treatment used in standard practice
  - **Permitted perspectives:** Funder (main) and social (additional)
- **Elements of P&R setting:** Value-based pricing, industry agreements, therapeutic value, unmet needs, innovation, budget impact and cost-effectiveness

HIGHLIGHTS

- ✔ **Using *Horizon Scanning* to anticipate future new therapies**
- ✔ **Orderly process with participation of different actors with voice but without vote**
- ✔ **Specification of the cost-effectiveness threshold modifiers**
- ✔ **Access model for ultra-rare therapies focused on the value demonstrated in real clinical practice**

France

- **Participating agents:** *Commission de la Transparence (CT), Commission d'Evaluation Économique et de Santé Publique (CEESP)* and *Comité Économique des Produits de Santé (CEPS)*
- **Separation of processes:** Clinical assessment, economic evaluation and pricing in separate processes
- **Total process time:** 180 days
- **Patient participation:** Represented and as support in the Committees
- **Clinical assessment:** Categorisation of the actual clinical benefit of the medicine into 5 levels and of the clinical benefit of the product into 4 levels
- **Type of economic evaluations:** Cost-utility and cost minimisation
  - **Comparator:** The clinically relevant
  - **Permitted perspectives:** Collective (main) and funder (additional)
- **Elements of P&R setting:** External reference pricing, in-country alternatives, value-based pricing, pathology severity, therapeutic value, unmet needs, innovation, budget impact and cost-effectiveness

HIGHLIGHTS

- ✔ **Fluent communication with the industry from the beginning of the process**
- ✔ **Industry participation in the Pricing Committee**
- ✔ **High degree of transparency, with publication of conflicts of interest of Committees/Commissions**
- ✔ **Explicit consideration of MCDA as an approach to decision support**

England

- **Participating agents:** *National Institute for Health and Care Excellence (NICE)* and *National Health Service (NHS)*
- **Separation of processes:** Clinical and economic evaluation separate from pricing
- **Total process time:** Almost immediate availability during the first year. After evaluation time: 290 days
- **Patient participation:** Represented and as support in the Committees
- **Type of economic evaluations:** Cost-effectiveness, cost-utility, cost-benefit and cost minimisation
  - **Comparator:** All potentially relevant
  - **Permitted perspectives:** Funder (main) and social (additional)
- **Elements of P&R setting:** Free pricing, value-based, industry agreements, budget impact and cost-effectiveness

HIGHLIGHTS

- ✔ **Explicit use of a cost-effectiveness threshold**
- ✔ **Transparency on the aspects discussed during the assessment process**
- ✔ **Justification of the criteria taken into account for the approval of funding**
- ✔ **Open participation of all actors involved in the assessment process**
- ✔ **Free access and free price once marketing authorisation has been received**
- ✔ **Clarity of the process and of the responsibilities of the parties involved**

Italy

- **Participating agents:** *Agenzia Italiana del Farmaco (AIFA)*
- **Separation of processes:** Clinical and economic evaluation separate from pricing
- **Total process time:** 180 days
- **Patient participation:** As support in the Committees
- **Clinical assessment:** Innovation algorithm based on unmet medical needs, added therapeutic value and quality of evidence
- **Type of economic evaluations:** Cost-effectiveness, cost-utility, cost-benefit and cost minimisation
  - **Comparator:** Treatment used in standard practice
  - **Permitted perspectives:** Funder (main) and social (additional)
- **Elements of P&R setting:** Value-based pricing, industry agreements, therapeutic value, unmet needs, innovation, budget impact, contribution to research programmes and quality of evidence

HIGHLIGHTS

- ✔ **Pharmaceutical innovation algorithm based on unmet medical needs, added therapeutic value and quality of evidence**
- ✔ **Specific funds to fund innovative and/or oncological medicines**
- ✔ **Innovative financial agreements linked to mandatory monitoring mechanisms**
- ✔ **Major development in medicines information and monitoring system**

Japan

- **Participating agents:** Central Medical Council of Social Insurance *(Chuikyo)*
- **Separation of processes:** No
- **Total process time:** 450-540 days
- **Patient participation:** No
- **Type of economic evaluations:** Cost-utility and cost minimisation
  - **Comparator:** Therapy that it replaces
  - **Permitted perspectives:** Funder (main) and social (additional)
- **Elements of P&R setting:** External reference pricing, in-country alternatives, value-based pricing, therapeutic value, innovation, cost-effectiveness, and premium system depending on drug characteristics (paediatric, orphan and others)

HIGHLIGHTS

- ✔ **Premium system to define the price of therapy, depending on different parameters**
- ✔ **System of explicit cost-effectiveness thresholds to modulate prices, with higher thresholds for medicines of special consideration**
- ✔ **Price premium for medicines with R&D carried out in Japan and approved in Japan before those approved in other countries *(Sakigake)***
- ✔ **National clinical trial data monitoring system to support access**

Netherlands

- **Participating agents:** *Zorginstituut (ZIN), Wetenschappelijke Adviesraad (WAR)* and *Ministerie van Volksgezondheid, Welzijn en Sport (VWS)*
- **Separation of processes:** No
- **Total process time:** 162-257 days
- **Patient participation:** As support in the Committees
- **Clinical assessment:** Based on 5 defined criteria (therapeutic benefit, adverse events, clinical practice, applicability and appropriateness) and evidence-based medicine
- **Type of economic evaluations:** Cost-utility and cost minimisation
  - **Comparator**: Treatment used in standard practice
  - **Permitted perspectives:** Social (main) and funder (additional)
- **Elements of P&R setting:** External reference pricing, value-based pricing, equity of access, pathology severity, therapeutic value, budget impact, system sustainability, cost-effectiveness, disease burden, fairness and equity

HIGHLIGHTS

- ✔ **Systematic integration of social elements into decisions**
- ✔ **Pilot system to speed up access to innovative therapies through parallel screening**
- ✔ **Transparency in the process and in the criteria used for decisions**
- ✔ **Use of cost-utility thresholds according to disease burden**
- ✔ **Use of a process integrating MCDA and accountability for reasonableness in the social impact assessment phase**
- ✔ **Implementation of a systematic programme to reassess the efficiency of the health system**

Portugal

- **Participating agents:** *Comissão de Avaliação de Tecnologias de Saúde (CATS), Direção de Avaliação das Tecnologias de Saúde (DATS)* and *Autoridade Nacional do Medicamento e Produtos de Saúde (INFARMED)*
- **Separation of processes:** Clinical and economic evaluation separate from pricing
- **Total process time:** 180 days
- **Patient participation:** As support in the Committees
- **Clinical assessment:** Based on 5 criteria, which are efficacy and safety, uncertainty about the outcomes, relationship between the outcomes presented and the probability that these are also demonstrated in routine clinical practice, risk-benefit assessment and quality of evidence
- **Type of economic assessment:** Cost-utility and cost minimisation
  - **Comparator:** All potentially relevant
  - **Permitted perspectives:** Funder
- **Elements of P&R setting:** External reference pricing, value-based pricing, therapeutic value, innovation, budget impact, and cost-effectiveness

HIGHLIGHTS

- ✔ **Transparency, albeit partial, of the process and results of clinical and economic evaluation, with monitoring indicators**
- ✔ **Well-defined methodological guidelines in terms of required documentation, clinical and economic evaluation implementation**
- ✔ **Systematic reassessment of medicines post-funding**

Sweden

- **Participating agents:** *Tandvårds- och läkemedelsförmånsverket (TLV), Folkhälsomyndigheten* and *Statens beredning för medicinsk och social utvärdering (SBU)*
- **Separation of processes:** Not available
- **Total process time:** 180 days
- **Patient participation:** As support in the Committees
- **Type of economic evaluations:** Cost-utility and cost minimisation
  - **Comparator:** Treatment used in standard practice
  - **Permitted perspectives:** Social
- **Elements of P&R setting:** Value-based pricing, solidarity, equity of access, pathology severity and cost-effectiveness

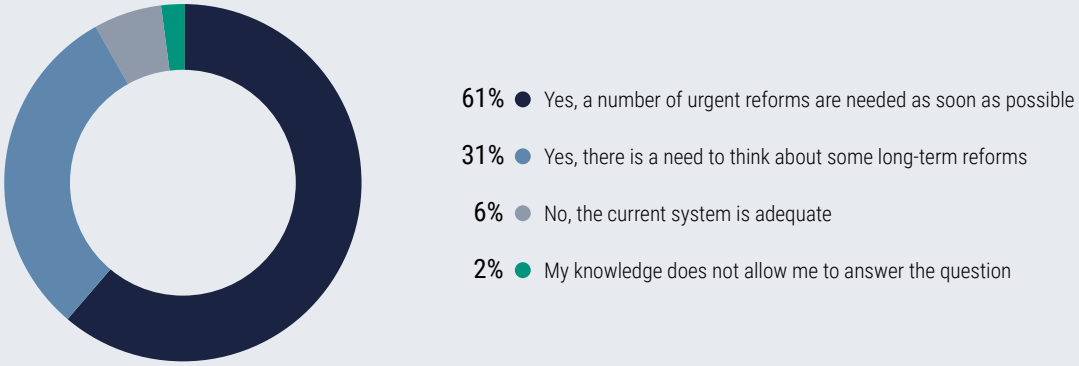
HIGHLIGHTS

- ✔ **Pioneer country in carrying out health technology assessment**
- ✔ **No use of international reference price systems**
- ✔ **Inclusion of social criteria in decisions, such as human value and necessity**
- ✔ **Economic evaluation from a social perspective, using the human capital approach to quantify labour productivity losses**
- ✔ **Compliance with the deadlines stipulated in the evaluation process**

Current situation and developments in Spain: survey results analysis

This section analyses the responses on the assessment and funding processes of medicines in Spain collected through a survey to different actors in the system, which was answered by a total of **49** actors with five different profiles.

Figure 2. In general, do you consider that changes should be made to the way innovative medicines are assessed in Spain?



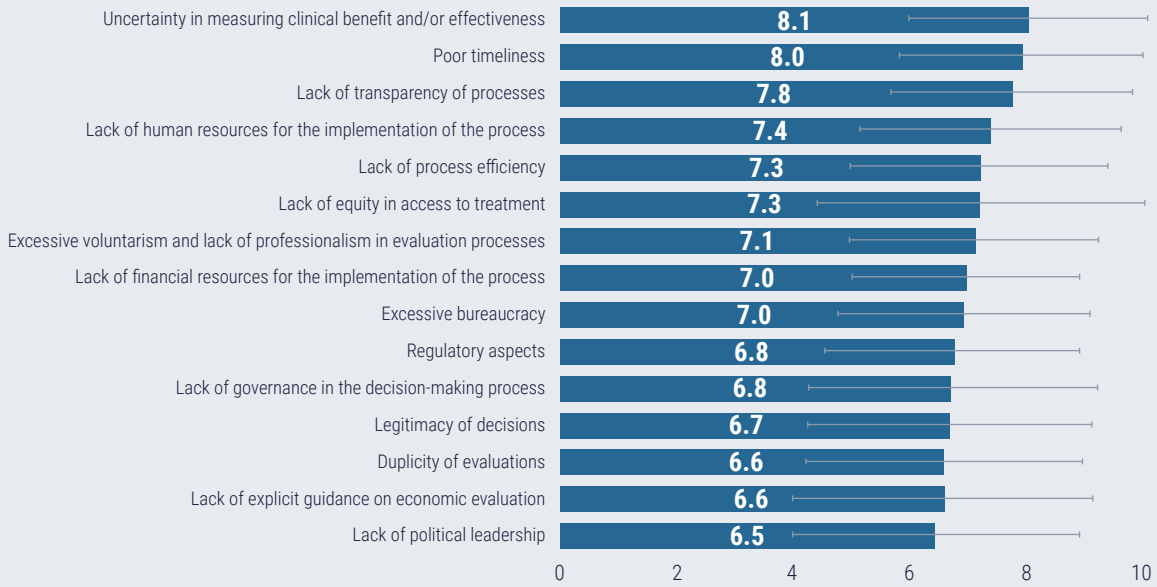
The vast majority of stakeholders consulted (more than **90%**) consider that the assessment of innovative medicines in Spain should be reformed: **61%** believe that reforms should be urgent, while **31%** believe that some long-term reforms are needed and only **6%** thought that the current system is adequate.

Figure 3. In general, do you consider that changes should be made to the way in which the price and public funding of innovative medicines is set in Spain?

Similarly, the majority of respondents (**86%**) believe that reforms are needed in the way innovative medicines are priced and publicly funded in Spain. Specifically, **57%** of stakeholders believe that reforms should be carried out urgently, while **29%** consider that changes are needed, but rather in the long term.

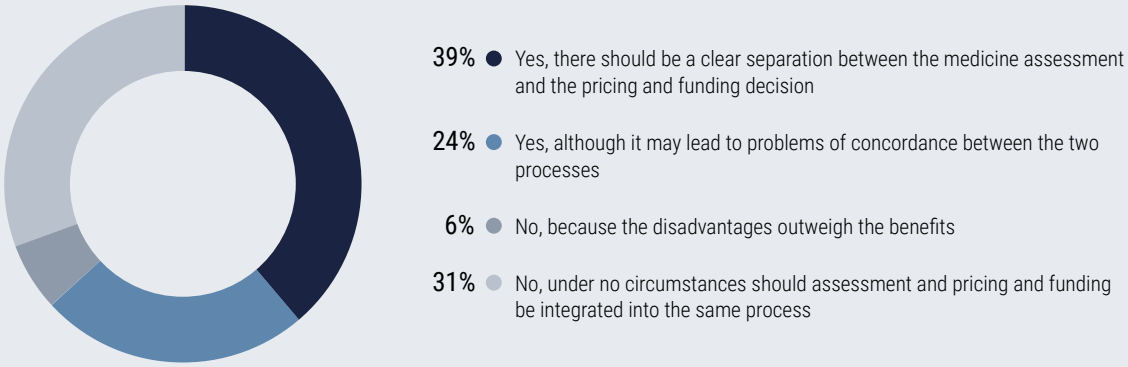
According to those consulted, the agents that should participate in the process of assessing a new medicine in Spain are the clinicians, the Ministry of Health and the scientific societies, and, to a lesser extent, representatives of patients' associations and the AACC. On the other hand, in the pricing and funding process, all respondents considered that the Ministry of Health should be one of the agents involved in the process, and to a lesser extent the representatives of the AACC, the Ministry of Finance and the pharmaceutical industry.

Figure 4. Challenges in the assessment and funding processes of innovative medicines in the NHS (0 being the least important and 10 the most important) (average score)



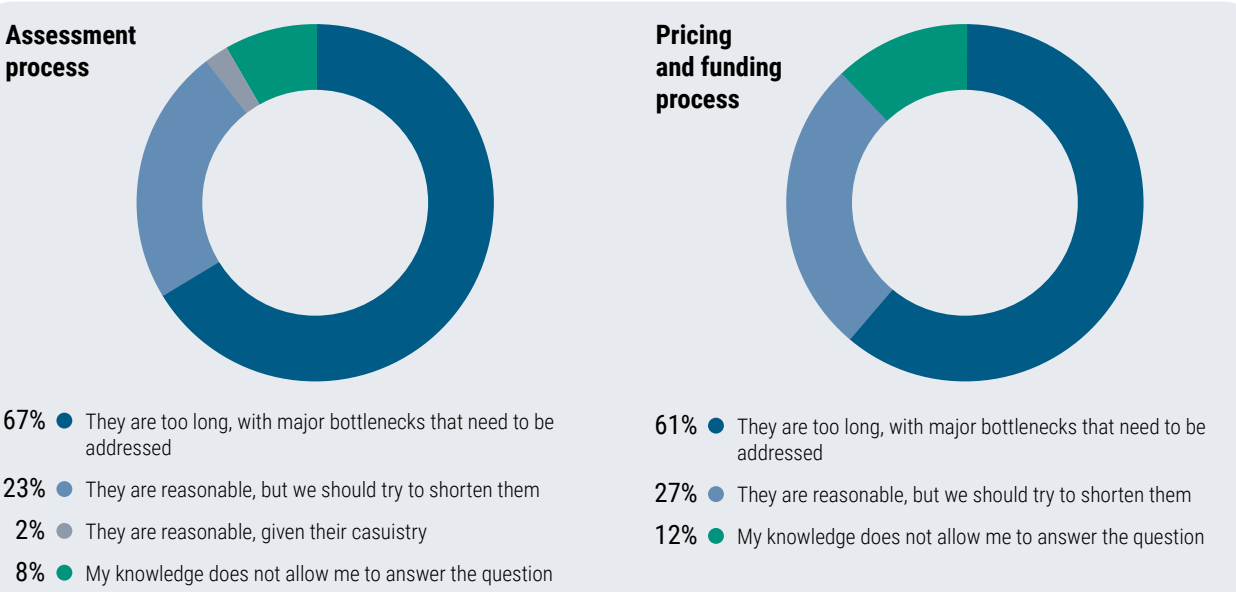
For the stakeholders interviewed, the most important challenges in the assessment and funding processes for innovative medicines are uncertainty in the measurement of clinical benefit, poor timeliness and lack of transparency in the processes.

Figure 5. Do you consider that there should be a separation between scientific/technical processes (assessment) and management/policy decisions (pricing and funding)?



39% of respondents believe that there should be a clear separation between the scientific-technical process of assessment and the decision to fund medicines, while **24%** are in favour of such a separation, although they believe that it may lead to inconsistencies between the two processes.

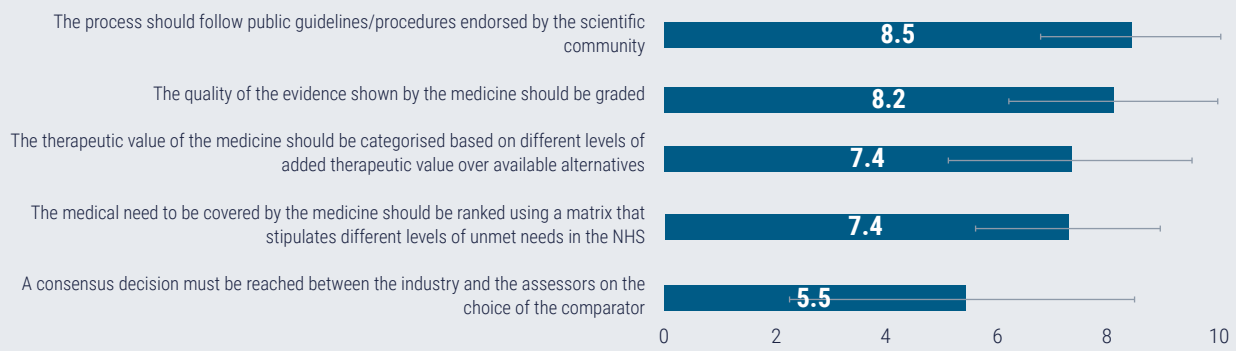
Figure 6. What is your opinion on the current timing of the assessment and funding processes for innovative therapies in Spain?



For the majority of respondents (**67%**), the current assessment times for innovative therapies in Spain are too long, with significant bottlenecks that need to be resolved, while **23%** say that the times are reasonable, but that efforts should be made to shorten them. Only **2%** think that the times are reasonable, given their casuistry.

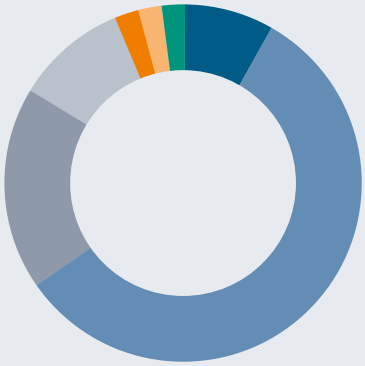
When asked about the timing of pricing and funding decisions, the percentage of agents who thought they were too long fell slightly to **61%**, while **27%** considered they were reasonable, but we should try to shorten them. In this case, no agents felt that they were reasonable, given their casuistry, and the proportion claiming that their knowledge did not allow them to express an opinion on this issue rose to **12%**.

Figure 7. Degree of agreement with the following points regarding the clinical assessment of medicines (0 being the minimum and 10 the maximum) (average score)



In relation to the process of clinical assessment of medicines, the agents consulted prioritise following public guidelines or procedures endorsed by the scientific community and, to a lesser extent, classifying the quality of the evidence shown by the medicinal product and categorise the therapeutic value of the drug at different levels compared to the available alternatives.

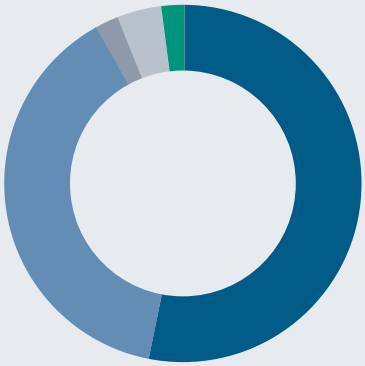
Figure 8. What is your opinion on the role of economic evaluation (efficiency or cost-effectiveness) in informing pricing and funding decisions for a new medicine?



- 8% It must be the fundamental criterion on which the decision is based
- 57% It should be an important criterion on which the decision is based
- 19% It should be just one more criterion on which to make a decision
- 10% Depends on the type of medicine evaluated
- 2% It should not play a major role in the decision
- 2% It should have no role in the decision
- 2% My knowledge does not allow me to answer this question

For **57%** of stakeholders, economic evaluation should be an important criterion on which to base the pricing and funding decision for a new medicine, while for **8%** it should be the main criterion, for **19%** it should be just another criterion and for **4%** it should not play a relevant role in the decision.

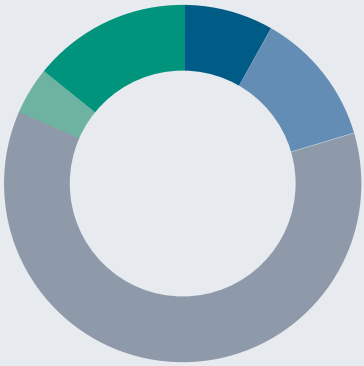
Figure 9. How do you consider that drugs targeting rare diseases should be assessed in Spain?



- 53% Using the same process as for other medicines, but with some different rules
- 39% With a differentiated assessment process and an *ad hoc* committee to assess and set the price of these therapies
- 2% With a distinction between the medicines themselves
- 4% In the same way as other medicines
- 2% My knowledge does not allow me to answer this question

More than half of the stakeholders consulted believe that drugs for rare diseases should be assessed through the same process as other medicines, albeit with certain different rules, while **39%** considered that a differentiated process and an *ad hoc* committee should be used to assess and set the price of these therapies.

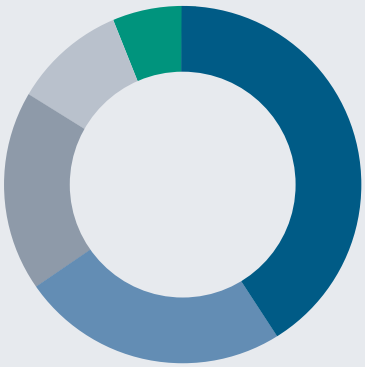
Figure 10. Do you consider that the current economic evaluation is conducted in a rigorous manner, with established methodological rules and standards for all assessed medicines?



For **61%** of respondents, the current economic evaluation should be applied more rigorously, based on clearly established rules and methodologies in the evaluation processes. On the other hand, **6%** believe that the rules are clear and rigorously applied, and **15%** believe that the current rules are clear but not rigorously applied.

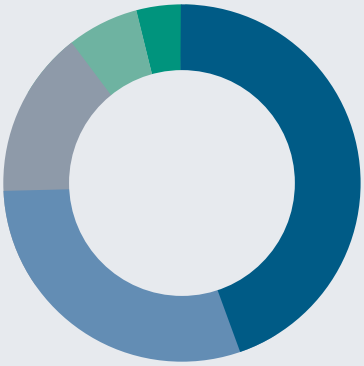
According to those consulted, the main challenge in terms of drug pricing and funding in Spain is the lack of explicit and transparent criteria in decision-making, followed by the absence of information systems to monitor results and the difficulty in implementing innovative financial agreements.

Figure 11. Do you agree that the pricing decision should be based only on the criteria set out in Article 92 of RLD 1/2015?



Acccording to **41%** of respondents, the criteria set out in the RLD 1/2015 on public funding of medicines should be the only criteria to be considered, while **25%** believe that additional criteria should be taken into account. About a **18%** consider that only some of these criteria should be taken into account and others not specified in the list should be added. Quality of evidence, health care costs avoided and social costs avoided are the three additional criteria most commonly mentioned by stakeholders to be taken into account in the funding decision. Finally, **10%** claimed that only some of these criteria should be taken into account, but not all of them.

Figure 12. Do you consider that a specific weighting should be defined for each of the criteria specified in the RLD mentioned above?



Regarding the relative weighting of each criterion set out in RLD 1/2015, **45%** of those consulted believe that it should be made explicit, while **30%** believe that this weighting (concrete or approximate) should be implicit, only for the internal use of the decision-making committee. On the other hand, **15%** consider that under no circumstances should each criterion be associated with a specific weighting.

Regarding the pricing and funding schemes, most respondents agree that a long-term view on the funding of medicines is necessary and that alternative financial schemes such as risk-sharing agreements should be implemented.

On monitoring mechanisms for medicines in Spain, respondents agreed that there is a need to improve the interoperability of existing mechanisms, that it is also necessary to have a system at national level that integrates the different monitoring mechanisms already in place, and that when there are doubts about real-life outcomes, funding should be linked to monitoring mechanisms.

Conclusions and decalogue of recommendations

In Spain, there have been significant recent changes in the process of assessing and funding medicines such as the planning of TPRs, the systematic incorporation of economic evaluation and the implementation of Valtermed.

Despite the progress made, there are some lines of improvement to be explored. Based on the review of other countries' processes and the questionnaire conducted among some of the agents in the system about the situation in Spain, it is possible to identify the following trends and good practices to be followed in the assessment and funding processes of medicines:

1. **It must be rigorous and consistent,** with clear and homogeneous criteria, and carried out by professionals with experience and solvency in this field.
2. **Capable of separating assessment and funding** into two distinct processes to avoid conflicts of interest, with different actors for the technical part and for the funding decision.
3. **Adjusted to the legally established timeframe,** to speed up the time between the authorisation of the medicine and its effective availability, and with the possibility of incorporating a fast-track process for certain pathologies with greater unmet needs.
4. **Endowed with adequate human, technical, economic and training resources,** reducing voluntarism, minimising the excessive workload of professionals and increasing the training of evaluation staff.
5. **Enhancing the involvement of other actors,** such as patients, scientific societies and industry.
6. **With maximum transparency,** both in terms of the standards and methodologies used, as well as the actors involved, the criteria taken into account and the timetable.
7. **Increasing the weight of efficiency in the funding decisions,** beyond the cost of the pharmacological treatment, and considering other issues, such as the quality of evidence, health or social costs avoided or ethical aspects.
8. **Promoting funding schemes that facilitate innovation and patient access,** such as payment-by-results agreements or conditional funding schemes.
9. **Promoting continuous assessment of interventions and decisions based on real-life data,** with the possibility for any of the parties involved to request reassessment.
10. **Promoting more integrated and interoperable monitoring mechanisms,** geared towards measuring health outcomes.

We live in a time of constant change, with innovations, uncertainties and challenges of all kinds. This applies to almost all areas of life, but it is of paramount importance in an environment as change-ridden as the one surrounding medicines. In this context, decision-makers are faced with the challenging task of bringing pharmaceutical innovations to patients, promoting innovation and ensuring the long-term sustainability of the system at the same time.

To address this issue, medicines undergo a complex assessment process to decide whether they should be approved, marketed and publicly funded. This process depends to a large extent on the combination of regulations and mechanisms in place, which in turn differ from country to country. Significant changes have taken place in recent years, and it is useful to analyse them in order to understand the main strengths and weaknesses of our medicines assessment process, thus allowing us to face the future with greater guarantees of success.

The **aim of this report** is to analyse in depth the assessment and funding processes of medicines in Spain and in other Organisation for Economic Co-operation and Development (OECD) countries, and to obtain the views of the main actors in the Spanish healthcare system on the functioning of the system. The aim is to provide a comparative framework of detailed, homogeneous and updated information that offers decision-makers ideas for improvement to address the various existing challenges, whether based on international best practices or on the opinion of stakeholders in the system.

The report is structured as follows. After an explanation of the methodology used, it describes how the assessment and funding processes of medicines is currently being carried out at the national level in Spain, first providing some relevant general data for contextualisation. This is followed by a summary of how 13 other OECD countries currently approach this process. In order to facilitate comparison between countries, the same aspects are analysed in all of them, and summary comparative tables are provided. The following section of the report provides a diagnosis of the situation in Spain and possible lines of improvement, based on first-hand data collected through surveys among different relevant agents in the system. Finally, the last section contains the main conclusions derived from the work, and some proposed lines of action to improve the assessment and funding processes of medicines in our country.

This project, led by Weber, has been carried out in several stages.

1. Advisory Committee

First, the strategy and scope of the project was defined, with the help of an Advisory Committee made up of **5** leading experts in drug assessment and pricing in Spain and other countries (**Table 1**). The committee also advised Weber on the points on which to focus the search for information and the countries to be analysed, validating the evidence found. In addition to Spain, it was agreed to review the assessment and funding processes of **13** other OECD countries, chosen for having differential characteristics and measures that could serve as good practices for Spain.

Table 1. Composition of the advisory committee

NAME	POSITION
Miguel Ángel Calleja Hernández	Head of the Pharmacy Service, Virgen Macarena University Hospital, Seville
Pedro Gómez Pajuelo	Former Secretary General of the National Transplant Organisation. Civil servant of the Ministry of Health on leave of absence
Jorge Mestre Ferrándiz	Consultant and researcher in the field of health economics. Associate Professor at the Carlos III University of Madrid
Juan Oliva Moreno	Professor, Department of Economic Analysis, Castilla-La Mancha University
José Luis Trillo Mata	Head of the Pharmacy Service of the Health Area of the Malvarrosa Clinical Department, Valencia

2. Analysis of the process in other countries: literature review

Once the approach was agreed, Weber conducted a review of scientific publications, reports, websites and press releases, using PubMed, Google, grey literature sources and websites of the various health authorities, drug assessment agencies, scientific societies and research institutes as search engines. The overall review was conducted between July and December 2021, although some items were subsequently updated.

The main items to be searched in the literature, based on the committee's recommendations, were the following: agents and processes; required documentation; characteristics of the clinical and economic evaluation performed; involvement of patients and scientific societies; elements of pricing and reimbursement decisions; and financial agreements and their monitoring, all related to the process of assessing and pricing medicines. In addition to Spain, the countries selected for analysis were Germany, Australia, Austria, Canada, South Korea, Scotland, France, England, Italy, Japan, the Netherlands, Portugal and Sweden. The committee reviewed each country's information in depth, and contributed to the final version of the report.

The extensive information collected for each country has been condensed in a homogeneous and detailed, albeit summarised, manner, providing figures that visually show the relevant points. In addition, final comparative tables have been prepared to facilitate the synthesis of information and comparison between countries (see section 2.1).

3. Analysis of the vision of the different national actors: questionnaire

Once the literature review was completed, with the help of the advisory committee, a questionnaire was designed to gather the opinion of the different actors in the system on the assessment and funding processes for medicinal products in Spain. The questionnaire included a total of **50** questions to diagnose the current situation regarding the assessment and funding processes for innovative medicines in Spain and potential actions for improvement (Figure 1) (Annex 1).

FIGURE 1. Topics and number of questions in the questionnaire

A total of **65** health system actors were invited to participate in the survey, with up to three respondents per entity. Although the sample was not representative and did not include all types of agents in the system, a total of **49** people responded to the survey, representing **32** different agents, with the largest subgroup of respondents (**45%**) being representatives of scientific societies and professional associations. Health authorities had the same relative weight as health economists or Health Technology Assessment (HTA) agencies and industry representatives, all with **14%** (**7** responses) (Table 2) (see annex).

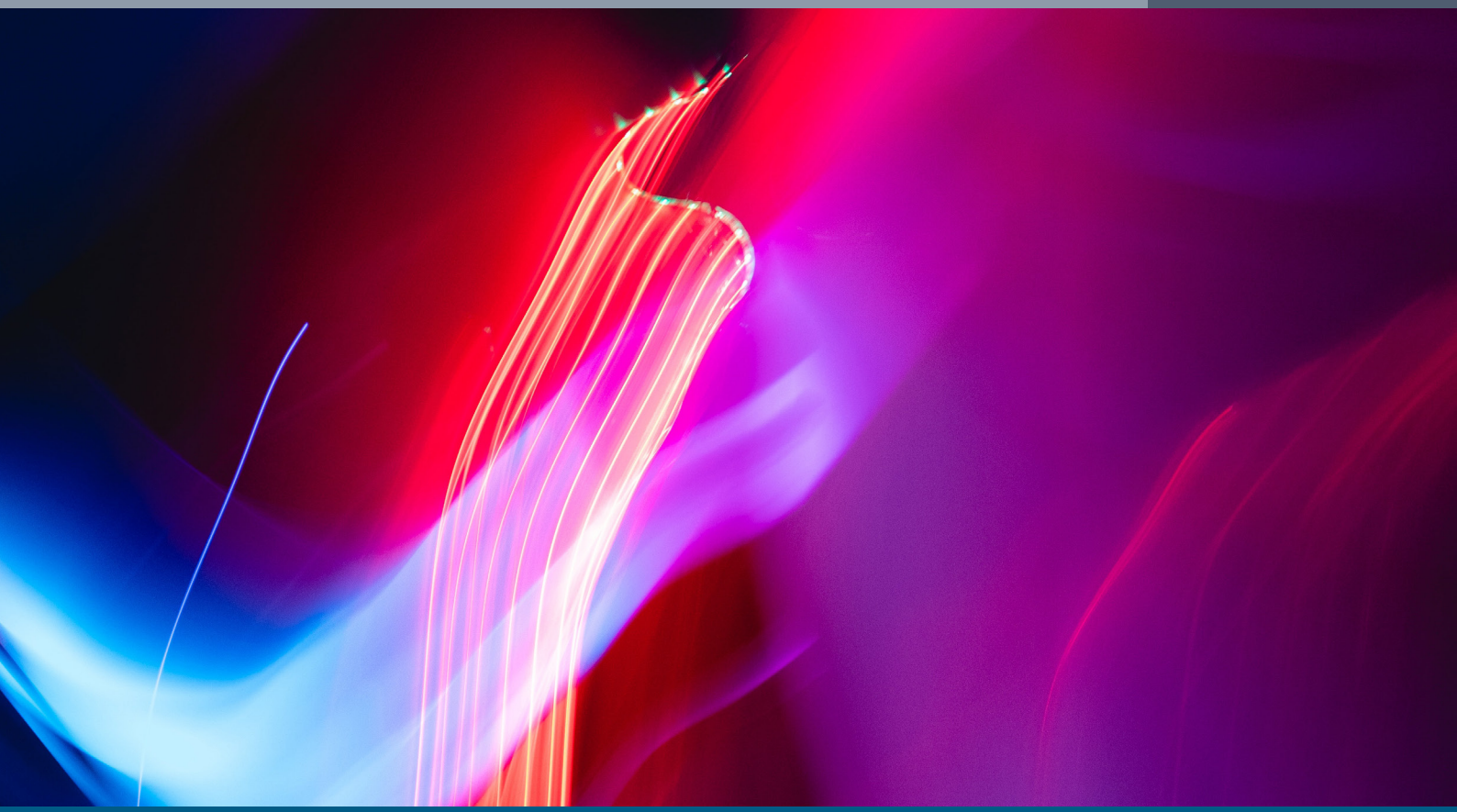
TABLE 2. Distribution of the agents and persons participating in the survey, by subgroup

	Nº. AGENTS	%	Nº. OF PERSONS	%
Health authorities	7	22%	7	14%
Scientific societies and professional associations	11	34%	22	45%
Pharmaceutical industry associations	5	16%	7	14%
HTA agencies and health economists	4	13%	7	14%
Patient associations	5	16%	6	12%
TOTAL	**32**	**100%**	**49**	**100%**

A descriptive analysis of the results obtained in the surveys was carried out, showing the average results and standard deviations of the total responses. In addition, for each question and whenever possible, sub-analyses were carried out by subgroups of agents, to contrast if there was variability in the opinion of the different types of agents surveyed.

INITIAL SITUATION IN SPAIN

1

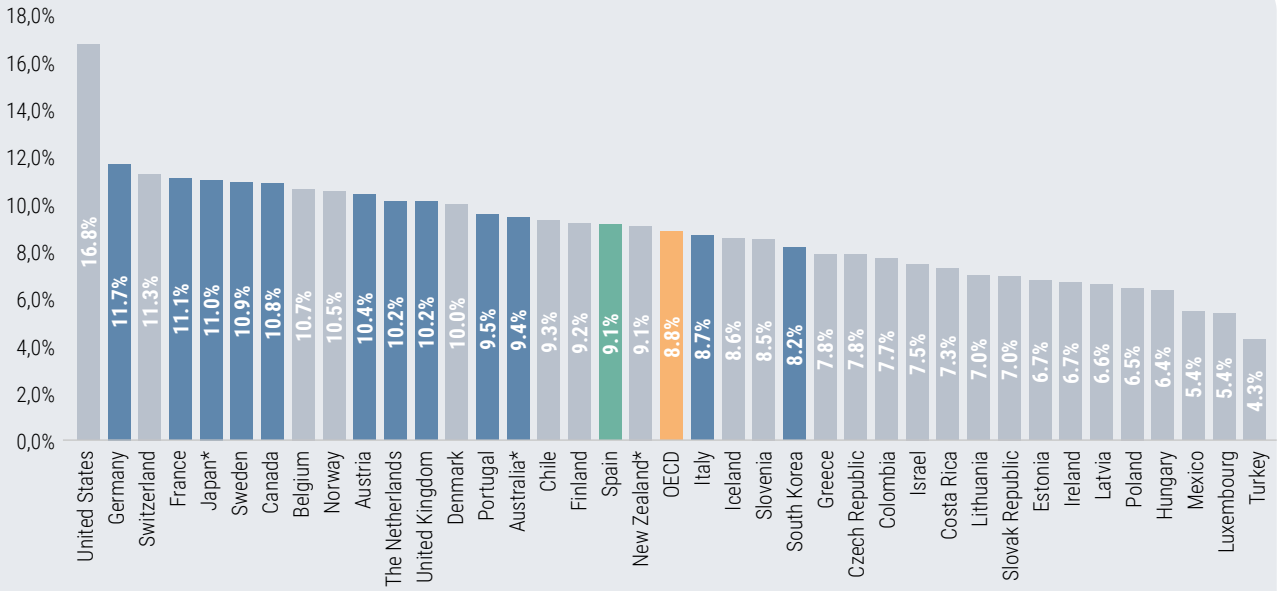


1.1. Contextualisation

Before beginning the analysis of the assessment and funding system in Spain, it is useful to know how Spain compares with other OECD countries in terms of some macro variables, in order to establish a suitable comparative framework.

In terms of health expenditure, Spain is in an intermediate position with respect to other OECD countries, with a total health expenditure of **9.1%** of its Gross Domestic Product (GDP) (**6.6%** public). Compared to the countries selected in this study, only Italy and South Korea, with **8.7%** and **8.2%**, respectively, have a lower level of health expenditure relative to GDP than the Spanish one (Figure 2)[1].

FIGURE 2. Total health expenditure as a share of GDP, OECD countries (2019)



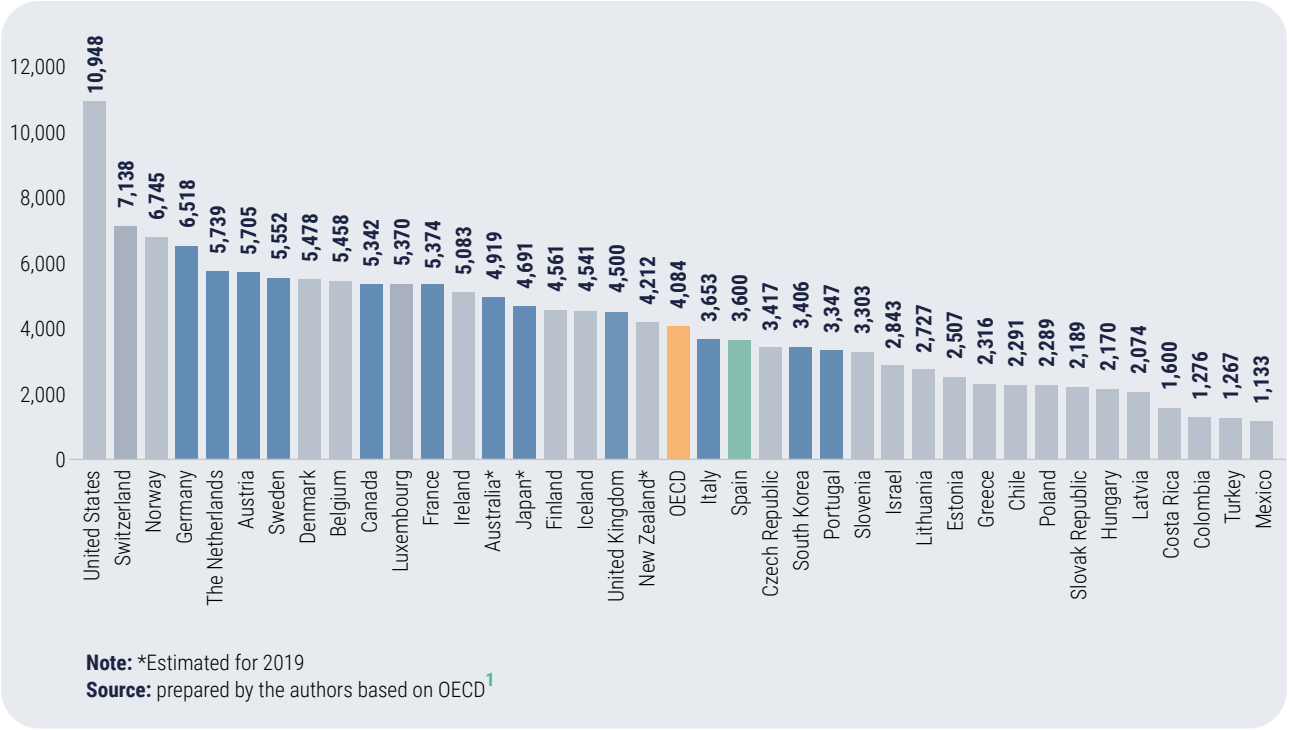
Note: *Estimated for 2019
Source: prepared by the authors based on OECD[1]

In terms of per capita health expenditure, Spain remains in an intermediate position among OECD countries, with an expenditure of $**3,600** per capita. Compared to the countries in the study, Spain's per capita expenditure is far from the $**6,518** in Germany and the $**5,739** in the Netherlands. In this case, only South Korea and Portugal have lower spending than Spain (Figure 3)[1].

Considering only public health expenditure, the situation in Spain does not change, although the differences compared to other countries increase given that the weight of public health expenditure in Spain is lower or equal to the rest of the countries in the study (except Portugal) (Figure 4)[1].

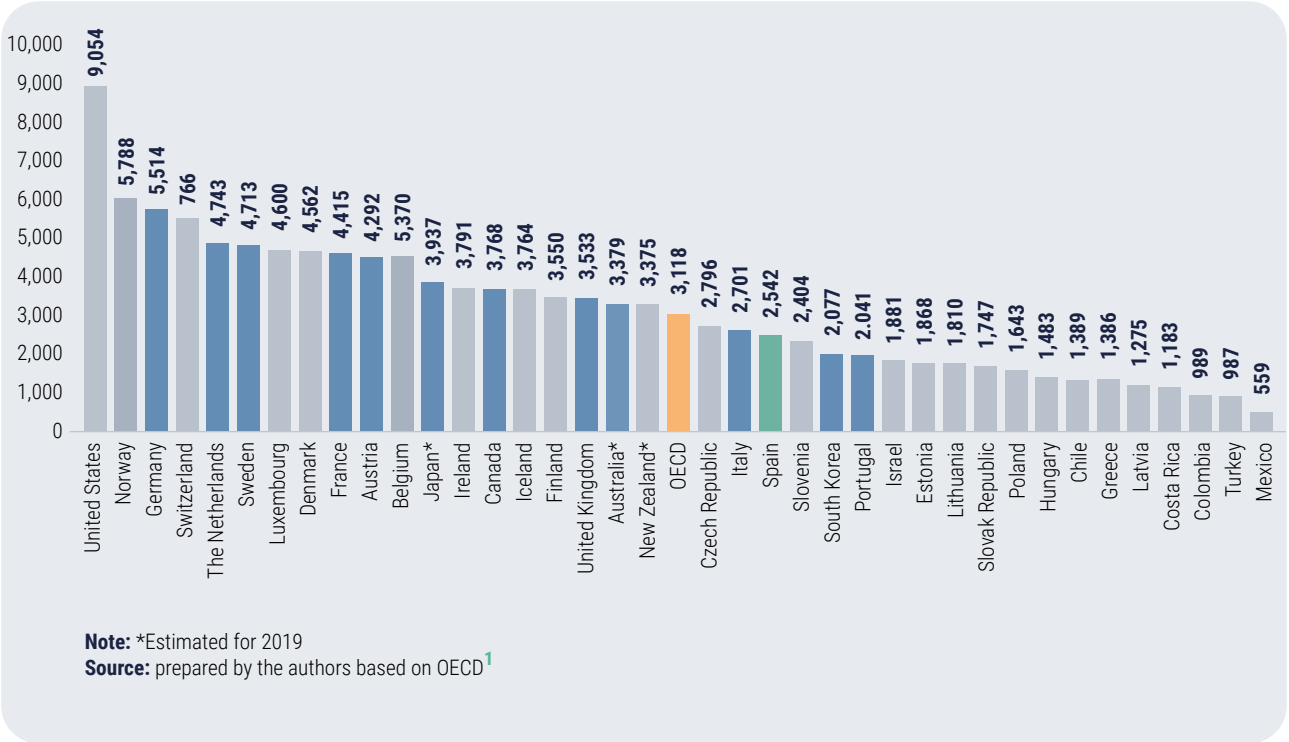
As a percentage of total health expenditure, Spain spends **14.8%** of its health expenditure on prescription and over-the-counter drugs. This places Spain in an intermediate position with respect to the OECD countries, below South Korea, Italy, Japan and Canada, all of which spend more than **16%**, but above others such as Germany, France, Australia, Austria and the United Kingdom. The Netherlands stands out for its low percentage of health expenditure spent on pharmaceuticals (Figure 5)[2].

FIGURE 3. Total health expenditure per capita, in dollars, OECD countries (2019)



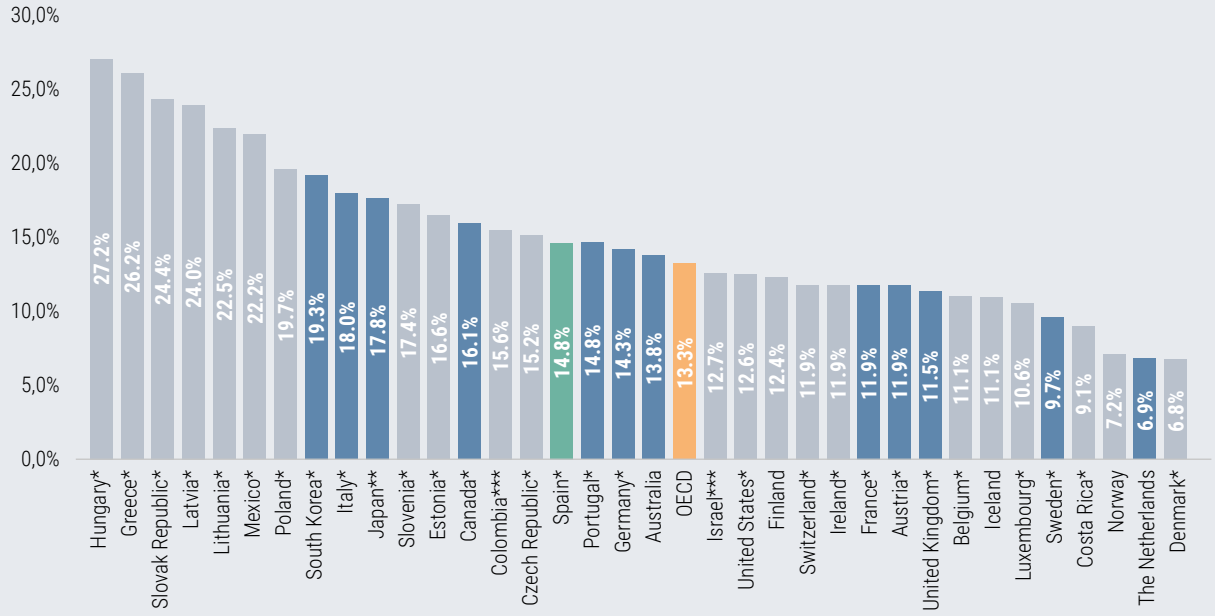
Note: *Estimated for 2019
Source: prepared by the authors based on OECD[1]

FIGURE 4. Public health expenditure per capita, in dollars, OECD countries (2019)



Note: *Estimated for 2019
Source: prepared by the authors based on OECD[1]

FIGURE 5. Pharmaceutical expenditure as a share of total health expenditure, OECD countries (2020)



Note: * Estimates for 2019; ** Estimates for 2018; *** Estimates for 2017

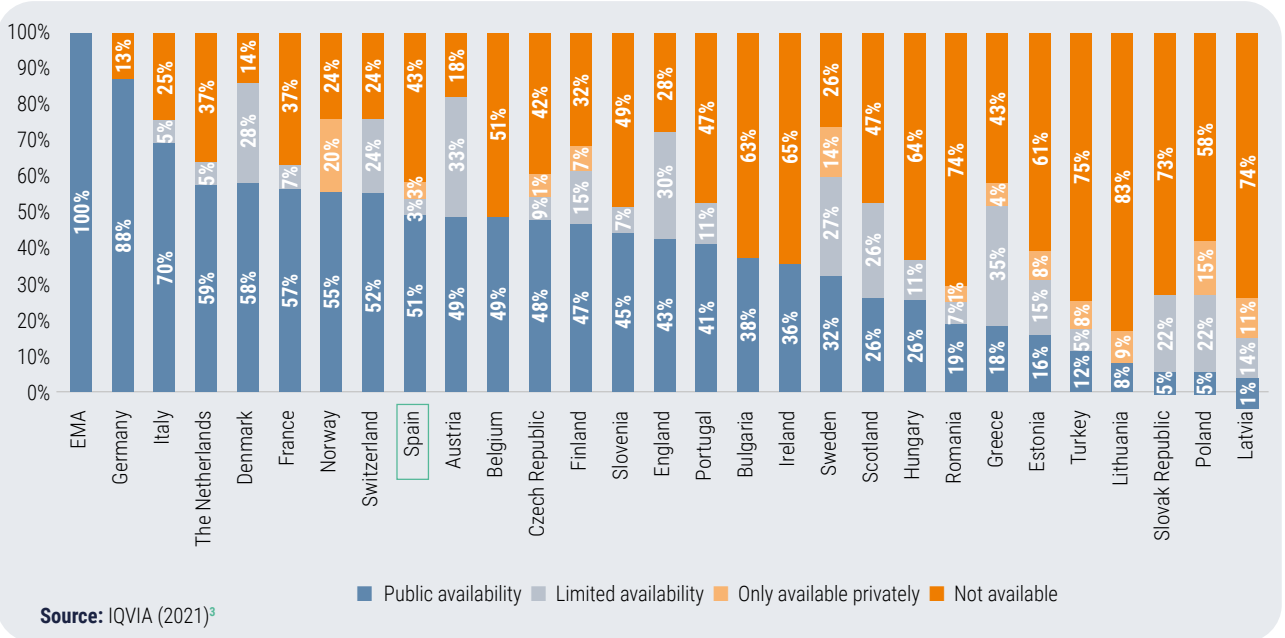
Note2: Data not available for Chile, New Zealand and Turkey

Note3: ⊙ Expenditure on prescription and over-the-counter medicines, excluding hospital medicines

Source: prepared by the authors based on OECD[2]

In terms of patient access to medicines approved by the European Medicines Agency (EMA), Spain is among the top ten countries. However, only **51%** of all medicines approved between 2016 and 2019 are publicly accessible, compared to **88%** in Germany, **70%** in Italy and **59%** in the Netherlands (**Figure 6**).

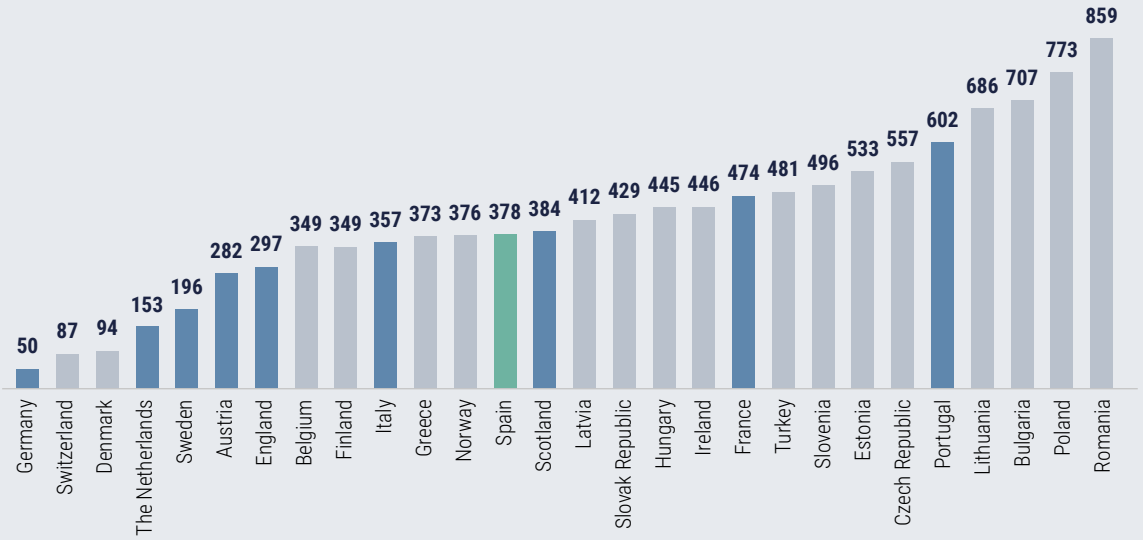
FIGURE 6. Availability of EMA-approved medicines (2016-2019)



Source: IQVIA (2021)[3]

As for the time elapsed between marketing authorisation by the EMA and availability of the medicine, the median for Spain is **378** days, close to other countries in the study such as Scotland (**384** days) or Italy (**357** days), but far from the Netherlands, Sweden, Austria or England, all of which are below **300** days. Germany is the country with the fastest access, with only **50** days of waiting time, given the characteristics of its process, as we will see below (**Figure 7**).

FIGURE 7. Median time (in days) between EMA authorisation and actual availability in the country (2016-2019)



Source: IQVIA (2021)[3]

1.2. The assessment and funding processes in Spain

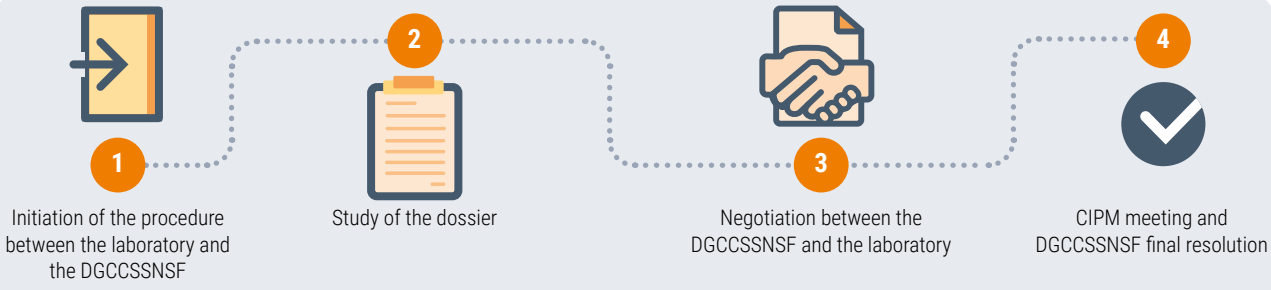
A specific feature of the Spanish model for the assessment and funding of medicines is the division of responsibilities. On the one hand, marketing authorisation is granted by the Spanish Agency of Medicines and Medical Devices (AEMPS), a state agency attached to the Ministry of Health. On the other hand, the procedure for determining their inclusion in the set of medicines that can be funded by the National Health System (NHS or SNS for its Spanish acronym) and setting the maximum authorised price lies within the competence of the Secretary of State for Health. However, it should also be borne in mind that the regional governments are responsible for managing the pharmaceutical services and for funding the expenditure.

Actors and process

Once the marketing authorisation has been notified by the AEMPS, the assessment and pricing of a medicine begins when the General Directorate-General of the Basic Portfolio of National Health System and Pharmacy Services (DGCCSSNSF), which reports to the Secretary of State of the Ministry of Health, sends the marketing laboratory an agreement to initiate the procedure. In this agreement, the DGCCSSNSF requests the necessary documentation on the medicinal product[4,5].

Based on the information obtained and the assessments made, the DGCCSSNSF and the laboratory enter into a negotiation process, the outcome of which, sometimes agreed and sometimes not, is sent to the Interministerial Committee on Pricing of Medicines and Healthcare Products (CIPM), which will take thedecision on whether or not to finance (and, if so, set the maximum authorised price) the medicine. In the case of the benefits and pricing of new indications for an already authorised medicine, the AEMPS transfers the marketing decision to the DGCCSSNSF, which likewise begins the process of including the authorised indications in the pharmaceutical benefits of the NHS[4]. Finally, the DGCCSSNSF, by means of a resolution, notifies the interested party of the CIPM's decision (**Figure 8**)[5].

FIGURE 8. Pricing and funding of medicines in Spain



Source: AIReF (2019)[5]

Note: CIPM: "*Comisión Interministerial de Precios de los Medicamentos*" (Interministerial Committee on Pricing of Medicines and Healthcare Products); DGCCSSNSF: "*Dirección General de Cartera Común de Servicios del Sistema Nacional de Salud y Farmacia*" (Directorate-General of the Basic Portfolio of National Health System and Pharmacy Services)

To determine the price of the medicine, the current regulation (although not very relevant in practice) dictates that the industrial price or laboratory selling price (LSP) is calculated as the addition to the full manufacturing cost of a percentage of the company's profit, which is set by the Government's Delegate Commission for Economic Affairs, according to RD 217/1990 and Information Circular No. 4/91[6,7].

Directorate-General of the Basic Portfolio of National Health System and Pharmacy Services (DGCCSSNSF)

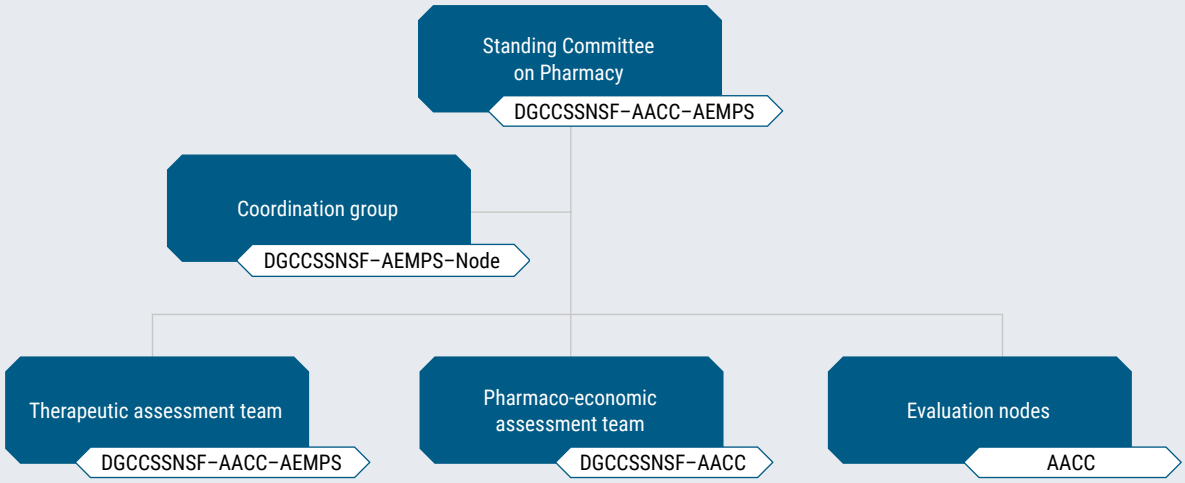
Among other functions, the DGCCSSNSF is responsible for the direction, development and execution of pharmaceutical policy, as well as the exercise of the State's functions regarding public funding and the pricing of medicines and health products[8]. In this area, the DGCCSSNSF, and specifically the Subdirectorate General for Pharmacy, is responsible for analysing the documentation submitted by the laboratory and gathering additional information, both directly and through the Therapeutic Positioning Report (TPR). The TPR is a therapeutic and economic evaluation document that positions the different medicines and is prepared using a standardised procedure. The preparation of the TPR has been subject to a recent reform in 2020, in which the economic evaluation of the medicine was included, and its elaboration has led to the creation of the REvalMed network of the NHS.

In turn, the DGCCSSNSF takes into account other sources of information, such as the technical dossier submitted by the laboratory, the European Public Assessment Report (EPAR) and assessment reports from other international agencies[5]. Another function of the DGCCSSNSF is to negotiate the price of the medicine with the laboratory. Based on the information provided and the price requested by the pharmaceutical company, a negotiation phase begins between the two entities, which ends with the referral to the CIPM and the subsequent resolution of agreement (or disagreement) on funding issued by the DGCCSSNSF. Finally, based on the CIPM's decision, the DGCCSSNSF issues a final resolution, ratifying the reached agreements[5]. The legislation establishes that the decision on price and funding of a new medicine must be taken within **180** days[9].

REvalMed

REvalMed is an evaluation network in charge of preparing the TPRs, which serves to offer a comparative therapeutic and economic evaluation of medicines, with the aim of providing relevant information, based on scientific evidence, on the positioning that the new medicine, or its new indication, occupies compared to existing therapeutic alternatives, pharmacological or otherwise. The DGCCSSNSF is in charge of coordinating the network evaluation system for medicinal products for human use, without prejudice to the function of functional co-ordination of the network attributed to the AEMPS[8]. The network is made up of the following actors (**Figure 9**)[10]:

FIGURE 9. Diagram of the structure of REvalMed in the Spanish NHS



Source: AEMPS (2020)[10] **Note: AACC:** Autonomous Communities; **AEMPS:** *Agencia Española de Medicamentos y Productos Sanitarios* (Spanish Agency of Medicines and Medical Devices); **DGCCSSNSF:** *Dirección General de Cartera Común de Servicios del Sistema Nacional de Salud y Farmacia* (Directorate-General of the Basic Portfolio of National Health System and Pharmacy Services)

- **Coordination group.** Its functions are to identify the TPRs to elaborate, to propose the prioritisation of the TPRs to be developed, based on the defined criteria, and to approve the TPRs. This group shall be composed of the Deputy Director General of Pharmacy of the DGCCSSNSF, the Head of the Department of Medicines for Human Use of the AEMPS, the coordinators of the evaluation nodes and representatives of the Autonomous Communities (AACC) that were not coordinating evaluation nodes.

- **Therapeutic assessment team,** whose function is to draft the TPR with regard to the therapeutic sections. It is made up of the merger of the medicines assessment teams of the AEMPS and the DGCCSSNSF. The team may be supported by designations made by the AACC.

- **Pharmaco-economic assessment team,** whose function is to prepare the draft TPR with regard to the pharmaco-economic sections. It is made up of the evaluation team of the DGCCSSNSF and may be supported by any designations made by the AACC.

- **Evaluation nodes.** Their function is to review the draft TPR and make any contributions they consider relevant. The nodes are made up of **120** expert management and clinical professionals designated by the AACC (at least two different AACC). Each node is coordinated and led by one Autonomous Community and co-ordinated by another. Coordination and co-coordination is rotated between those that volunteer, with a duration of **2** years. After these two years, the AACC that co-coordinates becomes the coordinator.

In turn, each AACC has, if it deems appropriate, professional experts to carry out the functions attributed to the node. The selection of experts is based on scientific issues and the declaration of confidentiality and conflict of interest.

There are currently **7** evaluation nodes, differentiated by clinical areas, leaving open the possibility of creating other nodes if necessary. These nodes are[10]:

- Immune-mediated diseases: rheumatic pathologies, dermatological pathologies and digestive pathologies
- Rare diseases (non-oncological) and advanced therapies
- Anti-infectives
- Oncology: digestive, renal and prostate; gynaecology and breast; lung and others
- Oncological haematology
- Central nervous system
- Pathology and cardiovascular (CV) risk factors, non-oncology haematology and respiratory

In the current reform of the TPRs, the clinical assessment is foreseen to take a maximum of **20** working days, while the economic evaluation would take a maximum of **10** working days. The development of TPRs is carried out through a 3-stage procedure, in which scientific societies, patient associations and industry can make comments and submissions (**Figure 10**)[10].

FIGURE 10. Procedure for the elaboration and approval of TPRs in Spain

Source: Ministry of Health (2020)[10]

In order to improve transparency and organisation in the elaboration of the TPRs, the plan establishes a prioritisation matrix based on the following criteria[10]:

1. Therapeutic gap (covers therapeutic gap in severe pathology= **10** points; covers therapeutic gap in non-severe pathology= **5** points; does not cover therapeutic gap= 0 points)
2. Potential incremental clinical benefit over funded therapeutic alternatives (YES= **10** points; Only in a subgroup of patients= **5** points; NO= **0** points)
3. Similar clinical benefit, but with a much better safety profile than funded alternatives that contributes to better outcomes (YES= **5** points; NO= **0** points).
4. New indications to already funded and marketed medicines (YES= **10** points; NO= **0** points)
5. Potential general interest for the National Health System regarding funded therapeutic alternatives (Scale from **0** [no relevance] **-20** points [high relevance]).

On the other hand, it should be noted that, in order to promote the adequate training of REvalMed technicians, as well as the implementation of the new TPRs, the Ministry of Health is going to carry out training for the professionals who are part of the network, with a budget of **3.5** million euros[11]. In May 2022, the Ministry of Health published a document specifying that the evaluations will be carried out by **143** experts from 18 different specialties (**66%** pharmacists and **7%** haematologists) (Tabla 3)[12]

TABLE 3. Number of experts in the REvalMED evaluation nodes, by speciality

SPECIALITY	NUMBER OF PROFESSIONALS	PERCENTAGE
Biology	2	1,4%
Biotechnology	1	0,7%
Cardiology	2	1,4%
Dermatology	1	0,7%
Digestive	2	1,4%
Health economics	2	1,4%
Endocrinology	2	1,4%
Hospital Pharmacy	95	66,4%
Pharmacology	3	2,1%
Haematology	10	7,0%
Internal medicine	1	0,7%
Family doctor	1	0,7%
Nephrology	1	0,7%
Pneumology	2	1,4%
Neurology	5	3,5%
Oncology	9	6,3%
Paediatrics	1	0,7%
Rheumatology	3	2,1%
Grand total	**143**	**100%**

Source: Ministry of Health (2022)[12]

According to the origin of the professionals, Castilla-La Mancha (**13%**) and Catalonia (**11**%) are the AACC that contribute most experts to REvalMed (Table 4). The document also indicates that, from its constitution until May 2022, **110** TPRs have been published, which is 1 TPR every 3 working days.

It should also be noted that in the first **5** months of the year 2022 the same TPRs have been carried out as in the whole of the previous year, which shows that the REvalMed constitution and methodology is becoming established, with a reduction in time and streamlining of the procedure[12].

TABLE 4. Number of experts in the REvalMED evaluation nodes, by Autonomous Community

UTONOMOUS COMMUNITY	NUMBER OF PROFESSIONALS	PERCENTAGE
Andalusia	12	8,4%
Aragón	5	3,5%
Asturias	13	9,1%
Balearic Islands	4	2,8%
Valencian Community	9	6,3%
Canary Islands	7	4,9%
Cantabria	12	8,4%
Castilla-La Mancha	19	13,3%
Castilla y León	5	3,5%
Catalonia	16	11,2%
Extremadura	8	5,6%
Galicia	4	2,8%
La Rioja	3	2,1%
Madrid	11	7,7%
Murcia	6	4,2%
Navarre	7	4,9%
Basque Country	2	1,4%
Grand total	**143**	**100%**

Source: Ministry of Health (2022)[12]

Interministerial Committee on Pricing of Medicines and Healthcare Products (CIPM)

Finally, the CIPM is responsible for setting, in a reasoned manner and in accordance with objective criteria, the industrial prices for the funding of the presentations of medicines that may be included, or are already included, in the pharmaceutical benefits of the National Health System, for which a medical prescription is required, and which are dispensed in Spanish territory. It is responsible for both funding decision procedures and price review procedures.

The commission is convened on a regular basis to evaluate and vote on all funding and pricing proposals[12]. According to Royal Decree 485/2017, the CIPM is composed of the following 11 members[4,12,13]:

- **Chairmanship:** The head of the State Secretariat for Health (**1** vote).
- **Vice-chair:** The head of the DGCCSSNSF (**1** vote).
- **Memberships:**
  - Two persons representing the Ministry of Economy and the Ministry of Industry, with the rank of General Director, who assess the budget impact of the evaluated medicine and the contribution to the GDP of the pharmaceutical company (**2** votes).

- Two persons representing the Ministry of Finance, with the rank of General Director, one of them representing the State Secretariat for Budget and Expenditure and the other representing the State Secretariat for Finance (**2** votes).
- Three representatives of the Autonomous Communities, at the proposal of the Interterritorial Council of the National Health System, elected from among its members on a rotating basis every six months (**3** votes).
- A civil servant of the DGCCSSNSF (**1** vote).
- The head of the Subdirectorate General Pharmacy, who shall act as secretary (**1** vote).
- Representatives of the other Autonomous Communities as listeners, who shall have the right to speak but not to vote.

The minutes of the agreements reached at CIPM meetings, as well as the calendar of meetings and the composition of the committee, are periodically published on the Ministry of Health's website[14]. However, these public agreements do not include the funded price, which is the price applied to prescription medicines included in the pharmaceutical benefits that are funded and dispensed in Spain[15], but rather the maximum Laboratory Selling Price (maximum LSP), known as the notified price. This is the maximum industrial price at which laboratories can sell the drug to non-NHS purchasers[12]. In general, the price at which the medicine is funded by the NHS will be lower than the industrial price of the medicine applied when it is dispensed outside the NHS[16].

Advisory Committee for the Funding of the Pharmaceutical Benefits of the NHS (CAPFSNS)

In 2019, the Advisory Committee for the Funding of the Pharmaceutical Benefits of the NHS (CAPFSNS) was created, which is a collegiate, scientific-technical body attached to the Ministry of Health. The purpose of this committee is, among others, to provide advice, evaluation and consultation on the relevance, improvement and monitoring of the economic evaluation necessary to support the decisions of the CIPM[17]. The technical reports produced by the CAPFSNS are available on the Ministry of Health website[18].

This Committee is composed of a Chair, a Vice-Chair and five members, all appointed by the Ministry of Health, from among professionals of recognised prestige, with proven experience and track record in pharmaco-economic evaluation, and its composition is publicly available[19].

Documentation

Although there are no guidelines or regulations in Spain that determine what information the laboratory must provide in order to obtain price and funding, in general, through the computer application for the processing of procedures for the funding and pricing of medicines by the NHS, GESFARMA[12,20], the drug manufacturer submits the following documentation in order to assess the potential funding of the medicine:

- Official price-fixing application form
- Laboratory data and basic drug information
- Requested price
- Three-year sales forecasts

- Similar therapies
- Prices of the medicinal product in other countries (in case the medicinal product is funded abroad)
- Fact sheet, package leaflet and labelling
- Therapeutic dossier
- Information on the disease
- Epidemiology
- Therapeutic arsenal available for the disease
- Value and importance of the medicine
- Pharmaco-economic studies
- Budget impact estimation of drug funding

Clinical assessment

Generally, the clinical assessment of new medicines is carried out by REvalMed's therapeutic assessment group. The therapeutic sections of the TPR indicate the main comparators to be used, the threshold of clinical relevance and the relevant clinical endpoints. In the case of clinical endpoints, morbidity or mortality variables, where no trials are available that have studied them, the surrogate and/or intermediate clinical variables or other variables that may be important shall be presented. Regarding the measure of efficacy used, the reference standard in clinical practice should be used primarily. In case of survival analysis, the Hazard Ratio (**95%CI**), cumulative odds at time t, in addition to median Overall Survival (OS) or Progression Free Survival (PFS) (or medians where appropriate)[10] should be expressed.

The characteristics of the drug and other relevant aspects of the administration or duration of treatment and relevant aspects of the authorisation (e.g. whether it is a new drug or a new indication, whether the drug has been designated as an orphan drug, whether it has conditional or exceptional authorisation, or if it is conditioned on the results of new studies) are also set out[10].

Quality Adjusted Life Years (QALYs) also have to be taken into account in the clinical assessment, although it is not specified which patient quality of life measurement questionnaires are recommended to a greater extent[21].

In terms of safety, the most significant adverse events (in terms of frequency or severity), provided in an objective manner, are included. In turn, the studies that have provided safety information and the number of patients included in the analysis should be explicitly specified, as well as the proportion of patients analysed who have had an adverse effect and the frequency of the different adverse events. For adverse events with the highest clinical impact, if possible, the number needed to treat shall be calculated[10].

Finally, an analysis of the value of the therapeutic benefit or its relevance to clinical practice is performed. At this point, comparisons are made with available treatments, assessing whether the magnitude of the treatment effect is of clinical relevance, whether there is therapeutic improvement or whether the treatments are equivalent therapeutic alternatives[10].

Economic evaluation

In the new TPRs, the economic evaluation will also be included in the reports. This section will be carried out by the pharmaco-economic evaluation team. The type of economic evaluation is chosen according to the available evidence, whether it is cost-utility analysis, cost-effectiveness or cost minimisation in cases where the alternatives compared are therapeutically equivalent[21]. The methodology established by the GÉNESIS Group[22] will be used to carry out the economic evaluation.

The perspective chosen for the economic evaluation will be, in general, that of the health system, leaving open the option of also including some information on the social perspective, provided that the characteristics of the pathologies generate relevant differences between the costs for society and the costs for the health system[22].

The choice of comparator should include as alternatives the comparator(s) from published clinical trials and alternatives currently being used in practice for that indication, including the option of doing nothing or supportive therapy if it is an alternative used in clinical trials or in practice, as well as the off-label use of a medicine, if it is being used routinely[22].

In general, a discount rate of **3%** will be used to value both costs and health outcomes. The time horizon of the evaluation is unspecified and will vary to capture the effects between the treatments evaluated, although it should be the same for costs and health outcomes[22].

In the case of cost-utility analyses, information should be presented in the form of QALY gains, cost increases and the resulting Incremental Cost Effectiveness Ratio (ICER) value: euros per QALY gained. It should be noted that in Spain there is no officially defined QALY threshold, although there are several studies that analysed funding decisions, extracting implicit willingness-to-pay thresholds from between **4,585** and **171,476** euros per QALY gained[23]. Among them, it is worth highlighting the one elaborated by Vallejo et al, which, from a supply-side perspective, obtain an implicit threshold of between €**22,000** and €**25,000** per QALY gained for funding decisions made between 2008 and 2012[24].

Regardless of the type of economic evaluation chosen, a sensitivity analysis should be carried out to assess the impact on the ICER of any variables, models or assumptions for which there is uncertainty in the initial calculation[10]. This analysis should preferably be probabilistic, although, understanding the difficulty it may entail, it is acceptable to include a deterministic univariate sensitivity analysis[22].

In addition to the economic evaluation, a budget impact analysis must be presented based on the estimation of the target population. The calculation will be performed, at the national level, for the baseline scenario and for the main alternative scenarios, based on the results of incremental cost per patient, incremental efficacy and/or the data on patients needed to treat obtained in the assessment report. The two main aspects of the sensitivity analysis to be assessed are the possible alternative drug acquisition costs and the variations in the quantification of the target population, depending on the different plausible scenarios[21].

Involvement of patients and scientific societies

In Spain, patients and scientific societies participate in the medicine assessment process by providing comments and allegations to the Phase 1 draft TPR[10]. These comments are sent to the relevant assessment team, either the therapeutic assessment team or the pharmaco-economic assessment team, for updating the TPR, before proceeding to the next phase of the TPR[10]. No information is available on the degree of impact of these comments, as the final text is adopted by the Coordination Group[21].

P&R decision elements

In Spain, the Price and Reimbursement (P&R) decision is based on several elements, which help in making a final decision.

Criteria for the inclusion of medicines in NHS funding

According to article 92 of the Royal Legislative Decree (RLD) 1/2015, of 24 July, which approves the revised text of the Law on guarantees and rational use of medicines and health products, the inclusion of medicines in the NHS funding is made possible by selective rather than indiscriminate funding, taking into account the following criteria[25]:

a) Severity, duration and sequelae of the different pathologies for which they are indicated.

b) Specific needs of certain groups.

c) Therapeutic and social value of the medicinal product and incremental clinical benefit of the medicinal product taking into account its cost-effectiveness.

d) Rationalisation of public spending on pharmaceuticals and the budget impact on the National Health System.

e) Existence of medicines or other therapeutic alternatives for the same conditions at a lower price or lower cost of treatment.

f) Degree of innovation of the medicinal product.

Reference Pricing System (RPS)

The RPS applied in Spain to establish the prices of medicines and their funding considers the prices of alternative therapies[10]. This system establishes the maximum amount at which the presentations of medicines included in each of the sets to be determined are funded[12], with the aim of generating savings for the public health system without jeopardising access to medicines, as well as encouraging the acceptance of generics and stimulating competition in pharmaceutical markets[10]. Each set comprises all presentations of funded medicines with the same level 5 of the World Health Organisation's anatomical therapeutic-chemical classification of medicines (ATC5)[26] and identical route of administration, including at least one generic or biosimilar presentation. The product with the lowest cost/treatment/day per defined daily dose (DDD) contained in each presentation is used as the reference price for all presentations belonging to the reference set. The composition of the sets and their prices are reviewed on an annual basis. This process of reviewing the composition and price of the sets takes place every year, using the Nomenclature data as of 1 April, and the annual review is published in the Official State Gazette once it has been completed. In this way, each year new sets are formed that include the launch of new generics or biosimilars (or sets disappear in the event that all laboratories - or all but one laboratory - stop marketing presentations that were previously included in the same set)[12].

"Although not explicitly, the price of medicines in other countries is taken into account when setting the price in Spain".

Financial agreements and their monitoring

In Spain, the use of discounts is a widespread practice, within the automatic price regulation mechanisms. These deductions and discounts established in RD 8/2010 vary in magnitude depending on the type of medicine[12]:

- **7.5%** for exclusive medicines marketed for a period of less than **10** years
- **15%** for exclusive medicines marketed for more than **10** years
- **4%** for orphan drugs

One issue to be taken into account in the pricing and funding system in Spain is the differences between the LSP (set at national level) and the actual price of the medicine (which is set at hospital or regional level). In this regard, a study comparing the price of medicines for hospital use has indicated that the differences between the LSP and the actual price have not stopped growing in recent years, reaching an average difference of **43.1%** in 2019 (median **82.3%**)[27]. These differences do not affect medicines funded through official prescriptions in pharmacies.

For its part, the process of negotiating the price and funding of medicines between the DGCCSSNSF and the laboratory may be conditioned by different financial agreements, with the aim of providing greater access to the medicine[12]:

- Setting expenditure ceilings for specific periods of time, so that the NHS does not have to pay for additional treatments once the ceiling has been exceeded.
- Maximum cost per patient, where a certain amount of expenditure per patient is fixed, regardless ofthe duration of the treatment, and the company assumes the additional cost in cases where this ceiling is exceeded.
- Risk-sharing or pay-for-health outcomes agreements, where the price of the medicine is determined by the health outcomes derived from its use or the achievement of the objectives stipulated in the contract. The first two CAR-T therapies have been included in this type of agreement, where a first payment was made when the drug was purchased and a second payment after 18 months based on whether or not the patient achieved the survival target[28]. However, little information is available on the details of such agreements, as they are confidential.
- Variable prices depending on the volume of purchase, whereby ranges of patients/packages are established so that the cost decreases as the number of patients/packages increases.

"The most common financial formula is the price-per-package agreement, which does not provide for differentiation by indication, with the use of other formulas being more sporadic".

"In 2021, the first split-payment financial agreement has been implemented, allowing the cost of a new therapy to be divided into four payments, one upon receipt of the medicine and the other three at the end of the first, second and third year, respectively".

Since 2019, Spain has had a corporate information system of the NHS to determine the therapeutic value in real clinical practice of the medicines used in the NHS, called VALTERMED. Although currently only high-impact medicines for the NHS are included, it is not ruled out that the system will be extended to other medicines[29]. The aim of this platform is to provide optimal information for appropriate decision-making inthe macro, meso and micro management of pharmaceutical benefits, at the different stages of the medicine cycle, determining the therapeutic value in real clinical practice of the medicines used in the NHS[30].

The data recorded are those of an administrative, clinical and therapeutic nature that make it possible to know the initial state and evolution of a patient after initiating pharmacological treatment. The variables to be recorded are those established in the pharmacoclinical protocols drawn up in a collaborative and multidisciplinary manner and coordinated by the DGCCSSNSF. The information is recorded by doctors or pharmacists at the NHS hospital[8,30].

By June 2022, VALTERMED has published **14** pharmacoclinical protocols, five of them in 2019, two in 2020, six in 2021 and one in 2022 (including the first two protocols in solid tumours). Ten of the protocols include drugs targeting RDs (**4** for cancer, **1** for complex fistulas caused by Crohn's disease, **1** for cystic fibrosis, **1** for hypophosphataemic rickets, **1** for retinal dystrophy associated with biallelic RPE65 mutation, **1** for mucopolysaccharidosis type VII and **1** for spinal muscular atrophy), while the four protocols with drugs not classified as orphan drugs target severe atopic dermatitis, COVID-19, small cell lung cancer and triple negative breast cancer[31]. In addition, it has published a first health outcomes report, in this case for atopic dermatitis.

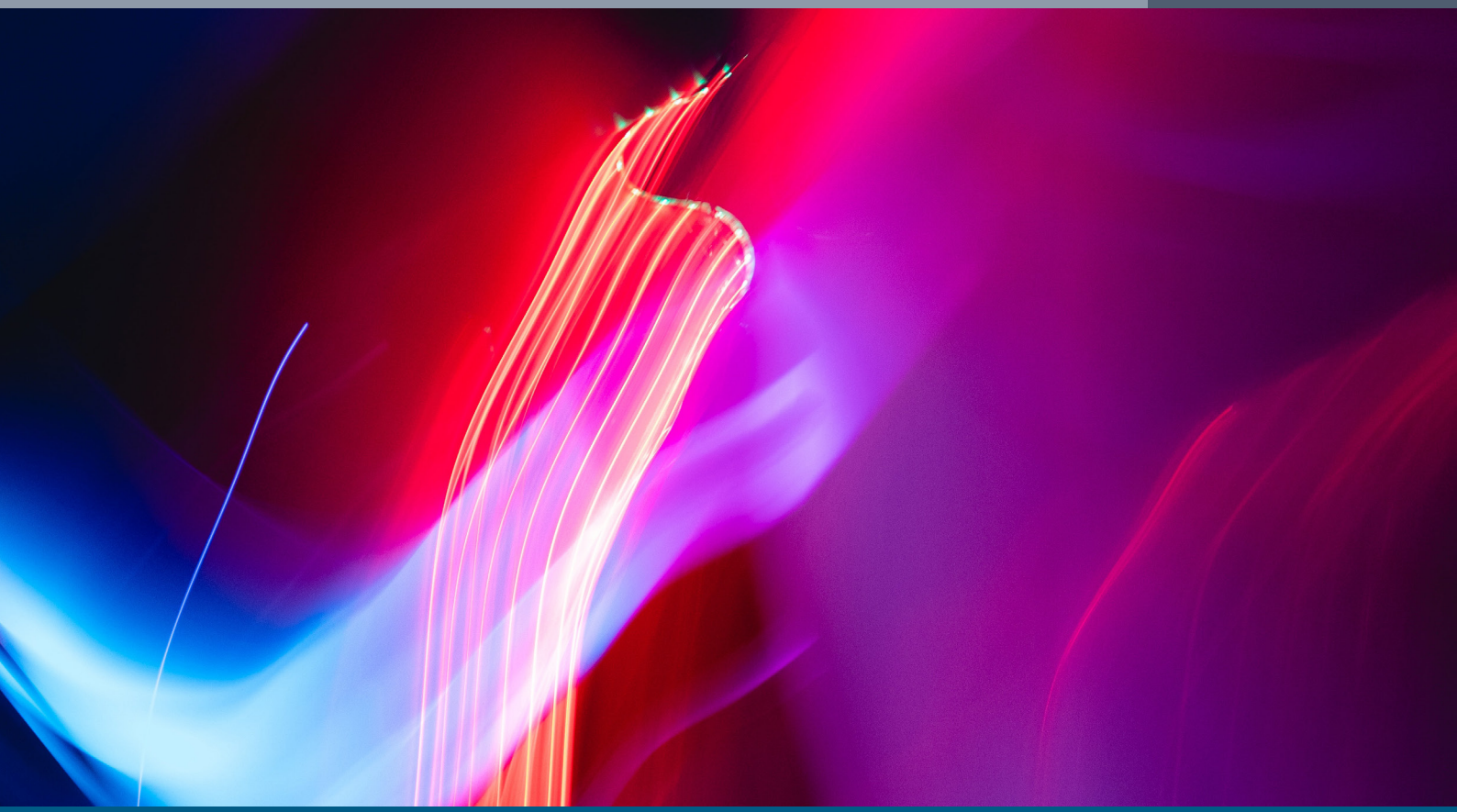
Work is currently underway on Phase **2** of VALTERMED, which will allow, in addition to practical functionalities, integration with the information systems of the AACC. Phase **2** began in July 2021, with the cross-referencing with the health card, which allows for the monitoring of the entire NHS of the patients included in the system, avoiding duplications and identifying deaths[32].

Similarly, some of the agreements reached in the CIPM establish that the expenditure of the medicine analysed should be monitored through the monitoring platform for the supply of medicines in the national market (SEGUIMED). This tool is responsible for monitoring the supply and distribution of medicines by laboratories and wholesale warehouses in Spain[33]. The incorporation of this data into the SEGUIMED tool has been mandatory since 2011[34]. An example of the use of SEGUIMED can be found in therapy with the compound atezolizumab, in which two of its indications are funded through pay-for-results agreements following VALTERMED pharmacoclinical protocols, while the monitoring and control of expenditure is carried out through SEGUIMED. In this case, the laboratory is obliged to report the sales of the medicinal product to the NHS on a monthly basis[35].

Likewise, in Spain there are other monitoring mechanisms, in this case for a single pathology, such as the information system for therapeutic monitoring of patients with chronic hepatitis C (SITHepaC), whose objective is the monitoring of therapeutic effectiveness and the analysis of the health outcomes of patients with hepatitis C treated with the latest direct-acting antivirals in Spain[36].

SITUATION IN OTHER COUNTRIES

2



In this section a review is made of how the process of assessing and funding medicines is currently carried out in other countries, with the aim of extracting international best practices.

For countries belonging to the European Union (EU), it is useful to first review some common considerations. First, in the EU, the approval of medicines is governed by the following four procedures, whose rules and requirements are identical[37,38].

- **National procedure:** the company submits an application for marketing in a selected country, to be assessed by the relevant national entity.

- **Decentralised procedure:** the applicant submits its application for authorisation simultaneously in several EU countries. The various agencies assess the medicinal product in a coordinated manner, with one of them acting as the coordinating agency so that all the agencies finally issue an identical authorisation that is valid in their territory.

- **Mutual recognition procedure:** this is used when a medicine already has a marketing authorisation in one EU country, and intends to market it in another.

- **Centralised procedure:** the applicant applies for a single authorisation for all EU Member States at the same time. In this case, the administrative process is carried out by the EMA and the scientific assessments are carried out by two Member States. Once a positive technical opinion has been issued by the Panel, the European Commission grants the applicant an EU-wide marketing authorisation.

Second, although pricing and reimbursement processes are a national competence, EU member states are obliged to comply with the European Transparency Directive 89/105/CEE, which stipulates that the maximum period for pricing and reimbursement of medicines is 180 days[39].

Third, the regulation and reimbursement of medicines accessed in "special situations", i.e. outside the common approval and funding processes of each country, present some common patterns.

- Compassionate use access, as set out in Regulation 726/200440 , allows access to medicinal products in the clinical research phase for patients with a chronic or severely debilitating disease who cannot be treated satisfactorily with an authorised medicinal product. Each member state can legislate in this sense, establishing other requirements, such as that the use of these compassionate therapies entails a realistic probability of therapeutic benefit, or requirements for additional information from the sponsor. Generally, such medicines are provided free of charge by the industry and require authorisation by national bodies.

- The use of a medicine in a different indication than the one authorised (off-label) is an alternative contemplated in all countries when there are no suitable therapeutic alternatives, although it must generally be authorised by health insurers (public or private) for funding. In such cases, these medicines are charged at the funded price for the approved indication.

- Access to non-publicly funded medicines is often not defined in the funding processes. In these cases, the list price is generally applied, to be paid in full by the patient or the patient's health insurance.

Access to medicines in special situations in EU countries

Spain. Access in special situations is determined by RD 1015/2009, which encompasses three types of special uses: compassionate use of investigational medicinal products, use in conditions other than those authorised, and medicinal products not authorised in Spain[41]. The uses in conditions other than those authorised "*shall be exceptional and shall be limited to situations in which there is a lack of authorised therapeutic alternatives for a given patient*". The use of medicinal products outside the authorised conditions must be authorised for public funding by the competent bodies of the health services of the Autonomous Communities.

Germany. For use outside the approved indications, German law states that insurance companies will only bear the costs when there is a positive decision of the Federal Joint Committee, the medicine is used as part of a clinical study and a declaration of assumption of costs is issued according to the Social Code law or if certain criteria are met[42]. In compassionate use, the pharmaceutical company must provide the drug free of charge, while health insurers will only cover the administration of the drug and, when necessary, the hospital stay[42]. In addition, the individual curative intent formula (the physician decides on his or her own initiative and with the patient's consent to use an unapproved medicine) can be used if other treatment options have been exhausted and the physician suspects a benefit for the patient concerned based on scientific knowledge[42].

Austria. Access to medicinal products for compassionate use, which has been provided for in Section 8 of the Medicines Act since 2009, requires authorisation by the Federal Office of Health Security. This authorisation is conditional on the applicant, which cannot be the company supplying the medicinal product, reporting annually to the Federal Office for Health Safety on the use of the medicinal product[43,44].

Scotland and England. For the Medicines and Healthcare products Regulatory Agency (MHRA), a 'special' medicine is one that is not authorised for use in the country, or for use outside the approved indication[45]. These medicines can only be provided to meet the special clinical needs of a particular patient if there is a need that cannot be met by available medicines and under the responsibility of the prescribing physician or pharmacist[46]. Data on the person to whom the special medicinal product is supplied, the quantity sold and any details of adverse reactions to the product sold should be kept for at least five years[46]. Generally, although the MHRA does not recommend off-label use, if the product authorised in the UK can meet the clinical need, even off-label, it should be used instead of an unauthorised product[46]. Reimbursements for these therapies are established by analysing a selection of prices from manufacturers of unlicensed speciality products and are recorded in the UK Drug Tariff Specials[47].

France. It has recently reformed the early access or compassionate access procedure, formerly known as ATU (*Autorisations Temporaires d'Utilisation*), by creating two new access systems in July 2021[48]: "early access", which is aimed at medicines that respond to an unmet therapeutic need, which may be innovative and for which the laboratory undertakes to submit a marketing authorisation or an application for reimbursement within the following two years; and "compassionate access", for medicines that are not necessarily innovative, which are not initially intended to obtain a marketing authorisation, but which respond satisfactorily to an unmet therapeutic need. This compassionate access concerns both medicines that are not authorised in France and those that are used for a different indication. Both types of medicinal products are provided by the laboratory holding the exploitation rights, either free of charge or in exchange for compensation, the amount of which is freely set by the laboratory (unless the medicinal product already has a price negotiated or set by the Economic Committee for Health Products).

Italy. There are procedures for early access to the medicinal product, in which free access to a medicinal product is allowed before the Italian health authority authorises its marketing or, for medicinal products already authorised, for

indications other than those for which the medicinal product has been authorised[49]. Law 648/1996 allows the dispensing of a medicine at the expense of the National Health Service, when there is no valid therapeutic alternative, for innovative medicines authorised in other countries but not in Italy, for medicines not yet authorised but undergoing clinical trials, or for medicines used for a therapeutic indication other than the authorised one[50].

The Netherlands. Five situations of unauthorised prescriptions are distinguished[51]: **a)** if the medicinal product is registered for an indication, with limited use as a third or fourth choice, and is intended to be used as a first or second choice medicinal product. **b)** if the medicinal product is prescribed for a group of patients other than the one for which the indication is intended. **c)** if there are insufficient data to prescribe the medicinal product in patients with severe impairment, while data are available in patients with less severe impairment. **d)** if children may be excluded from an indication because there are no scientific data or an appropriate dosage form and dosage is not available. **e)** if the medicinal product is used for a completely different indication.

Portugal. If the patient is at immediate risk of life-threatening or has severe complications, and there is no therapeutic alternative, NHS hospitals can apply to the National Authority for Medicines and Health Products (INFARMED) for the use of the drug before finalising the approval process. These requests must be made by the hospitals, after evaluation by the institution's Pharmacy and Therapeutics Commission (*Comisión de Farmacia y Terapéutica* - CFT)[52]. The transfer of medicines subject to authorisation for exceptional use is carried out within the framework of the Early Access Programme (EAP) for medicines[53]. INFARMED publishes monthly data on approved EAPs[54].

Sweden. It also has another type of access called "drug licensing", a permit requested by the prescribing physician for a pharmacy to sell a medicine that is not approved in the country. Justification must be provided as to why approved medicines cannot be used for the indication; what previous therapy has been used and its results; why the medicine for which the licence is requested is chosen; and clear information about the medicine in question[55].

Germany

The price evaluation and negotiation procedure in Germany is a particular process within the EU countries. The main difference is that pharmaceutical companies can market a new medicine for a period of **12** months without price and reimbursement approval by the country's authorities, once they have obtained marketing authorisation, either from the EMA, the German authorities or by mutual recognition procedure[56]. However, this does not mean that companies are completely free to set the price, as they are subject to a number of evaluation and pricing mechanisms that regulate and limit the prices of medicines[57].

Actors and process

The main actor in the evaluation and pricing processes in Germany is the Federal Joint Committee (*Gemeinsame Bundesausschuss* or G-BA), which is the public organisation in charge of the final decision making process, legally supervised by the German Federal Ministry of Health. The assembly of the G-BA consists of a chairman and two impartial members appointed by the Federal Ministry of Health, three representatives of hospitals, three representatives of physicians, one representative of dentists and five representatives of insurance companies.

All these actors have voting rights[58,59]. Patient representatives also attend G-BA meetings and are consulted by the Committee, but do not have voting rights[58].

The G-BA can commission an independent evaluation by the Institute for Quality and Efficiency in Health Care (*Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen* or IQWiG), which is a non-governmental institution responsible for clinical and economic evaluations. Based on the documentation provided by the laboratory and the results of the standard comparator in the indication, the IQWiG conducts an assessment of whether the new therapy offers an additional benefit compared to the standard of care[56]. This evaluation process lasts for **3** months[60].

If the new drug demonstrates a therapeutic benefit over the comparator, the pharmaceutical company enters into a price negotiation period with the National Association of Statutory Health Insurance Funds (*Spitzenverband Bund der Krankenkassen* or GKV-SV), which is the central association of health insurance companies in the country[61].

In 2011, the Pharmaceutical Market Restructuring Act (*Arzneimittelmarkt- Neuordnungsgesetz* or AMNOG) came into force, which provides for pricing freedom, but imposes a systematic assessment of the added therapeutic benefit of new medicines in order to negotiate the price within twelve months of the new therapy entering the market. In general, the evaluation and pricing processes are based on three main principles[58]:

- Manufacturers are free to set the price of medicines.
- All prescription drugs are reimbursed by insurance, unless they are included in a negative list.
- Medicinal products can be grouped into groups of products considered therapeutically equivalent and subject to maximum reimbursement prices.

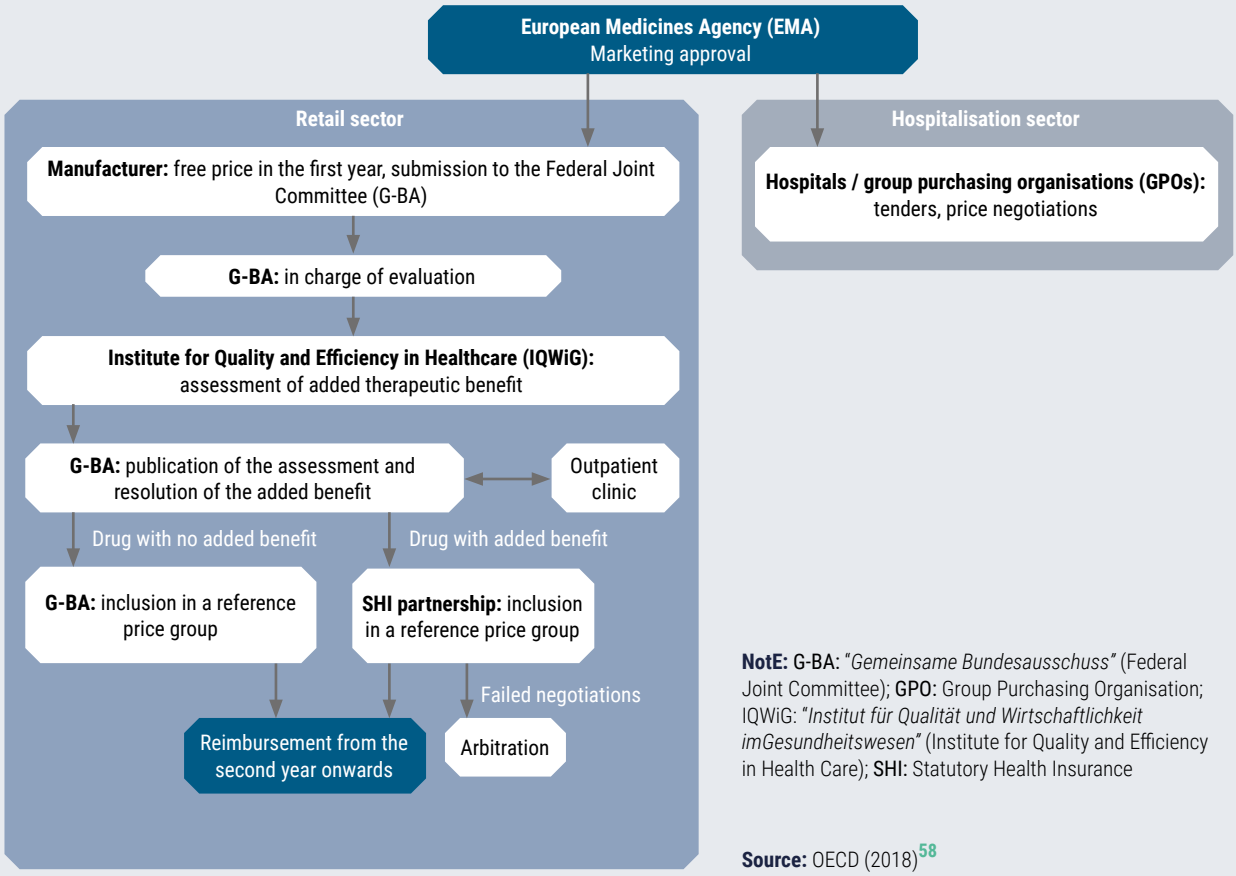
This process applies to all new branded medicines marketed in Germany, except for those with an estimated budget impact of less than €**1** million per year[58]. According to AMNOG, pharmaceutical companies must submit a dossier to the assessment committee within **3** months after the new drug enters the German market. At that time, the G-BA can ask the IQWiG to carry out an evaluation[62].

The result of this assessment is published on the internet and pharmaceutical companies, patient associations, scientific societies and medical experts can submit comments for a period of **3** months. After that time, based on the results of the assessment and the comments received, the G-BA makes a decision on the classification of the new drug[62]. In the event that the new therapy demonstrates additional benefit, the pharmaceutical company and the GKV-SV negotiate a reimbursement price, with a discount on the original sales price set by the company. If the two entities do not reach an agreement, an arbitration committee determines the final reimbursement price, taking into account international prices. If the GB-A concludes that the new drug offers no additional benefit, the drug can be transferred to the reference price system. If a medicine with no added benefit cannot be assigned to a reference price group, a reimbursement amount is also agreed, but the annual costs of the therapy cannot be higher than those of the comparator therapy (**Figure 11**)[58,62]. This negotiation process between the company and the GKV-SV has a maximum duration of **6** months, regardless of whether the medicine has demonstrated added benefit or not[60].

Due to the great importance of the choice of a suitable comparator in the assessment process, the G-BA facilitates meetings with the pharmaceutical company to advise on the appropriate comparator in Phase **3** clinical trials, as well as to inform about the requirements for marketing in Germany[63,64]. These meetings

offer the possibility to discuss the requirements and details of the assessment process, while the federal authorities can point out possible deviations in the trials of the therapy to be assessed[64].

FIGURE 11. Institutions and pricing process in Germany



NotE: G-BA: *"Gemeinsame Bundesausschuss"* (Federal Joint Committee); **GPO:** Group Purchasing Organisation; IQWiG: *"Institut für Qualität und Wirtschaftlichkeit imGesundheitswesen"* (Institute for Quality and Efficiency in Health Care); **SHI:** Statutory Health Insurance

Source: OECD (2018)[58]

In the event that new evidence emerges on a therapy that has already been evaluated, either the G-BA or the pharmaceutical company can request a reassessment of that therapy, although the G-BA is not obliged to conduct a reassessment at the request of the company[58].

The final assessment reports are published on the website of the *Bundesinstitutfür Arzneimittel und Medizinprodukte* (*BfarM*) and are publicly available[65].

In Germany, the prices of hospital medicines are negotiated directly between the hospitals (whether public or private) and the pharmaceutical companies. In contrast to outpatient medicines, where the health insurance is obliged to cover all medicines that are not explicitly excluded from reimbursement, hospitals have full autonomy in the purchase of medicines. The prices of these therapies are not explicitly regulated, although since 2017, the prices of outpatient medicines have been used as the upper limit for the hospital setting[58].

Documentation

From the first **3** months after the entry of the medicinal product into Germany, and if the cost impact is assumed to be greater than **1** million, the pharmaceutical company is obliged to submit a value dossier, including all clinical and economic evidence that demonstrates the benefit of the new therapy. By law, this dossier must include[58,66]:

- The therapeutic indications authorised in the country.
- The clinical benefit shown by the medicine, as well as the unmet needs in the disease and the prevalence and incidence of the pathology in Germany.
- The added clinical benefit over the selected comparator therapy. Prior to the preparation of the dossier, the company may consult the G-BA on the choice of the appropriate comparator. If the company finally chooses another comparator, it must provide sufficient justification explaining the choice of comparator.
- The therapy costs per patient for the compulsory insurance as well as the cost of the comparator. The number of treatments per patient per year, the duration of treatment in days and treatment days per year as well as the consumption per dose must be specified for the calculation of the costs.
- Specific requirements to ensure proper quality of patient care, such as diagnostic needs, the qualifications of doctors and other healthcare staff, the medical infrastructure needed for the medicine to be properly installed, as well as whether healthcare staff or facilities need to follow a specific safety protocol to administer the therapy.

In addition, the dossier should include all available evidence on ongoing and discontinued studies with the tested medicinal product. This also includes studies in which the manufacturer participates financially in some other way without being a sponsor. Similarly, the dossier should include information on third-party studies on the medicinal product, if available[58,67]. Before starting the assessment, the pharmaceutical company can send the dossier to the G-BA to verify whether it contains all the necessary information, without starting the assessment period[67].

Clinical assessment

The clinical assessment is carried out at the same time as the economic evaluation without a differentiated process between the two. When conducting a clinical assessment, the IQWiG takes into account the "relevant" benefits for the patient, determined by mortality, morbidity and health-related quality of life. As complementary aspects, time and form of the intervention are also taken into account, as they are related to an improvement in the patient's quality of life, but these two indicators cannot be used to determine the therapeutic benefit versus the comparator[68].

In general, the following outcome measures are taken into account for the clinical assessment[68]:

- Increased life expectancy
- Improving health status and health-related quality of life
- Reduction of the duration of the disease
- Reduction of adverse effects

According to the German authorities, the use of proxy variables is only justified if they have been validated in advance by appropriate statistical methods, without indicating any standard assessment method for such measures[68].

For the G-BA, a therapeutic improvement over the comparator comes from obtaining a relevant benefit for the patient[69]: **i**) due to a superior efficacy of the medicinal product to be evaluated compared to the standard of care or **ii**) due to a reduction in the frequency and/or severity of relevant adverse reactions in the therapy compared to the comparator.

The IQWiG quantifies the additional benefit of a medicine over its comparator on a scale of **6** levels (**Table 5**)[58]:

TABLE 5. Scale of benefit measurement by the IQWiG in Germany

TYPE OF BENEFIT	DEFINITION
Exceptional additional benefit	Sustained and substantial improvement in benefit. This is a highly relevant benefit that has not previously been achieved with the appropriate comparator, and can be identified by recovery from the disease, a significant increase in life expectancy, long-term relief of severe symptoms, or a highly relevant avoidance of serious side effects from the therapy.
Significant additional benefit	Significant improvement in benefit. It is relevant to the therapy, was not previously achieved with the appropriate comparator, and can be identified in particular by attenuation of severe symptoms, a moderate prolongation of life, a patient-noticeable "alleviation" of the disease, or the therapy's avoidance of important serious or other side effects.
Minor additional benefit	Moderate or mild improvement in benefit. It is relevant to the therapy, was not previously achieved with appropriate comparators, and in particular may be identified as a reduction in non-severe symptoms of the disease or that the new therapy avoids certain side effects.
Unquantifiable additional benefit	When the available scientific data do not allow for quantification.
No additional benefit	No additional benefit has been demonstrated.
Lower profit	When the benefit of the tested medicine is less than that of the comparator.

Source: prepared by the authors based on OECD (2018)[58]

For patient-reported outcomes (PROs), in addition to health-related quality of life, the assessment takes into account that PROs may encompass other dimensions, such as disease symptoms. This follows the good practices for the collection of health-related quality of life data as outlined by the EMA[70].

Special route for ODs

In the case of orphan drugs (ODs), the G-BA assumes an additional therapeutic benefit for them, taking into account the data provided by the pharmaceutical company for marketing authorisation, without considering any comparator, as long as the expenditure for compulsory insurance does not exceed **50** million euros per year. Manufacturers are exempted from submitting data to support this benefit, but the G-BA assesses the magnitude of the benefit to patients in order to create a basis for price negotiation. If annual sales exceed this threshold, the pharmaceutical company is required to submit data on the additional therapeutic benefit, and both the assessment and price negotiation of ODs follows the same process as medicines for prevalent diseases[58].

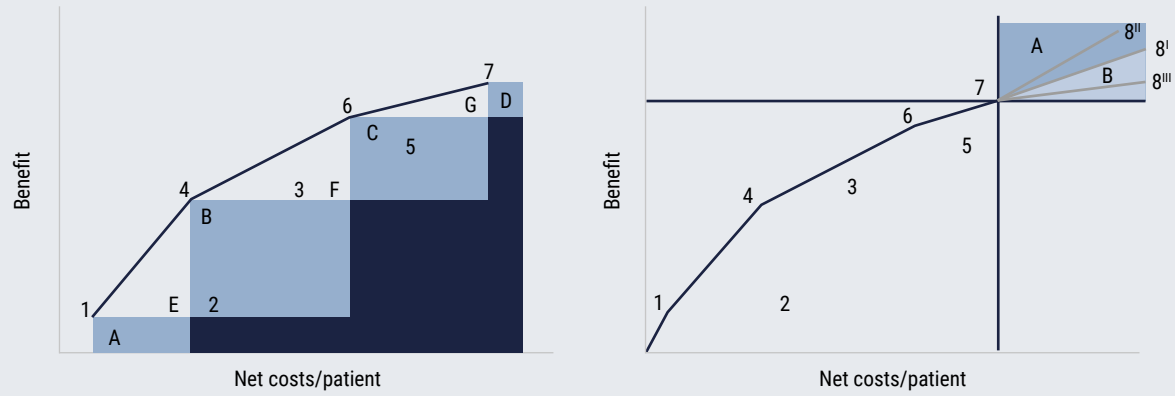
Economic evaluation

In Germany, the economic evaluation carried out by the IQWiG differs from other European countries as it does not uses a cost-effectiveness threshold, but instead bases its decisions on an efficiency frontier, consisting of all medicines approved in Germany according to their benefit (vertical axis) and costs (horizontal axis)[68].

Functioning of the efficiency frontier used in Germany

Interventions **1** to **7** are represented as comparators, of which interventions **1**, **4**, **6** and **7** form the efficiency frontier and thus the willingness to pay. New interventions (number **8II**) that lie above the frontier (area **A**), according to their benefit-cost ratio results, are more cost-effective than the last extrapolated segment of the frontier and will be reimbursed at the specified price. Conversely, if the intervention is in area **B** (intervention **8III**), its benefit-cost ratio will be lower than the previous ones, and therefore the decision-maker can negotiate a lower reimbursement price. Interventions with a constant benefit-cost ratio fulfil the criterion that their price is appropriate compared to the last therapy on the efficiency frontier (Figure 12)[68].

FIGURE 12. Efficiency frontier used in Germany



Fuente: IQWiG (2019)[68]

When assessing costs, the IQWiG takes into account different perspectives, depending on the therapy to be assessed. In general, it considers the perspective of compulsory insurance, social insurance, the insurer (which takes into account the co-payments of the insured) and the social perspective. The costs included in each of these perspectives can be found in Table 6[68].

TABLE 6. Different perspectives and costs considered in Germany

Cost category	Direct medical costss		Direct non-medical costs		Indirect costs	Transfer payments
Perspective	Refundable	Non-refundable	Refundable	Non-refundable	–	–
Society	Yes	Yes	Yes	Yes	Yes	Yes
Social security	Yes	No	Yes	No	No	No
SHI insurance community	Yes	Yes	Yes	Yes	No	No
SHI	Yes	No	Yes	No	No	Yes

Note: SHI: Statutory Health Insurance
Source: IQWiG (2019)[68]

The time horizon of the economic evaluation should represent at least the average duration of the study in order to be able to compare the benefits and costs of interventions. In general, the IQWiG recommends that time horizons should be as long as possible, especially in the evaluation of chronic diseases. Furthermore, costs and benefits should always take into account the same time horizon[68].

If cost data are from different time periods, they must be adjusted for inflation using the Harmonised Index of Consumer Prices of the German Federal Statistical Office. If costs and benefits occur over periods longer than one year, they are discounted after the first year with a constant rate of **3%**. Similarly, identical constant rates of **0** and **5%** must be used in sensitivity analyses, justifying any deviations[68]. The assessment also considers an analysis of uncertainty about the results, performing univariate and multivariate deterministic and probabilistic sensitivity analyses, following the recommendations of the ISPOR Joint Modelling Research Good Practice Working Group[68].

Involvement of patients and scientific societies

Patients are formally involved in the evaluation and reimbursement process for medicines in Germany as members of the G-BA therapy assessment group, contributing with their opinions, but without effective voting rights[58]. Patients involved in the G-BA committee are appointed by a Patient Coordinating Committee, which is made up of the four main patient associations in Germany. These patient representatives must fulfil a number of requirements, such as being free of conflicts of interest and having experience and expertise. G-BA meetings are open to both "permanent" patient representatives with general experience and expertise regarding the assessment process and patients related to the therapy to be assessed who can contribute their knowledge and experience with the pathology[71,72].

The contributions of the scientific societies are taken into account by the G-BA when making a final assessment of the therapies. In addition, these societies also collaborate in the development of monitoring tools, which are used to check the real-life results of therapies for which the G-BA deems it necessary[58,73].

P&R decision elements

Reference price systems

One of the main elements for pricing medicines in the German market is the use of the internal reference price system. If a medicine demonstrates some additional therapeutic benefit, the pharmaceutical company and the GKV-SV, as discussed above, enter into a price negotiation process in which the additional benefit and the cost versus the comparator form the main basis of the negotiations. If the new medicine does not demonstrate a greater benefit than the comparator, the maximum price at which the new medicine can be accessed is the price of the comparator used[57]. In the event that a patient selects a medicine with a price above the maximum price of its class, the patient must make a co-payment for the difference between the price of the chosen medicine and the maximum reference price[74].

A two-step process is followed for the establishment of reference prices in Germany[75]:

- First, the G-BA forms groups of medicines based on whether they contain the same active ingredients, whether they use pharmacologically and therapeutically comparable active ingredients, or if a therapeutically comparable action can be achieved. Secondly, the GKV establishes a reference price to which groups of medicines must adhere.

- In addition, prices paid in other European countries are also taken into account. The list of other countries used as a reference has to fulfil three conditions: they must belong to the European Economic Area (EEA), the sum of the population of these countries must be at least **80%** of the EEA population and the countries must be comparable to Germany in terms of economic performance[58].

Budgetary impact

In addition, the G-BA uses the budgetary impact of approved therapies as a further method in pricing and reimbursement. In this sense, the budgetary impact is assessed taking into account the perspective of compulsory health insurance, or any other relevant payer, and does not include other costs or savings to the system outside of these perspectives. In turn, given that the impact is likely to change with the introduction of the new medicine, the IQWiG estimates the impact for a period of **1-3** years[68].

Financial agreements and their monitoring

Regarding the financial formulas of the German system, the legislation includes the possibility of reaching agreements between insurance companies and pharmaceutical companies, such as a price reduction depending on the amount of sales, annual sales volume agreements with compensation of additional income or reimbursement agreements depending on the therapeutic successes achieved. In addition, in 2011 there was a legislative change that opened the door to other types of contracts (even becoming mandatory if the G-BA so stipulated), such as those dependent on the generation of evidence, where remuneration to pharmaceutical companies depended on evidence generated from real-world data[76].

However, due to the confidential nature of the negotiations reached between health insurers and pharmaceutical companies, few published evidence exists on the types of agreements reached, such as outcome-based funding, have not been widely used in Germany. On the other hand, the emergence of innovative therapies with non-definitive results and high impact, such as CAR-T therapies, has led to progress in the use of this type of formula. According to a recent study, the country's main insurance companies, representing almost **60%** of the population, reached agreements with pharmaceutical companies to reimburse the cost of drugs if patients did not reach certain milestones related to overall survival[28].

In 2020, the law on compulsory insurance was amended, giving the G-BA the possibility to oblige pharmaceutical companies to submit and collect real-world drug effectiveness and consumption data. The G-BA can require this data collection or evaluation from the first moment of marketing. But this evidence collection is limited to those medicines for which a low level of evidence is available, such as medicines with conditional approval, in exceptional circumstances or for rare diseases[59,73].

Once the initial documentation has been obtained, the G-BA decides whether data collection with real-world evidence is necessary and, if appropriate, commissions the development of a pilot project. This pilot should address the type, duration and scope of data collection, as well as the objective, the criteria for assessing the patient data to be recorded, the methodology of data collection and the evaluation by the pharmaceutical company.

This process must be completed within a maximum of **6** months. After that time, the G-BA, or the IQWiG on behalf of the G-BA, transmits the pilot version of the project to scientific societies, federal health authorities, interested pharmaceutical companies and other expert individuals and organisations for comments and suggestions for improvement[73].

Once comments are received, the G-BA determines the final requirements and timelines for the review of the data collection. There is no specific review period, but within a maximum of **18** months the G-BA reviews whether data collection is proceeding as required or whether adjustments to the specifications need to be made[73].

...TO BE HIGHLIGHTED IN GERMANY

- ✔ *Initial automatic marketing of the medicinal product without prior assessment, during the first year*
- ✔ *Use of the efficiency frontier to make the price and reimbursement decision*
- ✔ *ODs are not required to demonstrate additional therapeutic benefit if they do not exceed an annual expenditure of EUR 50 million*

Australia

Australia was one of the pioneers in introducing economic evaluation of health interventions as early as 1993. The drug approval process is governed by the Therapeutic Goods Act 1989[77] and rests with the Therapeutics Goods Administration (TGA), which is the drug regulatory agency of the Australian Government's Department of Health[78]. Once the TGA ratifies the drug for marketing approval based on quality, safety and efficacy, it is entered into the Australian Register of Therapeutic Goods (ARTG)[79,80]. The Australian government partially funds medicines included in the Pharmaceutical Benefits Scheme (PBS), which is a national list of medicines for which the patient pays a co-payment[81].

Actors and process

Once the TGA approves the drug for marketing in the country, the laboratory concerned can apply for the cost of the therapy to be funded under the PBS[82] . To access this assessment, the pharmaceutical company must submit an application to the Pharmaceutical Benefits Advisory Committee (PBAC), an independent body that makes recommendations to the government on the inclusion (or not) of the drug under the PBS[81]. The Australian system allows for parallel assessment of the TGA's marketing authorisation and the PBAC's assessment, but a drug cannot be included in the PBS unless it is included in the ARTG register[81].

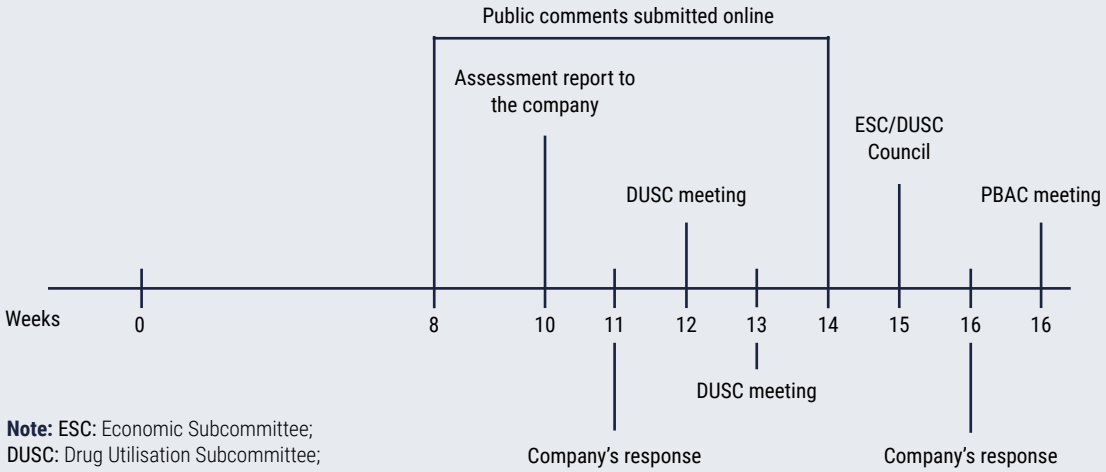
The PBAC is required by law to consider the efficacy and cost of the proposed drug in comparison with existing therapies[83,84]. It cannot make a positive recommendation for a drug that is substantially more

expensive than an alternative medicine, unless it is convinced that the proposed medicine also provides a significant improvement in health[83]. Likewise, the Australian government may not include a drug in the PBS unless the PBAC recommends its inclusion. The government may also choose not to include a drug recommended by PBAC in the PBS[81]. For example, when the budgetary impact of the drug exceeds AUD **20** million (approximately **13** million euros) in any of the following years, the Minister requests a reconsideration of its inclusion in the PBS[85].

PBAC's assessment of applications follows a **17**-week cycle, receiving applications **3** times a year, in March, July and November[81]. During the first **10** weeks, applications are assessed and a draft report is sent to the sponsor. The company has one week to comment on the draft and clarify any doubts raised by the evaluators. The submission, the assessment report and the company's response are forwarded to two technical subcommittees of the PBAC: the Economic Subcommittee (ESC) and the Drug Utilisation Subcommittee (DUSC). The advice provided by these subcommittees is provided to the company in week **15** after the initial submission and the company has **1** week to respond. Comments from interested patients, healthcare professionals and other interested parties can be submitted via an online form up to **3** weeks before the PBAC meeting. The PBAC meets approximately **17** weeks after the submission[81].

The outcome is communicated to companies **3-5** weeks after the PBAC meeting, with a public summary document published on the PBS website **16-18** weeks after the meeting (**Figure 13**)[81].

FIGURE 13. Australian medicines assessment process, in weeks



Note: **ESC:** Economic Subcommittee; **DUSC:** Drug Utilisation Subcommittee; **PBAC:** Pharmaceutical Benefits Advisory Committee

Source: Kim (2021)[81]

The public summary assessment document, in addition to the information on the medicine, contains data submitted by the company (censoring those that are commercially sensitive), as well as the PBAC's rationale for recommending inclusion in the PBS and input and comments from patients and stakeholders[86].

Pharmaceutical Benefits Advisory Committee

The PBAC is a body of independent experts appointed by the Australian government. According to the National Health Act, the PBAC must consider, in addition to the medical conditions for which the medicine is registered

in Australia, clinical efficacy, safety and cost-effectiveness (understood as value for money) compared to other treatments available in Australia[87,88]. The Australian National Health Act provides that the PBAC must consist of a chairperson and at least **11** other members, but not more than **20**. At least two-thirds of the committee members must be representatives of the pharmaceutical industry, consumers, health economists, practising community pharmacists, clinical pharmacists, primary care physicians and specialist physicians and are elected by their respective professional associations. The remaining members (if any) shall be persons whom the Minister considers to have the necessary qualifications or experience in a field related to the functions of the committee or whose contributions the Minister considers relevant. The Minister must also appoint one of the members of the Committee as chairperson of the Committee, and may appoint another member as vice-chairperson. Members of the PBAC belong to the PBAC until such time as the Minister deems appropriate[88]. The PBAC currently has **21** members, including physicians, health professionals, health economists and health consumer representatives, who provide a voice for patients. The PBAC meets three times a year, usually in March, July and November[87].

As mentioned above, the PBAC also has two subcommittees that provide advice and analysis on economic and drug utilisation issues[87].

Drug Utilisation Subcommittee

The Drug Utilisation Subcommittee (DUSC) is responsible for advising and reporting on applications to the PBAC, providing a document called DUSC advice, which is also provided to the applicant company[89]. The subcommittee estimates the use of the medicine, as well as the financial cost of the medicine. It also collects and analyses data on the actual future use of the medicine in the country, whether it is a new therapy, or the actual use, or whether the medicine is already marketed[90]. The DUSC does not assess medicines when their use and cost to the system has already been reviewed, nor when the entry of the medicine is unlikely to have a substantial impact on costs or routine clinical practice[89]. Examples of the latter are when there is a small, clearly defined patient group, or the market is stable, or when the medicine is indicated for a programme outside the PBS[91]. The DUSC publishes the drug utilisation analysis reports on the Australian Department of Health website, which includes both the methodology used by the subcommittee and the data available to analyse the drug under review[90].

Currently, the drug utilisation subcommittee is composed of **11** members, including primary care physicians, medical specialists, health economists, researchers, pharmacists, industry members and consumer representatives, including the PBAC chair and vice-chair[90].

Economics Subcommittee

The Economics Subcommittee (ESC) reviews and interprets the economic analyses submitted by the applicant and advises the PBAC on their quality, validity and relevance. The ESC is also responsible for advising the PBAC on methodological advances in the collection, analysis and interpretation of clinical and economic data[89]. This subcommittee is composed of health economists, primary care physicians and specialists, pharmacists, researchers, industry members and consumer representatives. As with the DUSC, the chair and vice-chair of the PBAC are members of the ESC[92].

Documentation

When the pharmaceutical laboratory is interested in having its medicinal product included in the PBS, it must submit a submission to the PBAC. According to the PBAC requirements, such a submission should follow the following structure (Figure 14)[83,93]:

- Section 1. **Context.** Describes the proposed medicine, its intended use in the PBS and the rationale for its funding, as well as the therapy(ies) most likely to be substituted by prescribers in actual practice. It is referred to as the main comparator(s).

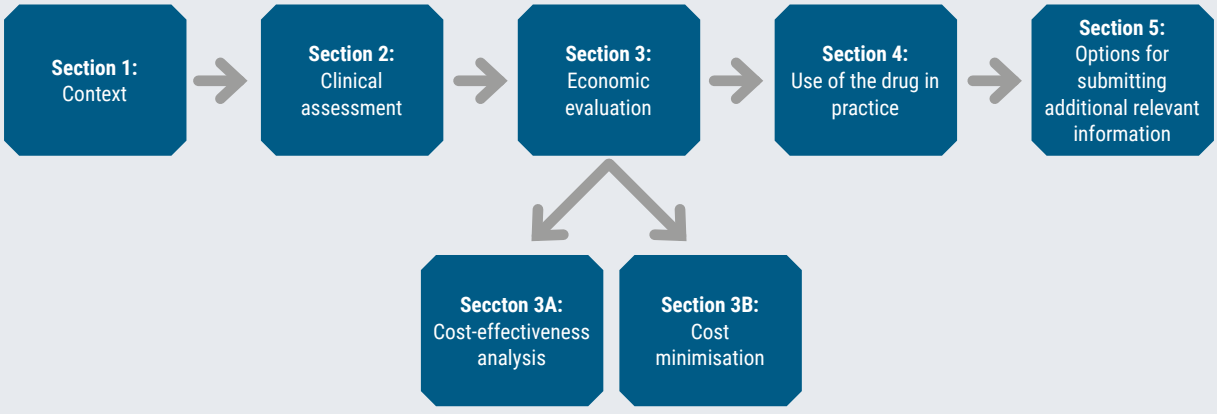
- Section 2. **Clinical assessment.** The best available evidence comparing the clinical performance of the proposed medicinal product with that of the main comparator (preferably from head-to-head randomised trials or, if not available, from other appropriate trials or studies) should be provided. It ends with a therapeutic conclusion indicating whether the proposed medicinal product is superior, non-inferior or inferior to the main comparator, taking into account any differences in the trial population and circumstances of use.

- Section 3. **Economic evaluation.** An economic evaluation of the consequences of substituting the proposed medicinal product for the main comparator in the context of the requested inclusion should be provided.

- Section 4. **Use of the medicine in routine practice.** Includes the intended extent of use of the medicine in the health system, and a financial analysis for the PBS and the Australian government health budget.

- Section 5. **Additional relevant information (optional).** Include any other relevant information to support the presentation.

FIGURE 14. Structure of the presentation for the medicines evaluated in Australia



Source: Australian Government Department of Health (2016)[93]

All submissions should contain an executive summary that clearly sets out the key aspects and issues presented in the main body of the submission. Additional information can be included as an annex or technical document[83].

Clinical assessment

The clinical assessment carried out by the PBAC is based on the information provided by the company concerned, which is structured in **4** components[83]:

- Systematic literature search to identify clinical trials relevant to the assessment, following the Cochrane handbook for conducting systematic reviews.
- Analysis and interpretation of the results of each clinical trial provided, against the designated comparator, which should be the one used in actual clinical practice in Australia.
- Additional analyses to estimate the comparative effect of the medicine when they cannot be derived from the population studied in clinical trials.
- Assessment of the application of the medicine in the Australian setting.

In general, the PBAC states that clinical trial data should come from randomised trials with direct comparisons between the tested medicine and the chosen comparator. Where such direct comparisons cannot be made, the company concerned must provide a justification for the use of indirect comparisons[83].

To perform the assessment, PBAC takes into consideration patient-reported outcome measurement (PROM) tools, which include global or disease-specific measures for which the assessment is presented. In addition, PBAC takes into account multi-attribute utility instruments, where the scoring method of the instrument is anchored on a scale of quality-adjusted life years between **0** (death) and **1** (full health). When using a patient-reported outcome measure other than the Health Utility Index, the EQ5D-3L or -5L, the SF-6D, the Assessment of Quality of Life (AQoL) instruments and the Child Health Utility 9D (CHU9D) index for children and adolescents, the company must provide a rationale or reference supporting the chosen quality of life measurement instrument[83].

Orphan drug assessment

Access to medicines indicated for rare diseases is articulated through the Life Saving Drugs Program (LSDP). This programme is responsible for fully funding drugs indicated for rare and life-threatening diseases, regardless of the process of listing the drugs on the PBS list. The LSDP covers the funding of drugs if[94]:

- They are clinically effective, but not cost-effective enough to be included in the PBS.
- They treat rare (defined as **1** case per **50,000** people or less in the Australian population) and life-threatening diseases.
- The pharmaceutical company (sponsor) requests that its medicine be included in the LSDP list.

The assessment of these medicines is carried out by the LSDP expert committee, which makes a recommendation (or not) for funding to the Minister of Health. Because rapid access of these medicines to patients is essential, this evaluation process is carried out within a maximum of **30** days. Currently, **16** drugs are available through the programme, treating **10** rare diseases. The programme reviews the performance shown by the drugs two years after their inclusion on the list[94]. Currently, **9** drugs are under review[95].

Economic evaluation

The PBAC determines that the economic evaluation can be a cost-effectiveness analysis (CEA), a cost-utility analysis (CUA) or a cost minimisation. The Committee explicitly states that a CEA/CUA should be performed when the clinical assessment has concluded that the assessed medicine is therapeutically superior to the main comparator, but may incur additional costs to the healthcare system, or is therapeutically inferior to the main comparator, but is likely to incur lower costs to the healthcare system. On the other hand, the PBAC states that a cost-minimisation approach should be taken when there is a therapeutic non-inferiority claim, the safety profile is equal or greater, and the use of the medicine is expected to result in similar or lower costs to the healthcare system. The use of other types of economic evaluations, such as cost-benefit analysis, is permitted, but only in support of the types of evaluations mentioned above[83].

The PBAC indicates that incremental health outcomes, in the form of quality-adjusted life years (QALYs) in the case of a CUA, and incremental health costs should be identified. In general, the PBAC prefers to present the economic evaluation in the form of a CUA rather than a CEA when data on QALYs gained are available, there is an improvement in quality but not quantity of life gained, or clinical trials report results using a multi-attribute utility measurement tool. When submitting a CEA, justification should be provided as to why the health outcomes of the medicine were not expressed as QALYs in order to present the economic evaluation as a CUA[83].

All relevant health states or clinical events throughout the course of the disease should be recorded for the economic evaluation, consistent with the information provided in the clinical part. The exclusion of any potentially relevant conditions or events identified in the literature should be justified[83].

The PBAC's preferred perspective is the health system perspective, which includes health and health-related resource use (costs and cost trade-offs), and health-related outcomes. A broader societal perspective can be presented and quantitatively incorporate considerations beyond the patient and the health system, but in a complementary way. The discount rate should be 5% per year for all costs or health outcomes occurring or extending beyond one year from the base year. The PBAC does not stipulate any preferred time horizon. However, where evidence is provided that the treatment affects mortality or quality of life in the long term, the lifetime of the patient should be used as the time horizon[83].

A univariate and multivariate deterministic sensitivity analysis must also be presented. The deterministic analysis shall be applied to all uncertain input parameters, using commonly adopted statistical standards to represent the uncertainty around their true value. Multivariate analysis should be used to test the combined effects of uncertainty on the true values of input parameters for which the univariate analysis was sensitive. In addition, the PBAC indicates that a probabilistic analysis can be performed. Sensitivity analyses should include discount rates of **0%** and **3.5%** per annum for outcomes and costs[83].

Involvement of patients and scientific societies

Currently, consumers, patients and any interested organisation can provide their views on medicines via one web interface. This participation programme is currently under review, and improvements are being developed to gather consumer views in a way that will promote more meaningful and useful contributions to the PBAC's assessment of medicines. The PBAC is committed to listen and understand consumer perspectives and to integrate them into its consideration of medicines[96].

These comments are reviewed and compiled by the PBAC, which produces a summary that is sent to the assessment committee and the applicant company. Input from these stakeholders is noted in the public assessment document which is available on the PBAC website. In addition, the consumer representative is the patient representative on the PBAC assessment committee and is able to influence the PBAC's decisions with his or her vote[96].

P&R decision elements

In general, the pricing of a new medicine is based on several principles, including the criteria defined by the PBAC, the internal reference prices of other therapies, and the financial impact of the evaluated medicine in the country. In addition, automatic price reductions of **5%**, **10%** and **15%** are applied when medicines have been on the PBS list for **5**, **10** and **15** years, respectively[97].

Criteria influencing the decision

PBAC decision-making is influenced by five quantitative factors (**Table 7**)[83]:

TABLE 7. Factors influencing the PBAC decision in Australia

FACTORS	DEFINITION
Comparative health benefit	It is assessed in terms of both the magnitude of the effect and the clinical significance of the effect, compared to the comparator. It is presented in terms of both efficacy and safety, as well as in the denominator of incremental cost-effectiveness or incremental cost-utility.
Comparative cost-effectiveness	It is presented in terms of incremental cost-effectiveness ratio (including incremental cost-utility ratio) or as a cost minimisation approach. It includes the full spectrum of health resources. The PBAC has not officially recognised any explicit cost-utility threshold for drug pricing. However, some research suggests that PBAC decisions are determined by an implicit cost-effectiveness threshold of AUD 50,000 (approximately €32,000)[98,99].
Affordability for the patient in the absence of PBS funding	It is presented as cost per patient and duration of treatment for acute therapy, or as cost per patient per year for chronic or continuous therapy.
Intended use in practice and financial implications for the PBS	Presented as the expected net annual cost for the PBS.
Intended use in practice and financial impact for the Australian government health budget	Presented as the estimated annual net cost per year.

Source: prepared by the authors based on Australian Government. Department of Health (2016)[83]

Other less quantifiable factors that also influence the PBAC decision are[83]:

- General confidence in the evidence and assumptions on which the presentation is based.
- Implicit ethical and equity assumptions, such as the age, socio-economic and geographical situation of the patient, which may vary from one proposal to another and need to be reassessed on a case-by-case basis.
- The existence of effective therapeutic alternatives. This helps to determine the clinical need for the proposed medicine.
- The severity of the medical condition being treated. Emphasis is placed on the nature and extent of the disease under current therapeutic management.

- The ability to target therapy precisely and effectively to the patients most likely to benefit from it.
- Public health issues, e.g. development of resistance to antimicrobial agents.
- Any other relevant factor that may affect the suitability of the medicinal product for inclusion in the PBS.

If the medicine is considered to be equivalent to the alternatives, without being a significant advance, the Australian government will fund it on the basis of the lower price of the comparator already funded in the country[97].

Budgetary impact

The budget impact submitted by the company to the PBAC can be done through two non-exclusive approaches: epidemiological approach and market share approach. The epidemiological approach estimates the patients eligible to consume the assessed medicine based on the information on the use of the medicine provided by the company concerned by the assessment. The market share approach is developed on the basis of market information for the indication in Australia and the substitution effect of other therapies that may be generated by the entry of the new drug[83]. The PBAC determines the use of a **6**-year time horizon, while indicating that the discount rate for both health outcomes and costs should be **0%**, and without considering inflation[83].

Financial agreements and their monitoring

In Australia, drug financial agreements between the company concerned and the government are organised through the signing of "deeds of contract", which are agreements designed to favour access to medicines, while taking into account the cost-effectiveness or cost-efficiency of the medicines. The Australian government stipulates two general types of agreements: special pricing agreements (SPAs) and risk-sharing agreements (RSAs)[100].

- SPAs are special and confidential pricing arrangements with a sponsor for the supply of a medicine that formalise a "published" versus "actual" price. The difference between the published price in the PBS and the price actually paid by the government is managed through a rebate agreement. These are implemented so that the Australian system can access medicines at a lower price without affecting the price of the product in other markets[100].
- RSAs are agreements reached between the government and companies that seek to minimise the risks associated with the inclusion of some therapies in the PBS, such as uncertainty in the results achieved in the real Australian population or the increase in patient volume[100].

An analysis of drugs approved by the PBAC during the period 2010-2018 shows that **14%** of positive PBAC recommendations contained an RSA (**Table 8**)[99].

TABLE 8. Relationship between positive PBAC recommendations and RSAs in Australia (2010-2018)

YEAR OF THE RECOMMENDATION	POSITIVE RECOMMENDATION	RSAs	SHARE OF RSA IN THE TOTAL (%)
2010	101	3	3
2011	100	5	5
2012	109	9	8
2013	127	26	15
2014	128	34	26
2015	174	23	12
2016	148	30	20
2017	134	12	8
2018*	55	10	22
2010 – 2018	1076	152	14

Note: * until March **RSAs:** Risk Sharing Agreements
Source: Lybrand and Wonder (2020)[99]

In Australia, the monitoring of medicines is not carried out on the basis of a single database, but rather the PBAC monitors the use of medicines taking into account data from scientific societies, pharmacies or ad hoc tools. For example, in the case of CAR-T therapies, the risk-sharing agreement signed between the company concerned and the Australian government indicated that in order to monitor the costs and health outcomes of the therapy, all patients receiving the drug should be included in the Australasian Bone Marrow Transplant Recipient Registry[101].

Another similar case is the approval of ipilimumab by the PBAC for metastatic melanoma in 2012. The drug approval document requested that, in order to reduce uncertainty about the drug's performance in Australia, a mechanism to verify the expected benefits of the drug on overall survival was required to be implemented, based on data from actual clinical practice in Australia. To this end, a website was made available to prescribing physicians to register all patients using the therapy, and online training was provided to familiarise them with the system[102].

In turn, the government monitors drug use based on data from hospital and community pharmacies to understand the clinical effectiveness and costs of medicines after their inclusion in the PBS[103].

...TO BE HIGHLIGHTED IN AUSTRALIA

- ✔ *One of the pioneer countries in economic evaluation*
- ✔ *Possibility of incorporating the social perspective in evaluations*
- ✔ *Clear and explicit criteria for which type of economic evaluation to apply: CUA/CEA if the drug is therapeutically superior or cost minimisation if it is not*
- ✔ *A system that allows the assessment of medicinal products to commence without a final marketing approval*
- ✔ *Differentiated assessment process to speed up access to ODs*
- ✔ *Incorporation of PROMs into the evaluation process*
- ✔ *Involvement of consumers who bring the patient's view into the process*
- ✔ *Public availability of the detailed assessment reports of the medicinal product and the reasons for its inclusion in the PBS*
- ✔ *Consideration of affordability for the patient when setting the price of the medicine*

Austria

Austria has a health care system similar to the German system, in which the entire employed population and their families are covered by various types of compulsory public health insurance, in addition to private insurance[104,105]. Since 2020, public insurance has been grouped under the umbrella organisation of social security institutions (*Dachverband der Sozialversicherung*)[106].

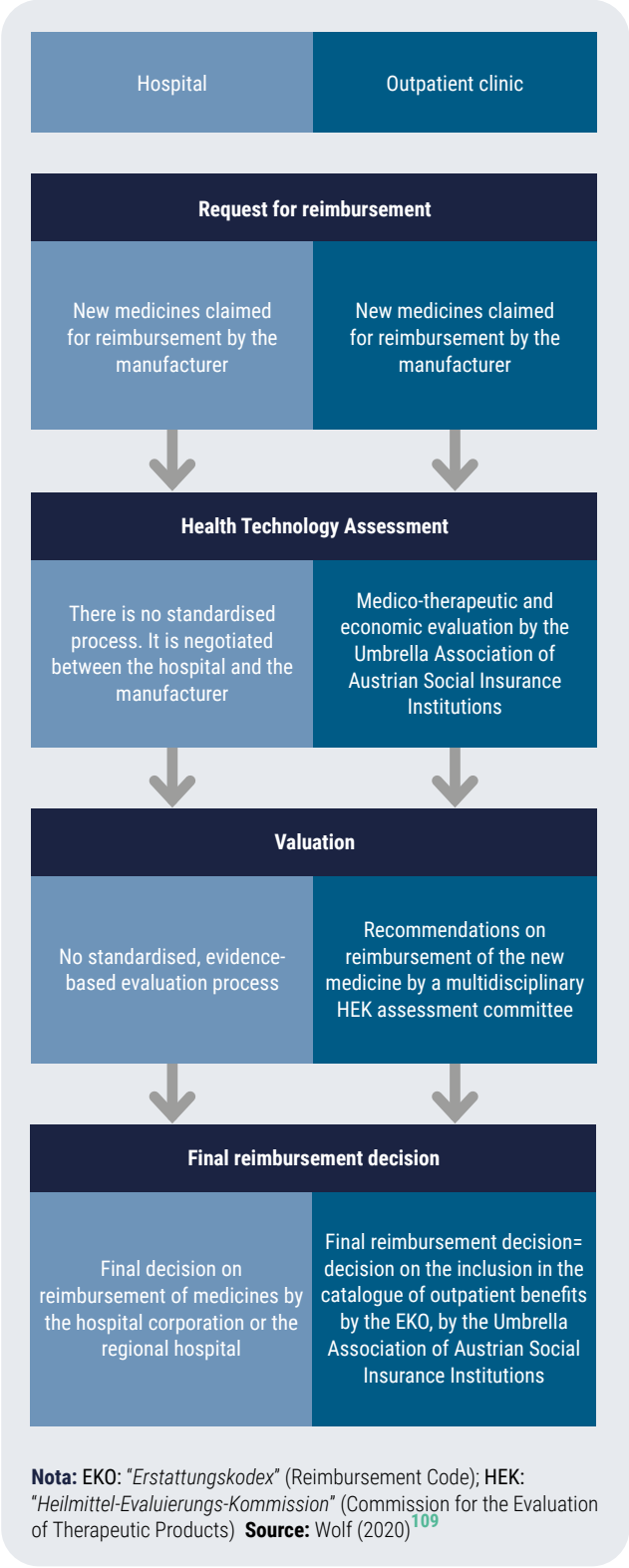
In the case of Austria, if a company wants to apply for marketing authorisation in Austria on a decentralised basis, it must apply to the Federal Office for Health Safety (*Bundesamt für Sicherheit im Gesundheitswesen* or BASG), which is a federal authority under the supervision of the Federal Ministry of Social Affairs, Health and Care of the Austrian government. The BASG conducts a review based on the efficacy, safety and quality of the medicine[107,108].

Actors and process

The evaluation and reimbursement process for medicines in Austria is divided into two parts, depending on whether the medicine is administered in the outpatient or inpatient setting. The price regulation by the social health insurance applies to medicines that apply for inclusion in the list of medicines administered to outpatients and to medicines that are not included in the list, but whose sales during the previous **12** months at the expense of the social health insurance exceed €**750,000**. If a medicine receives a positive reimbursement assessment, it falls under the Reimbursement Code (*Erstattungskodex* or EKO)[106,109].

In the case of hospital medicines, pricing is free, with the hospital or hospital groups individually negotiating the price of medicines with the pharmaceutical company, once the marketing authorisation has been obtained in the country (Figure 15)[106,109].

FIGURE 15. Evaluation and reimbursement process in Austria

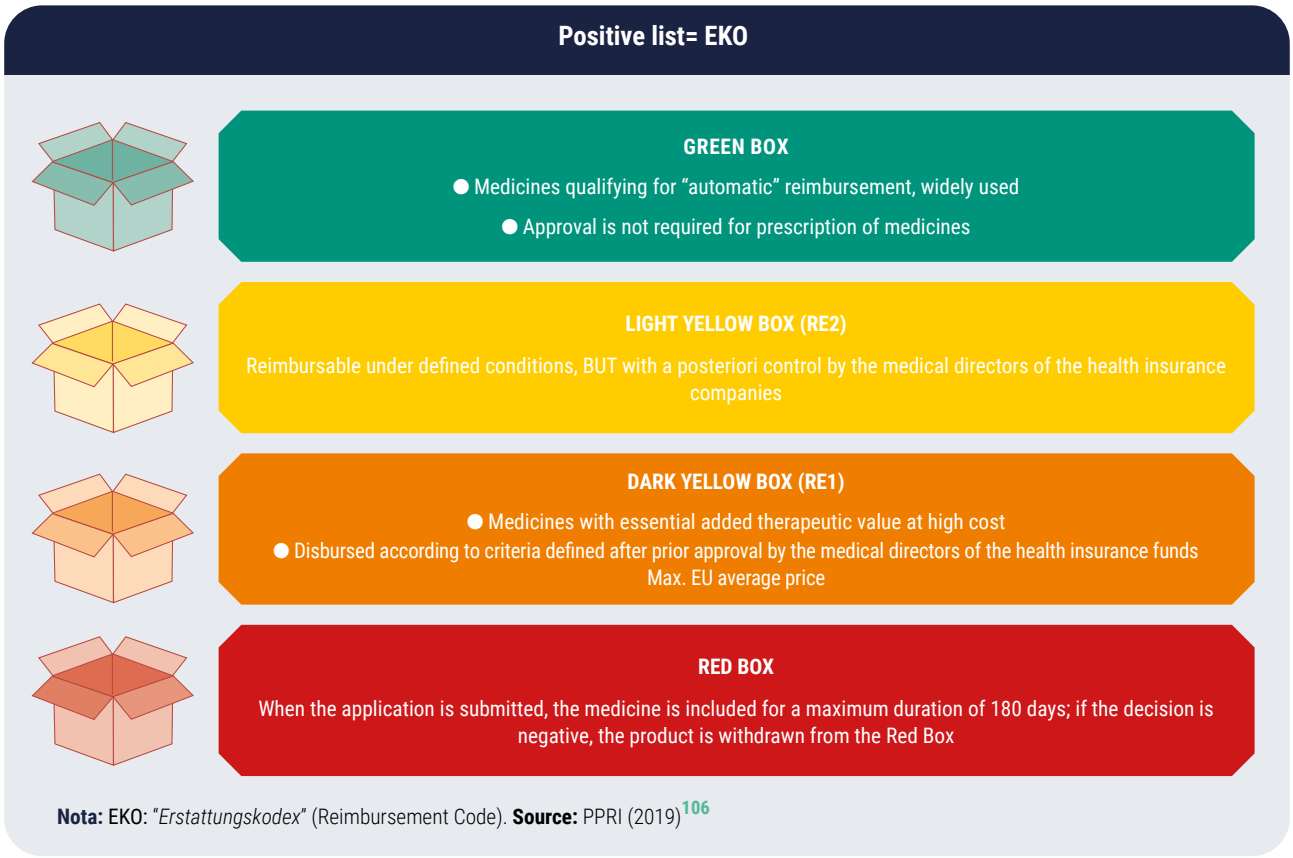


Nota: EKO: "*Erstattungskodex*" (Reimbursement Code); HEK: "*Heilmittel-Evaluierungs-Kommission*" (Commission for the Evaluation of Therapeutic Products) **Source:** Wolf (2020)[109]

All medicines included in the EKO are eligible for general reimbursement, but the prescribing rules differ. The EKO has three main categories: the "green box", the "yellow box" (with two subgroups) and the "red box" (Figure 16)[106,110,111]:

- The "green box" includes medicines that are eligible for automatic reimbursement; these can be prescribed by any contracted doctor. Some of the medicines in this box are not reimbursed for all indications, but only for the treatment of certain diseases.
- The "yellow box" includes medicines that have a significant added therapeutic benefit, but have not been included in the green box for medical or economic reasons. Reimbursement is only granted if defined criteria are met (e.g. a specific disease or age group). For medicines in the subgroup of the light yellow box, a posteriori control of the records kept by the prescribing physician may be applied.
- The "red box" is a temporary category (maximum 180 days) for medicines for which an application for inclusion in the EKO has been submitted for the first time. During this time, costs are only covered if the health insurance company has obtained the medical approval of the head of the social insurance medical review service. In such cases, the price of the medicine must not exceed the EU average price. And as long as an average EU price has not been determined, the price reported by the distributing company will be used. If the price commission determines that the Austrian provisional reimbursement price is higher than the determined EU average price, the distribution company must refund the difference to the social insurance institutions within six months of the request[112].

FIGURE 16. Classification of medicines within the reimbursement code (EKO) in Austria



Nota: EKO: "*Erstattungskodex*" (Reimbursement Code). **Source:** PPRI (2019)[106]

During the transitional period until the reimbursement comes into effect, the medical authorisation by the head of the medical review department for medicines assigned to both the red and yellow boxes will be replaced by a subsequent documentation check.

During the transitional period, any prescription of a medicine at the expense of the social insurances may only be made after the preparation of special documentation on the selection and prescription and under the authorisation of the head of the medical service. The Umbrella Organisation determines the admissible forms of documentation and transmits them to the Austrian Medical Association. The compulsory information to be documented when prescribing a medicine that is in the red box is divided into[112]:

1. The reason why no drug in the green box of the Reimbursement Code is therapeutically equivalent in that indication.
2. Justification as to why no medicine in the yellow box of the Reimbursement Code is therapeutically equivalent or if there is one in both the green and yellow boxes that is therapeutically equivalent, the reason for prescribing one in the red box.
3. Prescription data.
4. The complete diagnosis.
5. Medical history and pre-treatment data, as well as the results of medical findings, to the extent that they are relevant.

Pharmaceutical Evaluation Board

In Austria, the evaluation process is carried out by the Pharmaceutical Evaluation Board (*Heilmittel-Evaluierungs-Kommission*, hereinafter referred to as HEK)[113], which is attached to the Association of Statutory Social Insurance[114]. This commission is independent and is the main advisory body for the reimbursement decision[111,113].

The HEK consists of **21** voting members and is composed as follows[112]:

- Three independent representatives of science from relevant disciplines (pharmacologists and physicians from university institutes). The chairmanship of the commission rotates among these three members.
- Ten social security representatives.
- Two representatives of the Austrian Chamber of Commerce.
- Two representatives of the Federal Chamber of Labour.
- Two representatives of the Austrian Medical Association.
- A representative of the Austrian Chamber of Pharmacists.
- One representative of the federal provinces.

All members, except the representative of the federal provinces, have an alternate. In the event of a tied vote, the chairperson has a casting vote[113]. The Board meets at least twice a year with the aim of putting decisions into effect on 1 January and 1 July of each year[111].

Price Commission

The Umbrella Organisation of Social Security Institutions is responsible for setting the price of outpatient medicines. For this purpose, it has a Price Commission (*Preiskommission*), which is responsible for determining the average EU prices of the medicinal product to be assessed, on which the decision of the Umbrella Organisation will be based. This commission is composed of eight voting members[115]:

- The Federal Minister of Labour, Health and Consumer Protection, who is acting as chairman.
- A representative of the Ministry of Labour, Health and Consumer Protection.
- A representative of the Federal Ministry of Digitalisation and Economic Placement.
- A representative of the Federal Ministry of Finance.
- A representative of the Federal Ministry of Sustainability and Tourism.
- Three representatives from each of the following chambers: the Austrian Federal Economic Chamber, the Austrian Federal Chamber of Agriculture and the Federal Chamber of Labour.

If it considers it necessary, the Commission may request the opinion of experts in the medicinal product to be assessed[115].

Documentation

For the evaluation of a medicinal product, the pharmaceutical company must submit to the HEK a **4**-part structured document containing pharmacological, medical-therapeutic and health-economicinformation[113]:

- **General data:** name, marketing authorisation, indication and price requested, among others
- **Data for pharmacological assessment:** pharmacodynamics of therapy, dosage information, justification of the chosen dose, etc.
- **Data for the clinical-therapeutic assessment:** among others, the company must provide:
  - Information on the benefit to the patient compared to the available alternatives
  - Prevalence and incidence of the disease in the country
  - Need for diagnostic tests for drug delivery
  - Data from pivotal trials, justification for the choice of primary endpoint and secondary endpoints used, as well as type of randomisation and blinding used in clinical trials
- **Data for economic evaluation:** in this section the company must provide information on:
  - Sales expectations for the first three years in Austria
  - Sales in other EU countries
  - Comparison with prices of alternative therapies in the country
  - Comparison with drug prices in other EU countries
  - An economic evaluation (or, alternatively, an explanation of why it was not possible to do so) which should include the cost perspective used, quantification of the benefit to the patient, allocation of costs (separated into direct and indirect), discount rate and sensitivity analysis.

Clinical assessment

In Austria, clinical assessment is divided into two aspects: pharmacological assessment and clinical-therapeutic assessment.

Pharmacological assessment

The pharmacological assessment has two objectives, on the one hand, to classify and to pharmacologically assess the medicinal product in the context of the available therapeutic alternatives and, on the other hand, to determine the therapeutic alternatives and their dosage as a basis for the clinical-therapeutic assessment[112].

This assessment measures the degree of innovation of the new drug on an **8**-point scale, as follows (**Table 9**)[112]:

TABLE 9. Definition of the degree of innovation of new medicines in Austria

DEGREE OF INNOVATION	CRITERIA
8 (higher)	The medicine provides a first-time treatment for a particular disease.
7	The medicine provides a pharmacological treatment for a disease that was previously unmanageable with medicines.
6	The medicine has a new compound with a new active substance for the treatment of a disease already treated by its comparators.
5	The medicine introduces a new active substance that does not exist among its comparators.
4	The drug has a new dosage form compared to its comparators.
3	The medicine presents a new combination of active ingredients already existing among its comparators.
2	The medicine has the same active substance and the same or virtually the same dosage form as its comparators, but a new bioavailability.
1 (lowest)	The drug contains the same active ingredient, bioavailability and the same or virtually the same dosage form as its comparators.

Source: Main Association of Austrian Social Insurance Institutions (2018)[112]

Clinical-therapeutic assessment

The clinical-therapeutic assessment carried out by HEK has three objectives[113]:

- Define and quantify the patient groups eligible for treatment with the new medicine.
- Define and quantify the therapeutic benefit compared to available alternatives to the medicine.
- Review and determine the level of clinical evidence contained in the data submitted by the applicant.

The validity of evidence is measured according to the following classification:

a) Prospective, randomised, controlled clinical studies with blinded outcome assessment in a representative population, or meta-analyses of such studies.

b) Systematic reviews (e.g. Cochrane review) with meta-analyses of numerous studies with large numbers of patients, evidence of clearly defined endpoints yielding unambiguous statements for the population for which recommendations are made.

c) Randomised controlled trials (RCTs), or smaller studies or inconsistent results or with the study population not matching the recommended target population.

d) Non-randomised or uncontrolled studies: observational studies.

e) Consensus judgement by a committee of specialists, based on clinical experience (in the case of insufficient clinical literature).

f) Statements by individual experts.

Once the assessment process has been completed, HEK classifies the assessed medicine into 6 levels, ordered from least to most therapeutic benefit (**Table 10**)[113]:

TABLE 10. Classification of therapeutic benefit by HEK in Austria

TIPO DE BENEFICIO	DEFINICIÓN
No additional therapeutic benefit	The assessed medicine does not present any additional therapeutic benefit to patients compared to the alternatives because it is a successor product with the same active ingredients.
Additional therapeutic option	The assessed therapy is an additional therapeutic option with the same or similar therapeutic benefit for patients compared to other therapeutic alternatives.
Additional therapeutic benefit for a subgroup of patients	The assessed medicine has an additional therapeutic benefit for a subgroup of patients who are eligible for treatment with the new medicine compared to therapeutic alternatives.
Additional therapeutic benefit for most patients	The assessed medicine has an additional therapeutic benefit for the majority of patients who are eligible for treatment with the new medicine, compared to therapeutic alternatives.
Significant additional therapeutic benefit	The assessed therapy has a significant additional therapeutic benefit for a subgroup of patients who are eligible for treatment with the new medicine, compared to therapeutic alternatives.
Significant additional therapeutic benefit for most patients	The assessed medicine has a significant additional therapeutic benefit for the majority of patients who are eligible for treatment with the new medicine, compared to therapeutic alternatives.

Source: prepared by the authors based on Main Association of Austrian Social Insurance Institutions (2015)[113]

Economic evaluation

The economic evaluation is performed to assess the new medicine in the context of the available therapeutic alternatives, and is based on the outcome of the clinical-therapeutic assessment performed previously. For inclusion in the green zone of the Reimbursement Code, economic efficiency is assessed as follows[112]:

1. In cases where no additional therapeutic benefit is found, economic efficiency is assumed if a price reduction is made following the guidelines for generics or biosimilars leading to reductions from **30%** to **48%**.

2. In cases where the assessed medicine is an additional therapeutic option with the same or similar therapeutic benefit, economic efficiency is assumed if the treatment costs are sufficiently lower than the treatment costs of the cheapest comparator in the green area.

3. In cases where the medicine has an additional therapeutic benefit for a subgroup of patients, economic efficiency is assumed if the costs of treatment with the evaluated medicine are slightly higher than the costs of treatment with the comparator medicine in the green area.

4. In cases where the medicine has an additional therapeutic benefit for the majority of patients, economic efficiency is assumed if the costs of treatment with the new medicine are reasonably higher than the costs of treatment with the cheapest comparator medicine in the green zone.

5. In cases where the assessed medicine has a significant additional therapeutic benefit for a subgroup of patients or has a significant additional therapeutic benefit for the majority of patients, it is assumed to be efficient if its dispensation without medical approval by the head of service and control of the social security institutions is reasonable and justifiable from an economic-health point of view, in particular with regard to the expected cost/benefit ratio for the defined group of patients.

If there is no comparable medicine in the yellow section of the Reimbursement Code, inclusion in this section will be based on whether the expected benefit-cost ratio for a defined group of patients is understandable and justifiable in terms of health economics[112].

Involvement of patients and scientific societies

Neither patients nor scientific societies are involved in the evaluation and reimbursement process of medicines in Austria.

P&R decision elements

External price referencing applies to reimbursable medicines with an application for inclusion in the reimbursement code (*Erstattungskodex*, EKO), which is the positive list for outpatients. From 2019, the reference countries are all other EU Member States. The price of reimbursed medicines in Austria must not exceed the EU average[106].

The Price Commission (*Preiskommission*) is responsible for calculating the EU average price on the basis of price data submitted by the marketing authorisation holder. The price is determined within six months of receipt of the price application. Price assessments are mandatory after **24** and **48** months[106].

For "follow-on medicines" (generics and biosimilars) included in the EKO[106]:

- The first generic is priced at least **50%** lower than the original off-patent medicine.
- The second and all subsequent generics must have a price difference compared to the previously included generics (**18%** and **15%** respectively). The price of the original medicine has to be reduced by at least **30%** in the three months following the inclusion of the first generic in the EKO.
- In the case of a third follow-on, the marketing authorisation holders of the original medicine and the first and second generic have to reduce their prices to the price of the third generic.
- For biosimilars, the following percentages apply: the first biosimilar at least **38%** below the reference medicine; the second and third biosimilars at least a price difference over the first of **15%** and **10%**, respectively.

For all other medicines (including those for hospital use only), pricing is in principle free. However, pharmaceutical companies have to notify the Ministry of Labour, Health and Consumer Protection of the ex-factory price of new medicines and price changes. If a notified price is considered too high in the context of the Austrian economy, the Ministry can officially initiate a pricing process. If such a process is not initiated within six weeks, the notified price will automatically be granted[106].

In the case of hospitals, in most cases, procurement is done directly through negotiations between the marketing authorisation holder and the hospital (or group of hospitals), and a managed entry agreement may be concluded, although these are private[106]. In recent years, Austrian hospitals have moved in the direction of purchasing through tenders, which, although not the majority procurement process, has been increasing in recent years[106].

In addition, for medicines which are not included in the EKO but which exceed a sales value of EUR **750,000** (at ex-factory price) at the expense of the Austrian social health insurance during the last twelve months, prices are fixed ex-post on the basis of the EKO. If the EU average price determined by the Price Committee is lower than

the price set by the marketing authorisation holder, the company has to pay back the difference from the time when the turnover threshold was first exceeded[106].

Financial agreements and their monitoring

In recent years, managed entry agreements have been concluded for high-priced new medicines in both outpatient and inpatient settings. Most of them are based on financial agreements (e.g. price-volume agreements), but some experts note that outcome-based agreements are on the rise. The prices and content of the agreements are confidential[106].

"In actual practice, the final price of the medicine is an unknown quantity, as pharmaceutical companies and hospitals enter into different types of agreements such as managed entry agreements or price reductions."

In addition, on the basis of the provisions of a "pharmaceutical framework contract" ("*Rahmen-Pharmavertrag*"), signed between the statutory insurers and the pharmaceutical companies, the latter committed to pay a subsequent reimbursement to the Austrian health insurance funds. The last framework contract ran from 2016 to 2018 and has not been renewed[106].

Since 1997, Austria has been a pioneer in hospital data collection thanks to the performance-oriented hospital financing framework (LFK). Hospitals are obliged to report on the diagnosis and services provided by the hospital as defined by a Minimum Core Data Set (CMDB)[116]. These data must be created before any hospital stay and collect information regarding the patient, his or her diagnosis, use of hospital areas such as ICU, geriatrics and the cost of the hospital service[15]. Among others, the objectives of the LFK are the collection of a standardised and easy-to-manage data set, which allows for healthcare planning, resource optimisation and long-term cost containment[116].

...TO BE HIGHLIGHTED IN AUSTRIA

- ✔ *"Box" system for the reimbursement of medicinal products*
- ✔ *Rapid entry of therapies awaiting funding (red box)*
- ✔ *Using databases to contain hospital and pharmaceutical health expenditure*

Canada

Canada has a decentralised health care system, where the final decision on price and funding depends on a negotiation between the pharmaceutical company and the federal, provincial and territorial governments, within so-called "drug plans". These plans determine which drugs are prescribed and the access conditions for patients[117,118].

Marketing approval for medicines is granted by the Health Products and Food Branch's (HPFB) dependent on Health Canada, the Canadian government department responsible for health. The HPFB assesses and monitors the safety, efficacy and quality of medicines[119]. The work of this agency is equivalent to that carried out by other approval agencies such as the FDA or the EMA. It is worth noting that Canada is one of the pioneer countries in conducting economic evaluations, including them since 1994[120].

Actors and process

Once this initial marketing approval process has been completed, pharmaceutical companies submit an application for assessment to the Canadian assessment agencies, either the National Institute of Excellence in Health and Social Services (INESSS) or the Canadian Agency for Drugs and Technologies in Health (CADTH). INESSS advises Quebec decision-makers and CADTH supports public health services in the rest of Canada[121].

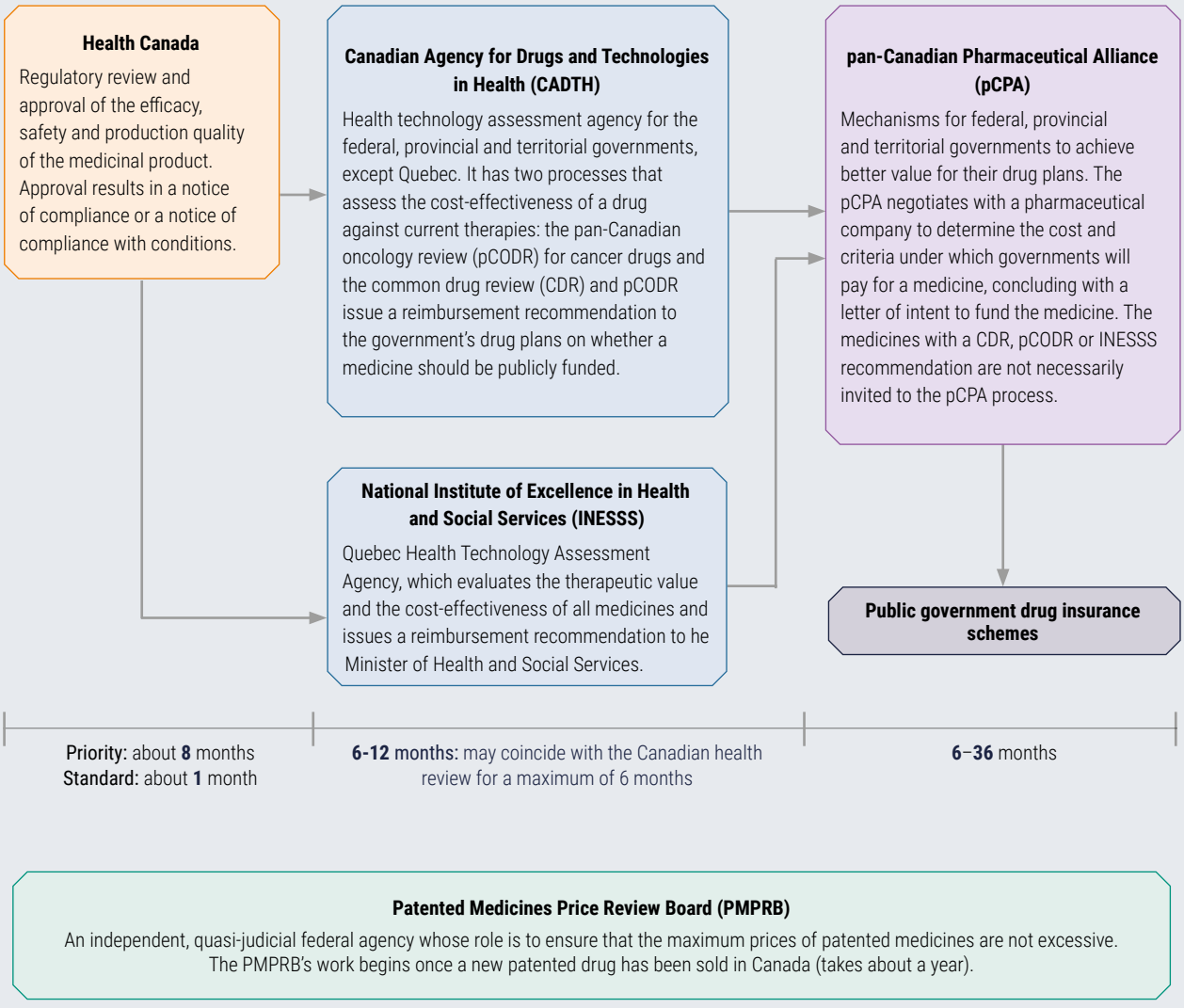
This assessment process can take **6-12** months and may overlap in time with the HPFB authorisation period (**Figure 17**)[117]. At the end, both institutions make a reimbursement recommendation to government drug schemes. Once the assessment is completed, manufacturing companies wishing to obtain public reimbursement for their medicines must apply for admission to the negotiation process established by each government, whether federal, provincial or territorial. Provincial and territorial governments, with the exception of Quebec, organised a process called the pan-Canadian Pharmaceutical Alliance (pCPA) to collectively negotiate prices for new drugs for their public funding plans. For private insurance reimbursement, pharmaceutical companies negotiate directly with insurance companies[117].

In the pricing decision, the agency that ensures maximum drug prices is called the Patented Medicine Prices Review Board (PMPRB), whose work begins once a new patented medicine has been marketed in Canada. Because the sale of a new drug may occur shortly after marketing approval, or after the drug obtains public or private insurance coverage, the start of this agency's assessment is variable[117].

Canadian Agency for Drugs and Technologies in Health (CADTH)

CADTH is an independent, non-profit organisation that provides health care decision-makers with objective evidence to help them make informed decisions about the optimal use of medicines in the Canadian health care system. CADTH is responsible for conducting assessments of the clinical effectiveness, cost-effectiveness, ethical, legal and social implications of new therapies[122]. For 2020, CADTH had a budget of approximately **26** million euros[123].

FIGURE 17. Assessment and reimbursement process and time required in Canada

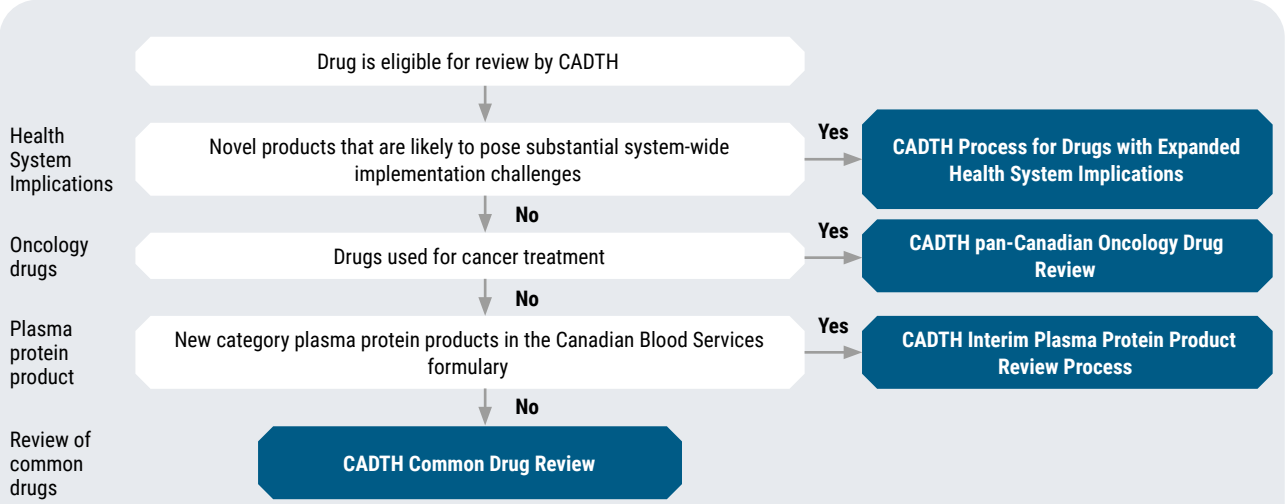


Source: Rawson (2018)[117]

Before being published, CADTH assessment reports are reviewed by external clinical, economic and methodological experts, as appropriate, and by internal staff. The results are summarised in reports that translate scientific and economic data into decision-relevant information. Once finalised, CADTH reports are published on the CADTH website, where they are freely available to anyone interested[122].

When assesing drugs, the CADTH uses an algorithm that divides the assessment into four processes, depending on the nature of the drug to be assessed, whether it is oncology, plasma products, innovative drugs that may pose a challenge in their implementation in the Canadian healthcare system, or the common procedure for other therapies that are not included in the above (**Figure 18**)[124]. Upon receipt of the information from the sponsor, the CADTH determines the type of assessment for each medicinal product to be assessed.

FIGURE 18. CADTH algorithm for the assessment process in Canada



Note: CADTH: Canadian Agency for Drugs and Technologies in Health
Source: CADTH (2021)[124]

In addition to the expert committee members, the following persons may attend a committee meeting as observers, but without voting rights[124]:

- Health ministry officials nominated by participating jurisdictions: can provide input on the practical considerations outlined in the decision-making framework.
- Representatives from the pCPA: may ask clarifying questions when necessary.
- CADTH staff: they can actively participate in the presentation of information.
- External experts (including clinical specialists): can provide information on the medicine, answer questions from the committee, and help establish and refine reimbursement conditions.

In general, the Common Drug Review (CDR), the CADTH pan-Canadian Oncology Drug Review (pCODR) and the Plasma Protein Products Interim Review (PPP) assessment procedures a **13**-step process[124]:

1) **Pre-submission meetings:** A pre-submission meeting is offered to facilitate the efficient preparation and submission of an application to the CADTH. The objective is to help the sponsor improve the quality, relevance and clarity of the information submitted for review.

2) **Prior notification procedure:** Developers must notify CADTH of all applications at least 30 working days in advance.

3) **Application Submission:** Sponsors must submit the application in accordance with the content, format and organisation stipulated in the CADTH reimbursement assessment procedures. All applications submitted by industry sponsors are subject to an application fee.

4) **Review of claims:** CADTH reviews claims in the order in which they are received in accordance with the requirements and checklists described in the reimbursement review procedures. The review period for an application is **10** working days.

5) **Patient input:** Patients contribute their experiences and perspectives of living with a disease for which a medicine under review is indicated, their experiences with currently available treatments, and their expectations of the medicine under review.

6) **Physician group input:** CADTH uses the input of the physician group in all phases of the review, including development of the review protocol, assessment of the evidence and interpretation of the results.

7) **Inputs from drug programmes:** Drug programmes provide information on each medicine that is reviewed through CADTH's reimbursement assessment processes, identifying issues that may affect its ability to implement a recommendation.

8) **Start of review:** All applications are assigned to the work programme on a first-come, first-served basis, based on the date they are accepted for review. All evaluations start within **1** to**10** working days of acceptance for review.

9) **CADTH review reports:** Depending on the type of assessment, CADTH prepares a clinical report, a pharmaco-economic report and an ethics report. The pharmaceutical company has the opportunity to review and comment on the draft report before it is finalised and distributed to the expert committee.

10) **Expert committees:** The following expert committees on medicines of the CADTH provide recommendations and advice:

- The Canadian Drug Expert Committee (CDEC) is used for medicines that are reviewed through the CADTH Common Drug Review process. It consists of **15** members with expertise in medicines assessment and utilisation, and public members involved in health-related ethics and care of the patient as a health consumer[125].
- The Canadian Committee of Experts on Plasma Protein Products (CPEC) is a subcommittee of the CDEC that is used for products that are reviewed through the Interim Review Process for Plasma Protein Products.
- The pan-Canadian Expert Review Committee for Oncology Drugs (pERC) is used for drugs that are reviewed through the CADTH pCODR process. It consists of up to **17** voting members from oncology, pharmacy and health economics, and includes three patient representatives, with a voice and vote[126].

The CADTH invites these expert groups to review the evidence and organises a meeting. Committee members are responsible for assessing the available information for the medicines being reviewed at the meeting. The information used during the committee for each medicine under review includes, but is not limited to:

- Contributions from the patient group (a summary and individual presentations)
- Contributions from the group of physicians (a summary and individual presentations)
- Drug programme contributions
- CADTH clinical and economic evaluation reports
- Sponsor's comments on the draft CADTH reports and the review team's responses

- Reimbursement status of the drug under review and its relevant comparators
- A summary of all CADTH recommendations issued for the same or similar indication as the medicinal product under review.

11) **Draft recommendation:** Draft recommendations are circulated to the sponsor and drug programmes 8-10 working days after the expert committee meeting.

12) **Final recommendation:** The recommendation is submitted to a vote. All members must vote unless there is a declared conflict of interest that prevents a member from voting. The reasons for the recommendation are drafted and discussed before members vote on a recommendation. Voting is anonymous and results are determined on the basis of a simple majority. The committee chairperson only votes in the event of a tie. When a final recommendation is issued, CADTH publishes a copy on its website. Before publishing this document, sponsors are responsible for identifying and requesting the omission of any confidential information included in the recommendation.

13) **Implementation phase:** Once the final recommendation is issued, CADTH provides drug plans with implementation support. This may include, among other things, improving reimbursement conditions, advising on drug implementation issues in the Canadian health care system, and establishing an interim funding algorithm for certain oncology indications. CADTH recommendations are not binding on drug plans.

As a final recommendation, expert committees may recommend that a medicine be reimbursed; that a medicine be reimbursed with conditions; or that a medicine not be reimbursed, as detailed in the table below (**Table 11**).

TABLE 11. Types of reimbursement recommendations issued by the CADTH in Canada

CATEGORY	DESCRIPTION
Reimburse	The drug under review demonstrates comparable or added clinical benefit and acceptable cost or cost-effectiveness relative to one or more comparators suitable for recommending reimbursement according to the patient population defined in the evaluation, which is usually the patient population defined in the indication approved by *Health Canada*.
Reimburse with conditions	Scenarios that could be considered under this category include: ● The drug under review demonstrates comparable or added clinical benefit and acceptable cost or costeffectiveness relative to one or more appropriate comparators in a subgroup of patients within the approved indication. In such cases, conditions are specified to identify the subgroup. ● The drug under review demonstrates comparable clinical benefit and acceptable cost or costeffectiveness relative to one or more appropriate comparators. In such cases, a condition may include that the drug be listed in a similar manner to one or more appropriate comparators. ● The drug under review demonstrates comparable or added clinical benefit, but the cost or costeffectiveness relative to one or more appropriate comparators is unacceptable. In such cases, a condition may include a reduced price. ● The drug under review demonstrates clinical benefit, with a greater degree of uncertainty and an acceptable balance between benefits and harms in a therapeutic area with significant unmet clinical need. In such cases, if the cost or cost-effectiveness relative to one or more appropriate comparators is unacceptable, a condition may include a reduced price.

Do not reimburse	There is insufficient evidence identified to recommend reimbursement. Scenarios that typically fit this recommendation category include: ● The drug under review does not demonstrate comparable clinical benefit relative to one or more appropriate comparators.. ● The drug under review demonstrates inferior clinical outcomes or significant clinical harm relative to one or more appropriate comparators.

Source: CADTH (2021)[124]

The timeframe for the review process according to the CDR varies, depending mainly on the feedback phase, in which the considerations made by the pharmaceutical company on the draft recommendation are addressed. From the beginning to the end of the review, at least 186 working days are needed (Table 12)[127].

TABLE 12. Expected timelines for the CADTH common drug review process in Canada

PHASE	MILESTONES	WORKING DAYS
Screening	Application received	0
	Requirements screened for acceptance	10
	Review initiated	1 to 10
Review	Draft report(s) prepared and sent to sponsor for comments	53[a]
	Sponsor reviews draft report(s) and provides comments	7
	CADTH's responds to comments[b] and revises reports (as required)	7
Draft recommendation	Committee reviews materials and prepares discussant reports	10
	Expert committee meeting	1 to 2
	Draft recommendation issued to drug programs and sponsor	8 to 10
	Sponsor identifies confidential information	2
	CADTH redacts confidential information	1
	Validation of redactions by the sponsor	1
	Draft recommendation posted on CADTH website	2
Feedback phase	Stakeholder feedback period	10
	Request for reconsideration	Variable[c]
Final recommendation	Final recommendation issued to drug programmes and sponsor (no reconsideration)	8 to 10
	Final recommendation issued to drug programmes and sponsor (after reconsideration)	8 to 10
	Sponsor requests redaction of confidential information in recommendation	2
	CADTH redacts confidential information in recommendation	1
	Validation of redactions by the sponsor	1[d]
	Final recommendation copy-edited and formatted for posting	7
	Final recommendation posted on CADTH website	1
	Sponsor identifies confidential information in reports	10
	CADTH redacts confidential information in reports	8
Posting CADTH reports	Sponsor verifies redactions in clinical and economic reports	5
	CADTH reports copy-edited and formatted for posting on	18
	CADTH reports posted	3

Notes: CADTH: Canadian Agency for Drugs and Technologies in Health

a The timing required to prepare the draft reports for a request for advice depends on the complexity of the request and the amount of effort required to address the request.

b Sponsors will be sent CADTH's responses and the revised reports 8 business days prior to the expert committee meeting.

c The time frame required to address the request for reconsideration depends on the amount of work needed to address the request, as well as the available dates for expert committee meetings.

d In the case of a disagreement expressed by the sponsor regarding redactions made in the review report(s), CADTH may require additional time to resolve the disagreement in consultation with the sponsor. This additional time could delay publication of the review report(s).

Source: CATDH (2019)[127]

National Institute of Excellence in Health and Social Services (INESSS)

INESSS is a health technology assessment body similar to CADTH and serves only the province of Quebec. One of INESSS's functions is to advise the Quebec government on which drugs should be reimbursed by the public drug plan. INESSS differs from CDR in that it adopts a social perspective when assessing a medicine[121].

Patented Medicines Price Review Board (PMPRB)

The Board aims to regulate the prices of patented drugs sold in Canada to ensure that they are not excessive and to report to Parliament annually through the Minister of Health. The PMPRB is an independent and autonomous quasi-judicial body. To ensure this independence and autonomy, the Act does not give any power, either expressly or impliedly, to the government to direct the PMPRB or to review its decisions and orders. The Board is composed of a maximum of **5** part-time members, appointed by the Governor of the Council, including a chairperson and a vice-chairperson. The chairperson is appointed, with the authority and responsibility to supervise and direct its work. Currently, the PMPRB is composed of pharmacists, primary care physicians, health economists and lawyers, all of whom are experts in pharmaceutical market regulation[128,129].

The PMPRB monitors the prices charged by patent holders on an ongoing basis. According to the law, pharmaceutical companies must submit pricing and sales information for their products at the time of introduction and twice a year thereafter for each dosage form[130].

The first step of price monitoring begins with a scientific review to assess the level of therapeutic improvement of the newly patented medicine. A committee of experts known as the Human Drug Advisory Panel (HDAP) recommends appropriate pharmaceuticals to be used for comparison. The level of therapeutic improvement of the medicine is used to determine a maximum price, known as the Average Maximum Potential Price, at the time of its introduction[130].

The HDAP reviews and assess the scientific information available to the PMPRB, and may also conduct its own research. HDAP recommendations are based on a majority vote[131].

If the Board considers that the price of the medicinal product is excessive, it will conduct an investigation, which consists of an in-depth review of the price of a patented medicinal product by the Board's staff. An investigation into the price of a pharmaceutical product will be opened when any of the following criteria are met[132]:

- The list price of any dosage form or strength appears to be above 5% of the corresponding "Interim Maximum List Price" (iMLP) or "Maximum List Price" (MLP).
- The potential excess revenue appears to exceed CAD **50,000** per year (approximately €**35,000**) for the drug in all dosage forms and strengths in one year.
- A complaint is received.

When the Board starts an investigation, the patent holder will be notified and the medicine will be considered as "Under Investigation", which could result in[132]:

- A Voluntary Compliance Undertaking (VCU): is a written commitment by the patent holder to comply with the Board's Guidelines, including adjusting the price to a non-excessive level and offsetting any excess revenue that may have been received as a result of selling the patented medicine at an excessive price in Canada[132,133].
- The issuance of a notice of hearing if the chairman considers it in the public interest. If the price appears excessive, the Board may hold a public hearing. If it finds that the price is excessive, it may issue an order to reduce the price and offset the revenue received as a result[130].
- The closure of the investigation without price review.

pan-Canadian Pharmaceutical Alliance (pCPA)

The pCPA is the office responsible for facilitating value negotiations between public drug plans and pharmaceutical companies. Currently, all public drug plans in Canada, including Quebec, participate in it. For branded drugs, once a recommendation from the assessment bodies is ready, the provinces determine whether a negotiation should take place and which province will voluntarily lead the negotiation. If agreement is reached in negotiation, a Letter of Intent (LOI) is issued, which forms the basis for contracts executed by each jurisdiction under the legislation, after which reimbursement is triggered.

The pCPA conducts collective negotiations on medicines with the help of experts, with the following objectives[134]:

- Increase access to clinically effective and cost-effective drug treatment options.
- Achieve consistent and lower drug costs for participating jurisdictions.
- Reduce duplication of efforts and improve the use of resources.
- Improve the consistency of decisions between participating jurisdictions.

Documentation

When submitting a drug to CATDH for assessment, the company must submit a cover letter, together with an executive summary and a monograph of the drug, as well as the marketing authorisation from Health Canada or a document specifying the expected date of that authorisation[124].

On the pharmaco-clinical section, the company should provide reports of pivotal and non-pivotal clinical studies, as well as a table of other studies of the drug. It should also provide a summary of efficacy and safety and a summary of biopharmaceutical studies and associated analytical methods[124].

For pharmaco-economic documentation, the standard procedure indicates that the following elements should be submitted[124]:

- A technical report on the pharmaco-economic evaluation
- An economic model (cost-utility analysis) or cost estimates (cost-minimisation analysis)
- A technical report of the budget impact analysis
- A budget impact model
- Additional documents: application summary, signed cover letter, executive summary, product monograph, claim letter, regulatory and HTA status, Health Canada documentation for compliance, epidemiological information, number of patients eligible for the new medicine, reimbursement status of comparators, pricing and distribution information, interim algorithm (for oncology medicines) and companion diagnostic (if applicable).

Clinical assessment

The clinical assessment of new medicines is conducted in different phases. First, CADTH develops a protocol to ensure that the assessment reflects the most relevant clinical information. This protocol specifies the intervention, comparators, affected populations, outcomes and study designs to be used to conduct a systematic literature review[124].

CADTH designs and conducts one or more systematic searches according to the protocol to complement the presentation material provided by the sponsor. A list of studies to be included in the clinical review is sent to the sponsor for information purposes. The CADTH documents strengths and limitations with respect to internal and external validity[124].

Input from patient groups and clinicians is summarised in the clinical report and, in discussing the available evidence, CADTH reflects on this input, in particular areas where there is an unmet therapeutic need for those living with the disease, the known advantages and disadvantages of currently available treatments and any expectations for new therapies (including the drug under review)[124].

CADTH review teams usually include at least one clinical expert who provides guidance and interpretation throughout the review. CADTH may establish a panel of clinical experts to provide insight into the potential use of the medicine in the disease. One or more clinical specialists with experience in the diagnosis and treatment of the disease for which the medicine is indicated provide comments in the clinical report on the medicine to be reviewed[124].

Economic evaluation

The economic evaluation of medicines is governed by the guidelines issued by the CADTH, which include the following elements (**Table 13**)[135]:

TABLE 13. CADTH guidelines for the elaboration of the economic evaluation in Canada

METHODS
In the reference case, the economic evaluation should be a cost-utility analysis (CUA) with outcomes expressed as quality-adjusted life years (QALYs). Any deviation from this approach must be clearly justified.
POPULATION
The target population must be clearly indicated, as well as the comparator(s), which must be medicines marketed in Canada.
PERSPECTIVE
The perspective of economic evaluation should be that of the payer of publicly funded healthcare.
TIME HORIZON
The time horizon should be long enough to capture all relevant differences in future costs and outcomes associated with the interventions being compared. It should be based on the likely impact of the intervention.
DISCOUNT
The discount rate should be **1.5%** per year and should be applied to costs and outcomes beyond one year. The impact of uncertainty in the discount rate should be assessed by comparing the results of the reference case with those of the non-reference case analyses, using discount rates of **0%** and **3%** per annum.
RESULTS
In the reference case, researchers must systematically identify, measure, assess and report on all relevant resources from the payer's perspective.
RESOURCE USE AND COSTS
Resource use and costs should be based on Canadian sources. If the decision problem reflects a broader societal perspective, it may be relevant to include the impact on patient and/or caregiver time. Where unit costs are only available for an earlier time period, costs should be assessed to ensure that they reflect current practice, and should be updated to the current year during the assessment.
ANALYSIS
The data obtained for economic modelling (e.g. clinical effects, resource use, utilities) should be analysed in terms of estimates of expected costs, outcomes and cost-effectiveness ratios.
UNCERTAINTY
Uncertainty about the results should be clearly stated. Three categories of uncertainty should be explicitly addressed: methodological, parameter and structural.
REPORTING
The economic evaluation report should be clear and detailed, and the analysis and results should be presented in a transparent manner.

Source: prepared by the authors based on CADTH (2017)[135]

Involvement of patients and scientific societies

Patient involvement in the drug review process in Canada is twofold: on the one hand, patients have a voice and a vote in the different review committees, either through the common procedure, or through the plasma or oncology product procedure, by means of health consumer representatives. On the other hand, in each review, patients affected by the pathology for which the medicinal product is indicated make statements providing their experiences and perspectives on the disease, the available treatments and the medicinal product under review. This information is used by the CADTH and the expert committees in all phases of the assessment, including protocol development, assessment and interpretation of the evidence, and development of recommendations[124].

P&R decision elements

External reference pricing

In Canada there is a reference price system that is based on the international reference price. This figure is updated annually and is estimated as the average price of a brand-name drug in France, Germany, Italy, Sweden, Switzerland, the United Kingdom and the United States[136,137]. If a medicine is sold in fewer than five countries at the time it is first sold in Canada, the international average price of the medicine is calculated and reassessed after three years. With

the upcoming reform of the PMPRB, Switzerland and the United States will be removed from the "basket" of reference countries[138]. Each province buys medicines from manufacturers and can use the reference price to set the prices of medicines in each province's public drug plan[136].

The average international price is the maximum price that can be charged in Canada. However, it is possible for manufacturers to charge above this price to certain customers, provided that this is offset by discounts to others, so that the average net price is at or below the maximum[137].

Criteria for pricing

In addition to the therapeutic improvement offered by the reviewed medicine, PMPRB uses five criteria to determine whether a pharmaceutical product is overpriced, as described in section 85 of the Act[139]:

- The prices at which the medicine has been sold on the relevant market
- Prices at which other medicines of the same therapeutic class have been sold on the relevant market
- Prices at which the medicine and other medicines in the same therapeutic class have been sold in countries other than Canada
- Changes in the consumer price index
- Any other factors that may be set out in the regulations

Budgetary impact

When pricing the therapy in Canada, the impact of the inclusion of the medicine in Canada is also taken into account. In this regard, the pharmaceutical company must submit, among other things, the following information on the budget impact analysis (BIA)[124]:

- **Target population:** The population presented in the BIA must match the population reported in the economic evaluation.
- **Perspective:** The base case should reflect a pan-Canadian drug plan perspective (excluding Quebec). No other perspective should be included in the analysis.
- **Time horizon:** Two time horizons should be used, one for the first year and one with a **3**-year forecast period.
- **Costs and resource use:** In the base case, the specific price of the medicine submitted to CADTH for the lowest dispensing unit should be used.

Cost-effectiveness threshold

According to a study that analysed CADTH funding recommendations, CADTH generally used two cost-effectiveness thresholds, **50,000** CAD/QALY and **100,000** CAD/QALY (approximately €**35,000** and €**70,000**) to suggest price reductions in order to approve orphan drugs for reimbursement. It is unclear why CADTH chooses the threshold of **50,000** CAD/QALY for some drugs and **100,000** CAD/QALY for others when recommending price reductions[140].

In the case of orphan drugs, the PMPRB has established a threshold for modifying the maximum price of CAD

150,000 or CAD **200,000** (approximately **105,000** and **140,000** euros) per QALY for drugs with a prevalence of no more than **1** in **2,000** people across all approved indications[140,141].

Financial agreements and their monitoring

The final step in the funding of medicines in Canada is the negotiation between the different provinces and pharmaceutical companies. In this regard, some provinces have years of experience with innovative financial formulas such as evidence-based or managed agreements, known as Product Listing Agreements (PLAs)[142]. These agreements are made on the basis of LOIs, and are private agreements and therefore no information is available on innovative financial formulas in the country[143].

In the field of rare diseases, a government proposal on the reform of the country's pharmaceutical system indicates that outcome-based agreements can be effective in ensuring that patients have early access to treatment and that real-world evidence is generated to address gaps, while sharing the financial risk between governments and drug developers, and recommends that the Canadian government use such financial arrangements for these types of diseases[144].

Although there is no data on the use of real-life data tracking mechanisms used in Canada, the Canadian government, in its pharmaceutical system reform project, recommends the use of this type of evidence, especially for rare diseases[144].

...TO BE HIGHLIGHTED IN CANADA

- ✔ *One of the pioneer countries in using economic evaluation*
- ✔ *Use of an algorithm to differentiate assessments of oncology drugs from non-oncology drugs, plasma and single drug innovations from other drugs*
- ✔ *Publication of technical review reports on the CATDH website*
- ✔ *Pooling of public payers for the procurement process of medicines*
- ✔ *Negotiation between provinces and pharmaceutical association to facilitate access to medicines*

South Korea

In 2000, all South Korean insurers were integrated into a single payer, the National Health Insurance (NHI). The NHI governs the drug pricing and reimbursement system, which is funded primarily through risk premiums and government subsidies. This system is operated by the National Health Insurance Service (NHIS)[145,146].

In 2019, **97%** of the population was covered by the NIH (the remaining **3%** was covered through the Medical Aid Program), contributing risk premiums averaging **6.9%** of their monthly income. Partly due to this low contribution, NHI coverage levels are lower compared to other developed countries, resulting in relatively high patient co-payment ratios (**30%** to **60%** for outpatient drugs and **20%** for inpatient drugs, except those for oncology and rare diseases, which have **5%** and **10%** co-payment limits, respectively[145,147]) and an extensive list of drugs not included in the reimbursement system ("unlisted")[145].

The funding process for any medicine in South Korea starts with an authorisation by the Ministry of Food and Drug Safety (MFDS). Good Manufacturing Practices (GMP), safety and efficacy criteria are taken into account in obtaining this approval, and the process usually takes **120** days[146].

Actors and process

The pricing and reimbursement process in South Korea is the same for outpatient medicines as for inpatient medicines. It was introduced in 2007 (South Korea was the first country in Asia to have a formal health technology assessment process[148]), through the Positively Funded Medicines List system. The process for inclusion on this list consists of three stages, following the application for reimbursement and funding by the manufacturer.

In the first stage, the Drug Benefit Coverage Assessment Committee (DBCAC) of the Health Insurance Review and Assessment Service (HIRA) assesses whether the drug meets certain criteria for funding (see Q&A decision elements)[146,149,150]. This process typically takes **240-360** days from MFDS approval of the drug (**120** days for HIRA assessment, **30** days for manufacturer agreement or disagreement, **60** days for price and volume negotiation, and **30** days for final decision). If the company does not agree with the assessment, it can request a reassessment and the HIRA has **150** days to carry out the reassessment[146,149]. To reduce these timeframes, in 2014 the government implemented a system whereby the reimbursement decision process can be carried out in parallel to the MFDS approval process[146,149]. A study analysing the first **18** months since the implementation of these parallel processes observed a reduction of **61** days in the average approval times for the **6** drugs included in this programme, compared to the previous sequential procedure[151].

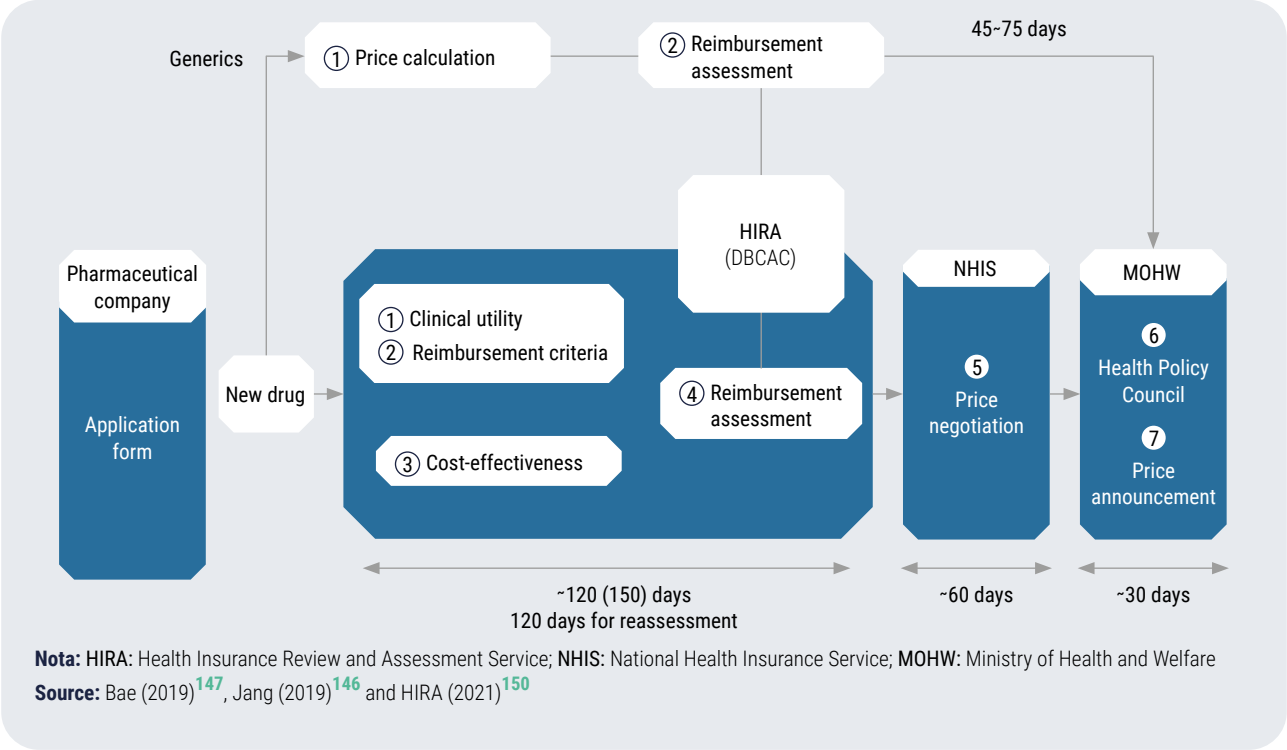
In this phase, one of the following three types of evaluation is used: (**1**) economic evaluation: drugs with clinical superiority and higher price than existing alternatives; (**2**) weighted average price: drugs with clinical superiority or non-inferiority, and lower price than existing alternatives; (**3**) no cost-effectiveness analysis required: drugs for life-threatening diseases, such as cancer or rare diseases, which lack robust scientific evidence due to the absence of therapeutic alternatives or the small target population for which they are intended[152].

In the period between 2007 and 2017, when **198** drugs were approved for funding, the most commonly used route was weighted average prices (n=123; **62%**), followed by economic evaluations (n=54; **27%**) and no cost-effectiveness analysis (n=21; **11%**)[152].

In the second stage, the price of the drug and the expected budgetary impact is defined through negotiation between the laboratories and the NHIS, as long as the proposed price is higher than the weighted average of the prices of their therapeutic alternatives. The price negotiation period lasts about **2** months[146,149,150].

Once the price is agreed between the manufacturer and the NHIS, the manufacturer informs the Ministry of Health and Welfare, which makes it public, after review by the Health Insurance Policy Council (HIPC). This final stage takes approximately 30 days (**Figure 19**)[146,150].

FIGURE 19. Drug pricing and reimbursement process in South Korea

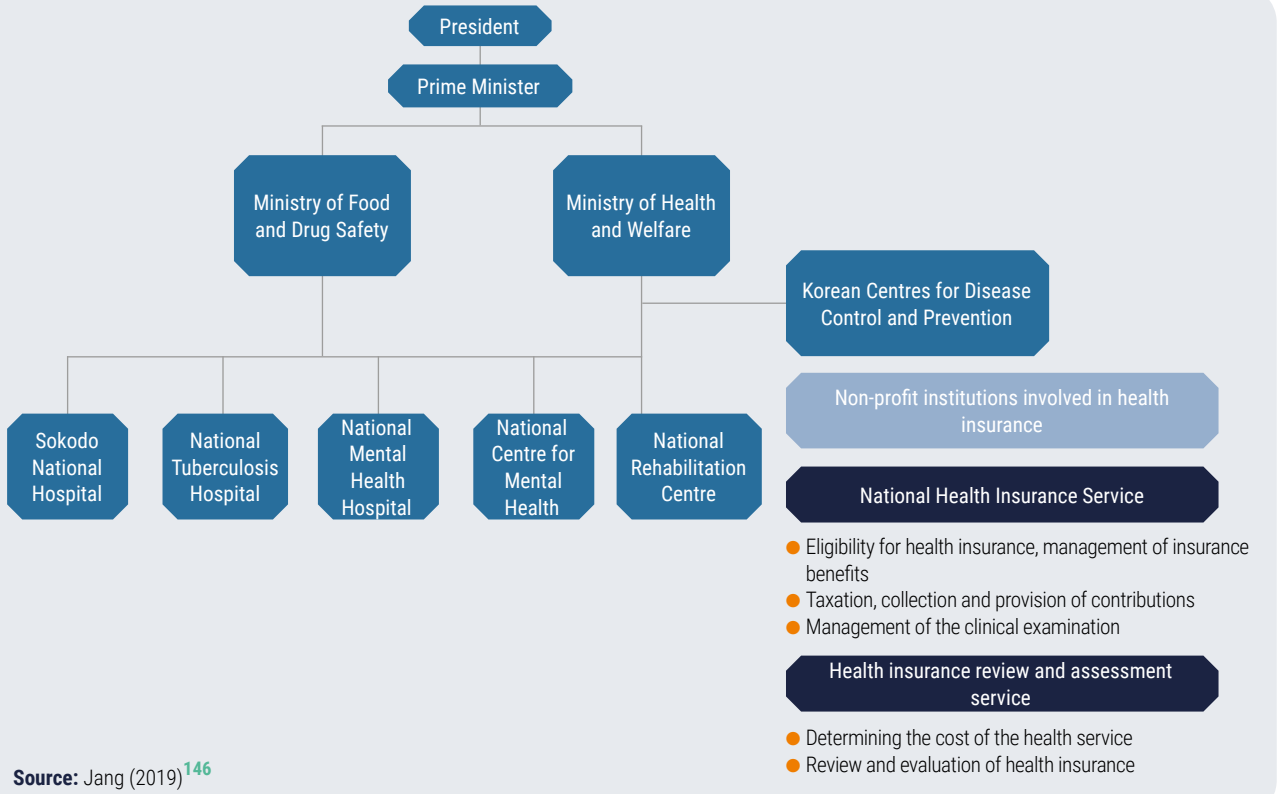


Nota: **HIRA:** Health Insurance Review and Assessment Service; **NHIS:** National Health Insurance Service; **MOHW:** Ministry of Health and Welfare
Source: Bae (2019)[147], Jang (2019)[146] and HIRA (2021)[150]

Medicines that have demonstrated efficacy, but not yet proven to be effective, are included in a provisional list, and are therefore reimbursable by NHI for a certain period of time, after which the drug undergoes a reassessment process[145]. According to the available information, most of these reassessments led to price cuts so that the drugs could be included in the list of funded medicines[153].

Regarding the main actors involved in the process, in general terms, the MFDS is responsible for the marketing authorisation of medicines, while the Ministry of Health and Welfare (MOHW) is responsible for pharmaceutical policy and NHIS reimbursement. The NHIS and HIRA are tasked with operating the NHIS pricing and reimbursement system (**Figure 20**)[146,149,150].

FIGURE 20. Actors involved in the pricing and reimbursement process for medicines in South Korea



Source: Jang (2019)[146]

National Health Insurance Institute (NHIS)

As a single payer, the NHIS manages the eligibility of NHI beneficiaries and their dependents, and imposes and collects contributions. In addition, it is responsible for payments of funded drugs to medical institutions and pharmacies. The NHIS is responsible for price negotiations with manufacturers prior to the introduction of new drugs on the market[146].

Health Insurance Review & Assessment Service (HIRA)

The HIRA is responsible for setting the scope and standards of services and products covered by the NHI, assessing the cost and quality of health products and services (including medicines) and monitoring or managing a wide range of health resources centrally. It is, together with the NHIS, responsible for the entire pricing and reimbursement process in the country. Its main activities are detailed below[146,154]:

- Design of the health benefits package.
- Economic evaluation of new drugs and recommendation for reimbursement to the NHIS.
- Design and implementation of healthcare provider payment systems.
- Review of requests for reimbursement.
- Collection and use of health data at national level (centralised activity) for monitoring the performance of health products and services.

In its organisational structure, it has an Executive Benefits Directorate, to which the drug benefits department reports[155].

Drug Benefit Coverage Assessment Committee (DBCAC)

The DBCAC is responsible for making recommendations on the inclusion of medicines on the NHIS list. Although the committee's role, as specified by law, is to advise the HIRA, in practice it has a decisive role as the HIRA's determinations always follow the recommendations of the DBCAC[147,156].

The committee is composed of approximately **102** experts, including members of (medical) scientific societies (n=60), pharmacists (n=13), patient representatives (n=12), government representatives (Ministry of Health and HIRA; n=6]), statisticians (n=3), health economists (n=3), specialists in health technology assessment processes (n=3) and hospital society representatives (n=2)[147,156].

Documentation

The documentation required for the pricing and reimbursement processes appears not to be publicly available.

Clinical assessment

The information used for the clinical assessment of the pricing and reimbursement processes appears not to be publicly available.

Economic evaluation

Korea has a guideline for the economic evaluation of medicines similar to the one developed by NICE (written in Korean), published in 2006[157] by HIRA and updated in 2011[158] and 2021[159]. The following are the requirements of this guidance[160,161]:

- **Perspective:** from the health system[161].
- **Time horizon:** long enough to include all important differences in the technologies being compared, in terms of costs and consequences. In addition, a short-term perspective should also be presented[160].
- **Type of evaluation:** cost-utility, cost-effectiveness or cost minimisation. Cost-benefit analyses are not allowed. Cost-utility models are recommended in cases where changes in health-related quality of life can be demonstrated. Cost-effectiveness analysis can be used when QALYs are not an appropriate measure[160].
- **Benefit and utility variables:** use of endpoints to measure benefits and QALYs to measure utilities (calculated through individual preferences, using the "*time trade-off*" and "*standard gamble*" methods, or through questionnaires to indirectly measure QALYs [EQ-5D, among others], based, whenever possible, on a cohort of Koreans with normative values of the country's healthy population). The use of disease-specific questionnaires is not recommended[160]. In the third edition, it is proposed to conduct a nationwide study to determine the usefulness[161].
- **Indirect comparisons:** In the absence of direct "*head to head*" drug comparisons, indirect comparisons are allowed[160].
- **Model:** as simple a model as possible should be used, reflecting actual clinical practice patterns in the

country, always including an explanation of the reasons for the choice of the structure used and thes statistical and clinical assumptions included[160].

- **Sensitivity analysis:** A thorough deterministic analysis (presented visually, e.g. through the use of tornado diagrams) is recommended, followed by a probabilistic sensitivity analysis, indicating the assumptions used[160].

Orphan drug assessment

To improve access for patients with cancer or rare diseases, for whom no alternative therapies are available, the South Korean legal framework exempts some of these drugs from the need for economic evaluation and enters into risk-sharing agreement processes[145]. In these cases, the maximum price will be based on the lowest price found in 7 reference countries (see "P&R decision elements")[145,148].

Involvement of patients and scientific societies

Korea involves patients in the pricing and reimbursement processes by asking them to comment on aspects such as the approach to the problem and certain evaluation reports[162].

In addition, it includes scientific societies and patient and society representatives in the DBCAC. Of the **102** current members, **60** are representatives of medical scientific societies from different specialisations (**6** in cancer, **4** in paediatrics, **4** in endocrinology, **4** in urology and **2** representatives from other specialisations, such as cardiology, haematology, rheumatology, mental illness, primary care, among others) and **12** are patient/society representatives (coalition for economic justice, environmental association, solidarity associations and other patient associations)[147,156].

P&R decision elements

The pricing of new drugs is determined through negotiation between the laboratories and the NHIS, based on criteria such as the HIRA DBCAC assessment, budget impact analysis, external reference prices, production capacity, patent status and R&D costs, among other factors[146].

International reference prices

South Korea does not use an official reference pricing system for the pricing of new medicines[146]. However, during the negotiation process with manufacturers, NHIS takes into account the price suggested by HIRA in its assessment, as well as prices from other countries, the "A7" countries, which are the United States, United Kingdom, Germany, France, Italy, Switzerland and Japan[145,146].

Criteria for pricing

The criteria used in the drug pricing and reimbursement decision processes in South Korea are as follows[148]:

- **Clinical benefits:** data from clinical trials, clinical practice guidelines, systematic reviews and expert opinions[148].
- **Cost-effectiveness:** based on therapeutic superiority over the comparator. In cases where the clinical benefit is equivalent, a cost-minimisation analysis is applied, and those drugs with lower costs are reimbursed. If

the drug has clinical superiority, but has higher costs than the comparator, cost-effectiveness analysis is used, based on a ratio of incremental cost per Quality Adjusted Life Years(QALYs).

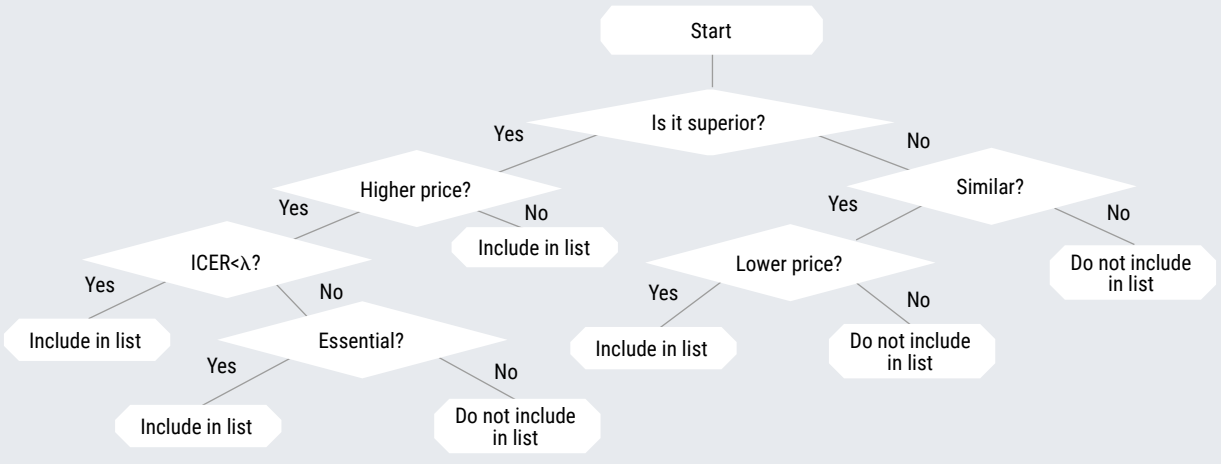
- **Budget impact analysis:** From 2021 onwards, a budget impact analysis is not required at the reimbursement decision phase by HIRA. However, in the price negotiation phase with the NHIS, sales volumes are estimated for each drug, which are used as a basis for future price adjustment decisions[148,161].
- Price and reimbursement situation in other countries (see "reference prices").
- **Public health considerations:** severity of the disease, existence of alternative therapies, among others[147].

"Although it is not done in an official way, price and reimbursement determination in South Korea also takes into account the decisions of 3 international health technology assessment agencies, such as the Australian, Canadian and British agencies[144]."

Economic evaluation is the main decision criterion in the reimbursement process in South Korea[146]. According to an analysis of all reimbursement decisions requiring economic evaluation in the period between 2006 and 2016 (n=91) the incremental cost-effectiveness ratio (ICER) was the main predictor of recommendation decisions (**86%** of cases). This analysis also suggested that for every increase in ICERs of **1** million South Korean won (approximately €**700**), the likelihood of a drug being approved for funding was reduced by **12%**[163]. Other important factors are disease severity (**19** times more likely to be funded compared to drugs for mild disease) and the existence of alternative therapies (**8** times more likely to be funded for drugs without alternatives compared to drugs with comparators already on the market)[163].

The following is the pricing and reimbursement decision algorithm (**Figure 21**)[147].

FIGURE 21. Pricing and reimbursement decision algorithm in South Korea



Note: ICER: Incremental Cost-Effectiveness Ratio. **Source:** Bae (2019)[147]

Budgetary impact

Budget impact analysis was recently excluded from the HIRA economic evaluation process[161]. However, at the price negotiation stage between manufacturers and the NHIS, an amount related to the economic impact of the medicine is estimated and used as a reference for the application of adjustments after market introduction (see "*financial formulas*")[145,146,152].

Cost-effectiveness threshold

The HIRA does not use pre-defined cost-effectiveness thresholds, but is based on per capita gross domestic product (GDP) (in actual practice, only medicines with thresholds below **2** times GDP per capita were approved) **148,163**, which in 2020 was €**27,100**[164]. Sixty percent had a cost below GDP per capita and **40%** had a cost between **1** and **2** times GDP per capita. By the end of 2016, **91** claims requiring economic evaluation had been assessed, of which **46** were approved. The average incremental cost-effectiveness ratio of the approved claims was approximately **23.1** million won/QALY (approximately €**17,000**). Of these, **37%** (n=17) had an incremental cost-effectiveness ratio higher than GDP per capita, but none exceeded twice this indicator[163].

Financial agreements and their monitoring

Financial agreements

South Korea has been applying volume-based agreements since 2007, as instruments frequently used by the NHIS for price adjustment. During the negotiation process with laboratories, expected volumes of drug utilisation (their estimated budgetary impact) are determined. If sales of the drug exceed **30%** of the determined volume one year after its inclusion in the funding system, further negotiations are conducted in order to reduce the price. The same applies in two other scenarios: (**i**) if sales of a drug exceed **60%** over the previous year; (**ii**) if sales increase by more than 10% over the previous year, but by more than **4** million euros (**5** billion won). Drugs with an estimated budget impact of less than **1** million euros (**1.5** billion won) do not fall under these volume-based agreements[145,146].

Since 2014, other types of financial agreements have also been implemented to increase access to oncology drugs, orphan drugs, drugs with no therapeutic alternatives, or drugs for very serious diseases or diseases with a high social impact. The standard term of these contracts is usually **4** years, extendable to **5** years. Four types of agreements apply[146,165]:

- **Expenditure cap:** the manufacturer refunds a proportion (specified in the contract) of the amount of sales exceeding the amount agreed with the NHIS.
- **Partial sales refund:** the manufacturer refunds a proportion (specified in the contract) of the total amount of sales of the medicine.
- **Utilisation cap or fixed cost per patient:** a utilisation cap or annual cost per patient is determined and the manufacturer refunds any amount exceeding these limits.

- **Conditional treatment continuation and money back guarantee:** the manufacturer returns sales related to patients who do not respond to treatment in actual practice.

As of mid-2019, **39** medicines (**77%** of them for cancer treatment) had been approved through different types of financial agreements (**46%** expenditure caps, **31%** partial sales refunds, **13%** a combination of expenditure caps and partial sales refunds, and **10%** other existing mechanisms)[165].

Likewise, an innovative drug produced by an R&D-intensive company can receive a **10%** premium over the prices of alternative therapies, and obtain accelerated access, with **100** days for a reimbursement decision and **30** days for a pricing decision[146].

For essential medicines for which the market is very limited, there may be financial compensation related to the cost of production, or financial incentives for their production[146].

Price reassessment

A price reassessment must be carried out if, based on a biannual investigation, it is verified that the actual price at which the drug is being marketed in the country (in hospitals or pharmacies) is lower than the funded price, to which a reduction of up to **10%** can be applied[152,166].

Monitoring mechanisms

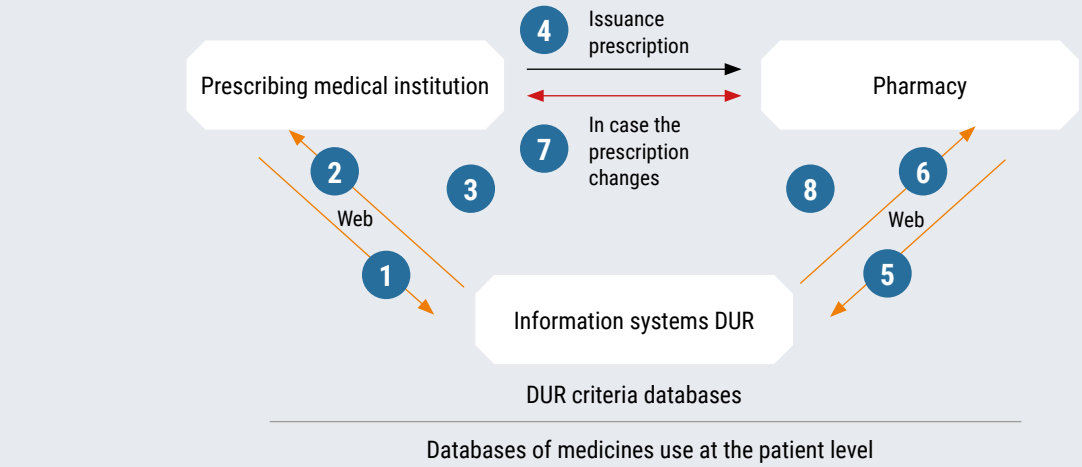
Monitoring of hospital medicines is done locally and optionally by the hospital pharmacy services themselves, with no nationally implemented mechanism[146]. Monitoring of outpatient medicines is done centrally at the national level through the Drug Usage Review (DUR) system, implemented in 2015[146,154,167,168].

The monitoring procedure of the DUR system (from the HIRA) is as shown in **Figure 22**. The physician uploads the prescription details into the system before issuing the prescription to the patient. the HIRA sends the prescriber an instant email alert in cases where prescription-related risk factors are detected in comparison to the patient's drug utilisation history, drugs removed from the positive list and DUR criteria (clinical and economic). The physician may then choose to change the prescription or to continue with the original prescription, explaining why the medicine should be used exceptionally. The final prescription information is sent to and stored in the system[146,167].

Pharmacists undergo the same process at the time of dispensing the medicine. If they receive an alert message, they can choose to change or proceed with the original prescription after consultation with the doctor. Detailed final dispensing information is also sent to and stored in the system[146,167].

In 2019, revisions were made to **1.5** billion prescriptions, generating estimated savings of around €**1.2** billion (**1.7**% of the total), avoiding an estimated **5.4** million prescriptions of unsafe medicines[154,167].

FIGURE 22. Drug Utilisation Review System (DUR) in South Korea



Note: DUR: Drug Usage Review. **Source:** Jang (2019)[146] and HIRA (2020)[167]

...TO BE HIGHLIGHTED IN SOUTH KOREA

- ✔ *Legal framework allowing the use of parallel marketing authorisation and price and funding assessment processes*
- ✔ *Certain oncological and orphan drugs are exempted from the need to undergo an economic evaluation process*
- ✔ *Use of cost-effectiveness thresholds based on GDP per capita*
- ✔ *Centre for Orphan and Essential Medicinal Products authorised to import and distribute certain medicinal products approved in other countries that have not yet obtained a national marketing authorisation*
- ✔ *Implementation of various price control and adjustment mechanisms*
- ✔ *Real-time prescription and dispensing monitoring system for outpatient drugs*

Scotland

Like England, Scotland has seen its medicines marketing approval process affected by the UK's exit from the EU in 2020. The Medicines and Healthcare products Regulatory Agency (MHRA) is responsible for formalising marketing authorisation for all medicines in the UK[169].

Actors and process

Scotland has a medicines assessment agency called the Scottish Medicines Consortium (SMC), which advises the NHS in Scotland on the value of newly available medicines[170]. The SMC reports to the Healthcare Improvement Scotland Board, which is one of the Special Boards within NHS Scotland[171,172].

The assessment of medicines is carried out by two committees, the SMC committee, which is the final decision-maker in the assessment, and the New Drugs Committee (NDC), a scientific committee under the SMC[173], whose role is to complete the technical assessment submitted by the company and make a recommendation on the use of the medicine to the SMC committee[174].

In Scotland, the pricing and funding process starts when the interested company submits a dossier of the medicine for review by the SMC. Once the company submits the new medicine information, the assessment and exchange of information between the SMC and the applicant company begins. The SMC committee meets to consider the medicine, taking into account other information, such as submissions from patient groups, and usually takes a broader view than the strictly evidence-based approach of the NDC.

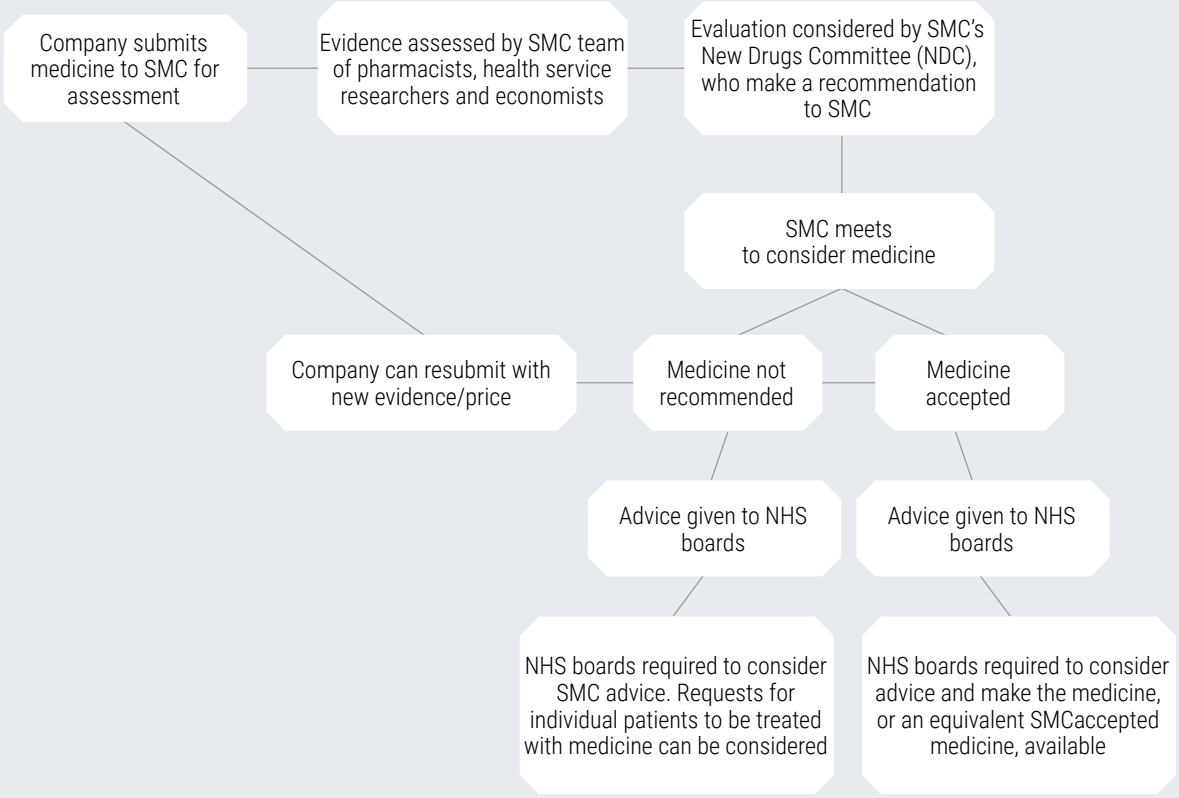
Both the SMC and the NDC meet monthly, with a six-week interval between the assessment of a medicine at the NDC and the SMC. The schedule of meetings is published at the beginning of the year and timelines are rigorously followed to ensure that decisions are responsive to the needs of patients, prescribers and the healthcare system. The total duration of the process is **18** weeks (**Figure 23**)[174].

The NDC is composed of physicians, pharmacists and two members from industry (in total, about **20** members). This committee meets monthly to evaluate the clinical and economic evidence submitted by companies for each new medicine[175]. After this first assessment, the NDC provides advice to the companies, allowing them to provide additional documentation to minimise any uncertainties that the NDC may have[176]. Finally, the NDC makes a non-binding recommendation to the SMC committee[174].

On the other hand, the SMC committee consists of around **40** members, mostly doctors and technicians from the Scottish national system. There are also three members from outside the NHS, as well as representatives from the pharmaceutical industry and a health economist. The committee reviews all the evidence provided by industry and the NDC and decides whether or not to accept the medicine for use in Scotland, as well as the conditions of use of the therapy[175].

For practical reasons, not all clinical specialties are represented on SMC´s committees, so the Scottish agency has established a network of clinical experts comprising physicians, surgeons, clinical pharmacists, general practitioners and clinical nurse specialists to support the various committees[176].

FIGURE 23. Medicines assessment process in Scotland



Note: NHS: National Health System; **SMC:** Scottish Medicines Consortium
Source: SMC (2018)[170]

The heterogeneous composition of both committees facilitates decision-making with a broad societal perspective, beyond clinical evidence (**Table 14**)[174]. Both committees are supported by a team of clinical reviewers consisting of pharmacists, health economists, health services researchers and statisticians with expertise in critical appraisal, health technology assessment and economic modelling. All members of the committees are required to publish a list of interests[177].

TABLE 14. Composition of SMC and NDC committee members during 2020 in Scotland

PROFILE OF COMMITTEE MEMBERS	NUMBER OF SMC EXPERTS	NUMBER OF NDC EXPERTS
Medicine	12	8
Primary care	1	–
Hospital care	11	8
Pharmacists	4	9
Health management	2	–
Public partners	3	–
Pharmaceutical industry	3	2
Health economists	1	–
Nursing	1	–

Note: NDC: New Drugs Committee; **SMC:** Scottish Medicines Consortium
Sourc: SMC (2020)[174]

Once the discussion of all proposals is completed, the meeting moves into a closed session and each voting member of the SMC casts its vote for each medicine electronically. The result is based on a simple majority and the vote is confidential[174]. Decisions at SMC meetings are taken by majority vote and only full members have voting rights. These members are clinicians, NHS managers, public decision-makers and members of industry. The SMC secretariat and staff, observers, (e.g. the health economist), NDC members attending as principal advisors or supporting SMC consultants do not have voting rights. Members declaring a specific personal interest do not participate in the discussion and are not entitled to vote[178].

At the end of the process, the SMC can make four types of decisions about a medicine[179]:

- Acepted
- Accepted with one or more restrictions. For example, the medicine can only be recommended for a particular group of patients. This is usually because the company has explicitly requested this in the submission
- Provisionally accepted. This means that the medicine can be accepted for use subject to ongoing review and reassessment, once more evidence becomes available
- Not recommended

In addition to the standard assessment procedure, the SMC allows for an assessment in which the opinion of doctors and patients has a stronger voice, through the Patient and Clinician Engagement (PACE) process. This type of process applies to rare diseases and *end-of-life* patients, and any company is eligible, as long as it can adequately justify that its medicine is indicated for a rare or *end-of-life* disease[180].

The main advantage of this procedure is that clinicians and patients have a greater voice in the assessment of these types of medicines and decision-making is more flexible. The aim of these PACE meetings is to describe the added benefits of the medicine beyond QALY, both from the patient's and clinician's point of view, which may not be fully captured in the conventional clinical and economic evaluation process. Examples include the ability to work or continue in education, psychological distress, as well as factors such as the appropriateness of the treatment, whether it enables self-care or the ability to maintain independence and dignity. Other factors such as the need to assist the patient with personal care, the impact on family life and any associated financial impact are also assessed[180]. In addition, companies may submit, at this stage of the process, alternative access arrangements to the usual process, through the new or revised Patient Access Scheme (PAS)[174]. If the NDC's advice for these products is "not recommended", the pharmaceutical company can also request that the SMC convene a PACE meeting. This process adds an additional **1** to **3** months to the assessment timelines[180].

If the PACE assessment is followed, the meeting interval increases from six weeks for the standard process to ten weeks for the PACE procedure. This time dilation results in a total duration of **22** weeks for the PACE process[180].

Orphan drug assessment

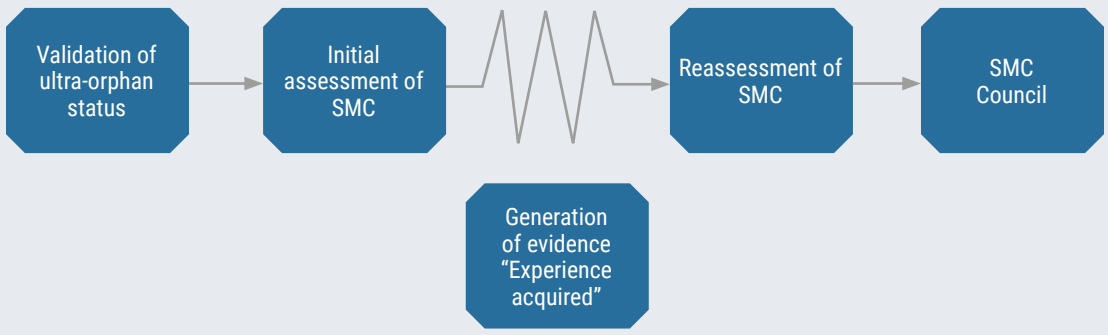
The SMC has an early access mechanism for so-called "ultra-rare" diseases. For a medicine to be approved through this process, it must meet the following conditions:

- Prevalence less than **1/50,000** people in Scotland
- Orphan marketing authorisation by the UK regulator
- Targeting a chronic and severely disabling disease
- Targeting a disease that requires highly specialised treatment

For the assessment of these types of therapies, SMC facilitates companies to submit preliminary information after obtaining marketing authorisation as an orphan drugs (ODs). Once the information is received, SMC conducts an initial assessment of the clinical and economic efficacy of the therapy (**Figure 24**). The SMC uses a broad framework to assess ODs, taking into account the following criteria[181]:

- Nature of the disease
- Impact of the medicine
- Value for money
- Impact of technology beyond direct health benefits
- Costs for the NHS and social services

FIGURE 24. Process of assessing ODs in Scotland



Note: SMC: Scottish Medicines Consortium
Source: adapted from SMC (2021)[181]

This authorisation is valid for three years while more information is gathered on actual clinical practice in Scotland. After that period, the company must submit the evidence shown for the medicine for the therapy to be reassessed by the SMC with a view to its inclusion for routine use on the NHS[181].

In addition to the procedures mentioned above, SMC gives companies the option to submit an abridged submission, with a shorter assessment period if the therapy to be assessed meets the following conditions[182]:

- Similar clinical efficacy to other medicines in the same therapeutic class. An indirect treatment comparison (published or internal analysis) can be provided to demonstrate similar clinical efficacy within the class, where necessary.
- The new medicine must cost the same or less, or have a limited net budgetary impact compared to comparators in the same therapeutic class.
- Any restrictions that apply to comparators within the same therapeutic class must apply to the new medicine.

Horizon scanning

In addition to conducting assessments of new medicines, SMC performs a horizon scanning function for the purpose of financial and service planning within the NHS. To this end, SMC is in contact with laboratories that are conducting Phase III clinical trials or that will be available to the general public in up to three years, and invites pharmaceutical companies to provide as much information as possible in order to encourage early entry of the drug[174].

Documentation

The documentation submitted by the laboratory must demonstrate that the reviewed medicinal product offers any of the following advantages[174]:

a) It provides additional health benefits compared to current Scottish practice that are valued by patients and are at an acceptable net cost to the NHS relative to other uses of the same resources.

b) It offers equivalent levels of health benefits to patients at an equivalent or lower net cost to the NHS.

The SMC makes available to pharmaceutical companies a form called "*New Product Assesment Form*" which companies must fill in with all the information, both clinical and economic, of the therapy to be reviewed. The company must provide the following clinical data on the product[183]:

- Studies demonstrating the clinical benefit of the medicinal product in the indication under review, relative to the comparator(s) used in clinical practice. Controlled studies are recommended, but if not available, details of placebo-controlled or uncontrolled studies should be included. Placebo-controlled and uncontrolled studies may also be included if they provide evidence of relevant clinical benefits not demonstrated in active controlled studies.
- For placebo-controlled and uncontrolled studies assessing primarily an efficacy outcome, details should be provided on the type and frequency of adverse effects that might be expected in clinical practice with the medicinal product in the indication(s) under review.
- Studies providing evidence of adverse effects of the medicinal product in the indication.

- If appropriate, the company should also provide details of ongoing studies that should provide additional evidence for the medicine in the indication under review and when this additional data is expected (within up to **5** years).

With regard to pharmaco-economic information, it is mandatory for the company to provide the relevant economic evidence in order for the medicine to receive a recommendation from the SMC[184].

The interested company must also complete the form available on the SMC website on the budgetary impact that the application of the reviewed medicine will have on the Scottish national system. The file should contain all the estimates made, both for the base case and the alternatives studied[183].

The requirements for evidence of efficacy include quantifying the effect of the medicine on the course of the disease, the effect of the medicine on patients' health-related quality of life (HRQoL), and assessing those effects in a way that reflects the preferences of the general population. According to the SMC, analyses should use the best available evidence, be explicit about data limitations, and quantify as fully as possible how data limitations are reflected in the uncertainty of the results of the analysis[184].

In turn, the company must provide a version that is relevant to the knowledge of patients and the general public. The SMC team sends these documents to any patient group that submits an application for the new medicine[184].

Clinical assessment

The clinical assessment is carried out centrally by the SMC for the whole of Scotland. As with its English counterpart, the Scottish agency does not conduct a clinical assessment in a differential way from the economic evaluation, but instead conducts an evaluation focused on the cost-effectiveness of the therapy, which brings together both clinical effectiveness data and economic data. The clinical effectiveness of a therapy should be shown in terms of quality-adjusted life years (QALYs)[184].

On the clinical side, the comparator selected must be that used in routine clinical practice in Scotland. The claim that a treatment represents routine use or best practice must be supported by data confirming that the treatment is routine, established and accepted clinical practice in the majority of the country's territory[184] . Normally, the comparator chosen is a licensed product in most circumstances; however, comparators may include off-label or unlicensed products, as long as they are in routine clinical use in the Scottish national system[184].

The SMC may accept some medicines on a conditional basis, subject to further assessment. All medicines with an EMA conditional marketing authorisation are eligible for this option. The SMC may issue a provisional acceptance opinion (or provisional acceptance with a restriction) if the committee considers that additional efficacy and/or safety data requirements in the specific EMA obligations are expected to address key uncertainties in the evidence submitted by the applicant company. The company should submit a full update to the SMC when the conditional marketing authorisation becomes a standard marketing authorisation, usually after **2-3** years[174].

Economic evaluation

All companies applying for funding approval in Scotland must submit an economic appraisal. The economic evaluation must collect data in the context of NHS Scotland[184]. In general, cost-utility is the SMC´s preferred form of evaluation, using both the national health system perspective and the societal perspective. Other forms

of economic evaluation, such as cost minimisation analysis, are also allowed, as long as the studies provided demonstrate that the medicine under review is equivalent to the selected comparator. This type of analysis is also allowed when there are extremely small differences between the compared treatments in terms of QALYs. Alternative approaches may also be considered in circumstances where QALY may not be the most appropriate outcome measure, always with due justification[184].

The time horizon selected in the economic evaluation should be long enough to reflect any differences in costs or outcomes between the medicines being compared. The results in terms of the incremental cost-effectiveness ratio (ICER) should be reported at different time intervals, such as at the end of study follow-up, at **5**-year follow-up and thereafter at **5**-year intervals[184].

The discount rate for both costs and potential savings from therapy implementation should be **3.5%** per year. Where the results are potentially sensitive to the discount rate used, a sensitivity analysis should be performed with discount rates ranging from **0%** to **6%** per year[184].

Involvement of patients and scientific societies

The SMC encourages patient involvement by making available a form that is completed by patient associations (not by individual patients), which allows relevant information from the patient's point of view to be provided to the SMC committee. It also allows patient representatives to identify patient priorities and preferences and what the added value of a particular medicine may be[175].

On the other hand, patients also collaborate more actively in the PACE process, in particular by providing their views on the effects on the quality of life of patients and caregivers, as well as the potential impact of the drug to be reviewed, in the discussions. These considerations, together with those of the physicians, are a fundamental support in the decisions made by the SMC, in which the patient's perspective is taken into account more directly[185].

P&R decision elements

Cost-effectiveness threshold

The price decision in Scotland is delimited, but not the only element, by the demonstrated "value" of the drug relative to its comparator, where value is defined as the ratio of the demonstrated benefit to the cost difference. In this regard, SMC provides the following information as a guide[184]:

- Below an ICER of £**20,000**/QALY earned (approximately €**23,500**), the decision to recommend the use of a therapy is usually based on the estimated cost-effectiveness and acceptability of a medicine as an efficient use of NHS resources.
- Above an ICER of £**20,000**/QALY gained, judgements on the acceptability of the therapy as an efficient use of resources will specifically take into account the following factors:
  - The degree of certainty surrounding the ICER. In particular, the Committee will be more cautious about recommending a technology when it is less certain about the ICERs submitted.
  - Whether there are compelling reasons that the assessment of change in health-related quality of life has been inadequately captured and may therefore misrepresent the health utility obtained.
  - The innovative character of the technology, in particular whether the innovation adds demonstrable and

distinctive benefits of a substantial nature that may not have been adequately captured in the reference case's QALY measure.

- The technology meets the criteria for special consideration as "end-of-life treatment".
- Aspects related to non-health objectives of the NHS.

As the ICER of an intervention increases in the range of £**20,000-30,000** per QALY gained (€**23,500-35,000**), the Committee's judgement on the acceptability of the technology as an effective use of NHS resources will make explicit reference to the relevant factors listed above.

- Above an ICER of £**30,000**/QALY gained (approximately €**35,200**), SMC will need to identify more robustly one of the above criteria to support the technology as an effective use of NHS resources.

Modifiers of the ICER for decision making in Scotland

Cost per QALY is only one of the factors by which the value of the medicine is assessed, but not the only one. The SMC calls these additional decision factors "modifiers"[174]. These modifiers include (but are not limited to)[186]:

- Evidence of substantial improvement in life expectancy (with sufficient quality of life to make extra survival desirable). A substantial improvement in life expectancy would normally be a median gain of **3** months.
- Evidence of substantial improvement in quality of life (with or without survival benefit).
- Evidence that a subgroup of patients may derive a specific or additional benefit and that the medicinal product in question can, in practice, be targeted to this subgroup.
- Absence of other therapeutic options of proven benefit for the disease in question and provided by the NHS.
- Possible bridge to another definitive therapy (e.g. bone marrow transplantation or curative surgery) in a given patient population.
- The appearance of an authorised medicinal product as an alternative to an unauthorised product that is established in NHS Scotland clinical practice as the only therapeutic option for a specific indication.

The SMC also examines other special issues that may have been highlighted by the drug manufacturer, clinical experts and/or patient groups. Modifiers are only applied for a relatively high cost per QALY when the committee is convinced that the clinical and economic case for the medicine is strong.

Agreements between industry and payer

As in England, drug prices in Scotland are influenced by agreements between the Association of the British Pharmaceutical Industry (ABPI) and the UK Department of Health through the Voluntary Scheme for Branded Medicines Pricing and Access (VPAS). These agreements between industry and government rely on industry compensating the UK's national health system when pharmaceutical expenditure on branded products exceeds a **2%** growth over the previous year's bill. In the case of Scotland, pharmaceutical companies returned £**70** million (€**84** million) to the NHS for spending in 2019[187].

Financial agreements and their monitoring

Patient Access Schemes (PASs) are funding schemes proposed by pharmaceutical companies to improve the cost-effectiveness of medicines by facilitating patient access. Patient Access Schemes are considered by the NHS to facilitate patient access to medicines that are not, or may not be considered cost-effective in the first instance by the SMC[174].

The Patient Access Scheme Assessment Group (PASAG) is responsible for conducting an objective and independent assessment of PAS submitted by companies at the national level. Manufacturers must submit any PAS at the same time as they make their submission to the SMC for review. The PASAG evaluates and issues a recommendation on the proposed PAS to the SMC for consideration in conjunction with the manufacturer's submission to the SMC. For medicines intended to treat terminal or orphan diseases, if the NDC recommendation is "not recommended", the company has the option to submit a PAS at that time, or to modify the current PAS. Submission of a PAS is a necessary condition for entry into the ultra-orphan pathway[174].

NHS Scotland provides for two types of PASs: simple discount schemes and complex schemes. A simple discount scheme involves a discount on the NHS list price that is applied at the point of billing when supplied through secondary/tertiary care, home care or a third party; and a retrospective confidential rebate for any supply in primary care (community pharmacies, dispensing doctors and prisons)[188].

As part of single discount schemes, the discount or rebate is applied to all purchases of the medicine during the life of the PAS and individual patients do not need to be identified and tracked. Single discount schemes are the preferred type of scheme within the NHS in Scotland as they do not impose any significant additional burden on the NHS or pharmaceutical companies[188].

Complex schemes include all other types of PASs, such as reimbursement (when the medicine is provided through specialist doctors/hospital-based or home-based care), therapies provided at zero cost, dose/expenditure limitation, or outcome-based systems (based on patients' response to treatment)[188].

In Scotland, the NHS has three funds in place to cover certain diseases that have a high financial impact on the different health boards in the country. The first of these funds was approved in 2018 to fund ultra-orphan pathologies and as of a 2020 reform, it also funds a small amount of medicines for extremely rare conditions that have been accepted by SMC outside of the new process for ultra-orphan medicines[189]. Another fund is used to provide the necessary funding to support the acquisition of medicines indicated for inherited blood diseases such as haemophilia. Finally, SMC uses a fund to finance inherited metabolic diseases (IMDs), which include rare diseases such as Gaucher disease and Fabry disease[190].

In addition to these three funds, since 2013 Scotland has had a Rare Diseases Medicines Fund, for diseases with a prevalence of less than **1/2000** inhabitants. Since 2014, this fund has been called the New Medicines Fund and finances orphan, ultra-orphan and end-of-life medicines. By 2021, the fund has funding of £**50** million (approximately €**58.9** million). The funding for this fund comes from agreements signed between the pharmaceutical industry and the UK government (VPAS)[191].

To support the monitoring of therapies dispensed in Scotland, the Hospital Medicines Utilisation Database (HMUD) was established in 2007 to provide NHS staff with access to information to support the assessment and monitoring of the cost and clinical effectiveness of medicines used in hospital. Information on medicines is available by different pharmaceutical preparations, which can be aggregated by pharmaceutical substance or therapeutic class BNF or ATC. This application collects more than **1.1** million entries each year and collects anonymised patient data. Access to HMUD data is only available to authorised healthcare staff and the NHS does not publish any data to enable analysis of this database[192].

…TO BE HIGHLIGHTED IN SCOTLAND

- ✔ *Using horizon scanning to anticipate future new therapies*
- ✔ *Orderly process with participation of different actors with voice, but without vote*
- ✔ *Specification of the cost-effectiveness threshold modifiers*
- ✔ *Model for access to therapies for ultra-rare diseases focused on the value shown in actual clinical practice*

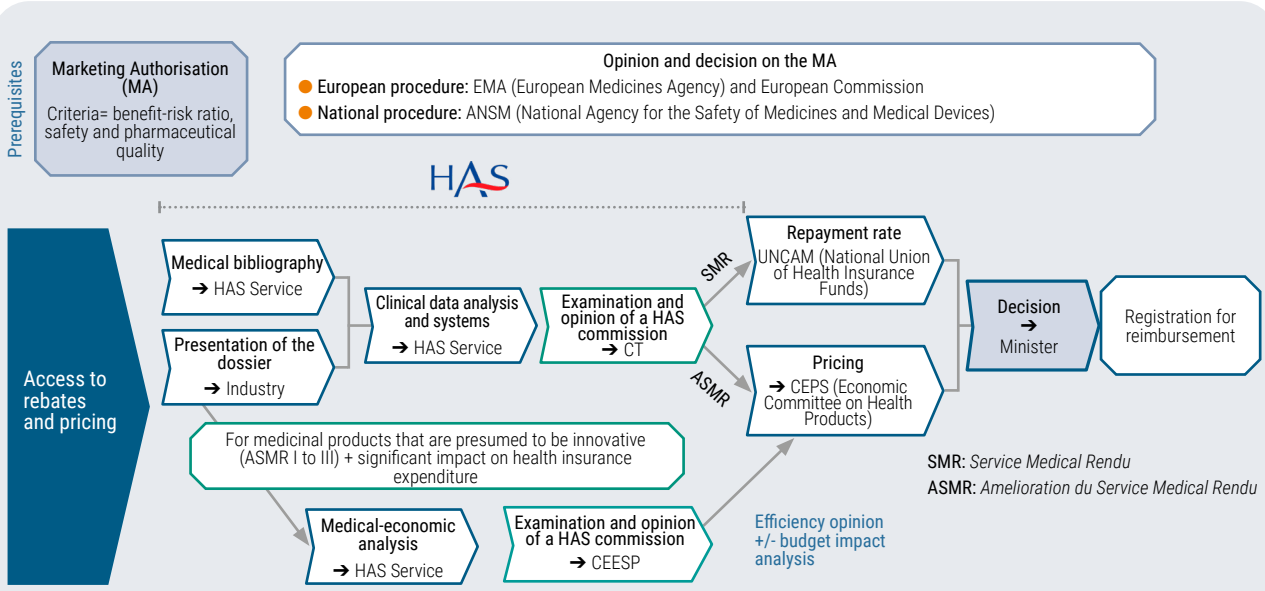
France

The assessment, pricing and funding system in France is the responsibility of the *Haute Autorité Santé* (HAS), which is the independent scientific public authority in charge of carrying out the assessment of health care procedures or services and contributing, through its opinions, to the preparation of decisions on the registration and funding by the health insurance system of all health technologies (health products, procedures or services), as well as their specific reimbursement conditions[193]. In general, this assessment begins when the medicinal product is granted marketing authorisation in France by any of the established centralised, national, decentralised or mutual recognition procedures[194]. To carry out these tasks, HAS has a budget of more than **55** million euros and a staff of **415** employees[195]. The French health system consists of compulsory insurance covering hospital care and treatment, outpatient care and medicines on the reimbursable lists[196].

Actors and process

The three main actors involved in the pricing and reimbursement process are the Transparency Commission (TC), the Economic and Public Health Committee (CEESP) and the Economic Committee on Health Products (CEPS) (**Figure 25**).

FIGURE 25. Pricing and reimbursement process in France



Note: **CEESP:** Economic and Public Health Committee; **TC:** Transparency Commission; **HAS:** "*Haute Autorité Santé*" (High Health Authority)
Source: HAS (2017)[197]

Transparency Commission

The Transparency Commission is a scientific body, composed of physicians, pharmacists and epidemiologists. Its mission is to assess medicinal products that have obtained a marketing authorisation and wish to be included in the list of medicinal products reimbursable by the French national health system[198]. In particular, the TC gives an opinion from a scientific/medical perspective based on the therapeutic benefit provided by the product through the SMR (*Service Médical Rendu*) which is automatically associated with a reimbursement level between **0** and **100%**, depending on five degrees of improvement (ASMR - *Amélioration du Service Médical Rendu*) depending on

the severity of the disease; the efficacy and safety of the drug; the position in the therapeutic strategy; the impact on public health; and the type of treatment: preventive, curative or symptomatic.

The TC is composed of **22** voting members for a period of **3** years, renewable twice, up to a maximum of **9** years. The chairman of the commission is elected by the HAS president, while the remaining **21** members are elected by the HAS council[198,199]. Two of the TC members are elected from among members of patients' and health system users' associations, from a list of **10** names proposed by the National Union of Authorised Associations of Health System Users, a body representing patients and health system users composed of different patient organisations[200].

The TC also has **7** alternates who provide advisory support, **6** of whom are appointed by the HAS and the other is a patient representative, elected in the same way as the two full members of the TC who are responsible for the representation of patients and users of the health system. These alternate members will replace the full members at the end of their term of office.

The TC also has the support of **6** members in an advisory capacity: the Director of Social Security, the Director General of Health, the Director General of Health Care, the Director General of the National Agency for the Safety of Medicines and Health Products, and the directors of the National Health Insurance Fund and the Central Fund of the Agricultural Social Mutual Benefit Society[199]. In turn, the commission leaves open the possibility of including, in an advisory capacity, any qualified person or person it considers to be of special relevance[199].

In addition to the members of the Commission, each review can draw on the expertise of external health professionals who are experts in the subject to be reviewed. These experts prepare a report to be presented and discussed at the meeting with the other members of the Committee. Similarly, patient and user associations can contribute to the assessment of medicines, expressing their opinions using questionnaires made available by the HAS. The HAS can also directly contact the associations that it considers potentially interested. Contributions from patient organisations are sent to TC members during the review and are published on the HAS website[201].

Economic and Public Health Committee

The Economic and Public Health Committee (CEESP) was created in 2008 following the reform of the law on social security funding and is in charge of[202]:

- Establish and disseminate recommendations and economic opinions on the most efficient care, prescription or management strategies and assess the impact on health insurance expenditure.
- Validate economic studies that put the beneficial effects of health technologies at the same level as the resources mobilised.
- Providing an economic opinion on health care procedures, products and services.

CEESP's objective is to actively contribute through its reports to ensuring that the efficiency or opportunity cost dimension is taken into account both in public decision-making and in the decisions of professionals[202].

CEESP's composition is similar to that of the TC: **22** members with full voting rights for a period of **3** years, renewable twice. Of these, **21** are appointed by the HAS council and one (the chairperson) is appointed by the HAS president, all of them for their competence in the field of health, economic evaluation and public health. Two of the members are elected from among representatives of patient and user associations of the health system[202,203].

As in TC's composition, there are **7** alternates who attend in an advisory capacity, **6** of them with a technical profile due to their expertise in health, economic evaluation and public health and the other is appointed by the HAS from among the patients' associations. These advisors are appointed by the HAS council and will replace the full members. Finally, the CEESP has **6** members who participate in an advisory capacity: the Director of Social Security, the Director General of Health, the Director General of Health Care Supply and the Directors of the National Health Insurance Fund, the Central Fund of the Agricultural Social Mutual Benefit Society and the National Union of Health Insurance Funds[202,203].

The HAS may also request a report, as an interested party, from associations that it identifies as being able to provide useful elements for the assessment. These contributions are sent to CEESP members during the review and are taken into account in the review of the dossier[204].

The criteria on which the TC's and CEESP's decision is based, the number of meetings, the date of the meetings, as well as the names and positions of the different members of the commission are public. The minutes of the meetings are also published on the official HAS website[198,202].

Economic Committee for Health Products

Finally, the Economic Committee for Health Products (CEPS) is primarily responsible for setting the prices of medicines covered by compulsory health insurance. It is an inter-ministerial body under the joint authority of the ministers responsible for Health, Social Security and Economy and is divided into two sections: the medicines section and the medical devices section[205].

CEESP's decisions are taken by consensus, in accordance with the guidelines it receives publicly from the ministers, and under the control of the administrative judge. The Committee implements the guidelines it receives from the relevant ministers regarding the pricing of medicines, cost control and financial regulation of the market. Prices or tariffs are preferably set by means of agreements concluded with the companies that market the products or, in the case of certain medical devices, with the professional organisations that represent them[205].

To carry out this action, the committee may enter into agreements with companies on the price of medicines and their evolution, discounts and/or commitments on the appropriate use of medicines and sales volumes[205].

CESP consists of the following **11** members[206,207]:

- A president and two vice-presidents, one responsible for medicinal products and the other for medical devices, appointed for a period of three years by joint order of the ministers of social security, health and economy.
- Director of Social Security.
- Director-General for Health or his representative.
- Director-General for Competition, Consumer Affairs and Fraud Control.
- General Manager of companies.
- Three representatives of the national health insurance bodies appointed by the board of directors of the National Union of Health Insurance Funds.

- A representative appointed by the board of the National Union of Complementary Health Insurance Organisations.

The chairman seeks the agreement of the committee members on the dossiers submitted to him. In the event of disagreement, decisions of the committee are taken by a simple majority of the members present and in the event of a tie vote, the chairman has a casting vote[206].

In general, the drug assessment process has a stipulated duration of **90** days, while the price setting or negotiation process by CEPS has a maximum duration of **90** days. Thus, the assessment and pricing processes for a medicine in France lasts a maximum of **180** days, from the time the company submits the dossier until the final price is determined[208].

All agents participating in the different committees and commissions must carry out an exercise in transparency and are obliged to make a public declaration of interests to demonstrate the impartiality of those involved in decision-making by analysing the conflicts of interest declared in relation to the files examined or the functions performed[205].

In terms of other routes of access to medicines, France has a fast-track for two different cases: the case of pre-marketing authorisation submissions and for innovative medicines. France refers to innovative medicines as those that meet the following criteria[209]:

- A new way of managing the disease either by the novelty of the therapeutic class or by its mechanism of action.
- The medicinal product is likely to provide a clinically significant and relevant advance over standard clinical practice.
- Fulfils an unmet need.

For medicinal products examined under the centralised procedure and in the case of submission prior to marketing authorisation, it is possible to start an early submission procedure for an application for registration prior to the granting of the marketing authorisation, as soon as a favourable opinion is received from the Committee for Medicinal Products for Human Use (CHMP). In the case of mutual recognition, this pre-submission can take place as soon as the draft summary of product characteristics is available[209].

Documentation

Because the evaluation process for medicinal products in France is divided between clinical and economic, the documentation provided is different, depending on the committee to which it is addressed.

Documentation for clinical assessment

The clinical part assessment dossier should include: a letter of application addressed to the HAS, with copies addressed to the Ministers of Social Security and Health, a model dossier with the characteristics of the medicinal product and the marketing authorisation document[210].

The dossier should be compiled with all information on the medicinal product that is relevant to the assessment[210]:

- Reason for assessment: stating the reasons for the assessment by the HAS, either as a new registration, an extension of the indication or a reassessment as new data becomes available.
- Indication: if it is a new registration, all indications included in the marketing authorisation should be included. If it is a reassessment, specify whether it is limited in scope with respect to the marketing authorisation (e.g. a new subpopulation).
- Level of SMR and ASMR requested for each of the indications.
- Target population.
- Medical necessity: describing the context of the disease, prevalence/incidence and current therapeutic management.
- Relevant comparators: the chosen comparator should be clinically relevant, whether pharmacological or not.
- Information on the internationally reviewed indication: wording on the FDA authorisation and, if applicable, information on the ongoing review if it is being conducted in the following countries: United Kingdom, Germany, Netherlands, Belgium, Spain or Italy.
- Efficiency: efficiency data explaining the main details of the clinical trial(s).
- Quality of life data: should be presented in the same way as efficacy data, detailing, in addition, the type of comparison made and the measurement scale, argumentation of the minimal clinically relevant differences, among others.

Documentation for economic evaluation

As in the case of clinical assessment, the HAS provides laboratories with a document that serves as a guide for the preparation of economic evaluations and includes the main CEESP requirements for laboratories. This document also contains **27** recommendations grouped into **5** different areas, ranging from the time horizon and the perspective used to the method of evaluating indirect costs, among others. Among others, the economic evaluation dossier defines the following elements to be included (**Table 15**)[211]:

TABLE 15. HAS guidelines for the preparation of an economic evaluation in France

METHOD TO BE USED
● Cost-utility or cost-effectiveness, depending on whether or not quality of life is an important variable for the intervention being evaluated.
● The HAS makes explicit that there are other ways to analyse efficiency to aid decision-making, such as through cost-consequence analysis and Multi-Criteria Decision Analysis (MCDA), provided that international methodological recommendations and good practices are followed[212–214].
PERSPECTIVE
● The chosen perspective is the collective perspective, which is defined by all the people or institutions involved in the production of global care, whether they belong to the domestic sphere (users and their informal carers), the health sphere (producers of care) or the medical-social sphere.
● When the collective perspective cannot be used, it is acceptable to choose a perspective restricted to the health system (health system perspective). It differs from the collective perspective in that it is only concerned with the production of health care, whereas the collective perspective is concerned with the production of integrated care for the individual.
● The use of social perspective is not recommended.
TIME HORIZON
● The lifetime of the patient or a shorter time horizon than life expectancy may be chosen if health outcomes are no longer observed beyond a certain period of time or if the uncertainty inherent in extrapolating observed data across the life span is not acceptable.
DISCOUNT RATE
● It varies between **2.5%** for studies with a time horizon of less than 30 years, gradually reducing to a minimum of **1,5%**.
RESULTS
● In the reference case, researchers must systematically identify, measure, assess and report on all relevant resources from the payer's perspective.
QUALITY OF LIFE
● Measured by the EQ-5D questionnaire whenever possible.
INCERTIDUMBRE
● Inclusion of a probabilistic sensitivity analysis, based on a second-order Monte Carlo simulation, and deterministic sensitivity analysis that identifies the parameters (or combinations of parameters) that most influence the results of the assessment.

Note: EQ-5D: EuroQol-5D **Source:** prepared by the authors based on HAS (2020)[211]

Clinical assessment

For new medicines to be reimbursed in France, the Transparency Commission conducts a careful review of the degree of clinical benefit compared to available treatments, which ultimately determines, among other factors, the maximum price of the medicines and the reimbursement status for the whole country. The TC considers the level of innovation that the medicine brings to the market, as well as its importance for the health of French citizens. The improvement of the actual clinical benefit of the medicine (*amélioration du service médical rendu,* ASMR) is compared to the current standard of care and is assigned a **5**-level rating (Table 16)[198,215].

TABLE 16. Levels of categorisation of actual clinical benefit (ASMR) in France

LEVEL	DEFINITION	PRICING IMPLICATIONS
I	Innovative product with substantial (life-saving) therapeutic benefit. Reserved for very few medicines that have been shown to have an effect on mortality in a serious disease.	Faster access (price notification instead of negotiation) and price consistency with other European countries with comparable total market size (Italy, Spain, Germany and the UK).
II	Significant improvement in terms of efficacy and/or reduction of adverse effects (changing the course of the disease).	Faster access (price notification instead of negotiation) and price consistency with other European countries with comparable total market size (Italy, Spain, Germany and the UK).
III	Moderate improvement in terms of therapeutic efficacy and/or utility (makes a substantial therapeutic contribution over existing therapies).	Faster access (price notification instead of negotiation) and price consistency with other European countries with a comparable total market size (Italy, Spain, Germany and the UK).

LEVEL	DEFINITION	PRICING IMPLICATIONS
IV	Minor improvement in terms of efficacy and/or symptom reduction.	If the new medicine targets the same population as the comparator medicine, the best possible outcome is a price equal to the comparator. The price may be higher than the comparator if the new medicine has a better effect in a narrower population.
V	No improvement over existing options, but can still be recommended for reimbursement (e.g. generics and me-toodrugs).	The medicine can only be included if the costs are lower than the cost saving comparators for the French National Health Insurance (NHI). Discounted prices for the new medicine are typical.

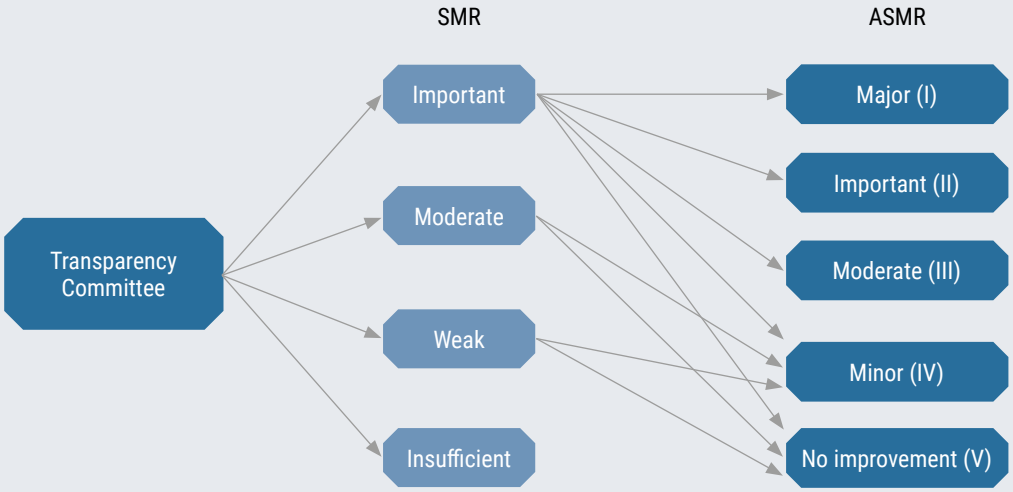
Fuente: prepared by the authors based on Rézumat (2013)[216], Código de la Seguridad Social (2019)[217], GlobalHealthPR (2020)[215] y Vogler (2020)[218]

The TC also determines the clinical benefit of the medicine (*Service médical rendu*, SMR), which allows to assess the validity of the reimbursement[201]. The SMR clinical benefit is defined by the following conditions[197]:

- Severity of the condition
- Efficacy (amount of effect) and adverse effects of the medicine
- Preventive, curative or symptomatic nature of the medicinal product
- Position in the therapeutic strategy, in relation to other available therapies
- Public health interest: severity of the disease, prevalence, medical need and response, impact on quality of life, impact on morbidity and mortality and on the organisation of care

The ASMR and SMR ratings described above are determined at the same time[215]. Although the two ratings are independent, there is a relationship between the level of SMR and ASMR (**Figure 26**)[219].

FIGURE 26. Relationship between SMR level and ASMR, France



Note: ASMR: "*Amélioration du Service Médical Rendu*" (actual clinical benefit); **SMR:** "*Service Médical Rendu*" (clinical benefit of the medicinal product).
Source: BioPharma (2019)[219]

Meetings with laboratories with medicines under review are held in sessions where all the TC's doubts are grouped together and defined annually for better visibility of the process. This organisation establishes a period of **45** days to listen to the laboratory that requests it[210].

In its opinions on medicinal products, the Transparency Commission may request additional studies called post-registration studies. In most cases, these are "real-life" studies, i.e. studies conducted in the context of routine patient management to describe the use of the medicine in current practice and to assess its clinical benefit and adverse effects after marketing[201].

In view of the problems associated with delays in market access for medicinal products, the Transparency Commission has established early assessment methods to allow manufacturers to submit their applications as early as possible and to reduce the time between the approval of the medicinal product and the opinion of the commission. These procedures are initiated by the laboratories and can be of two types: early assessment for "medicinal products that are presumed to be innovative" and for any other medicinal product: pre-submission of a dossier for assessment[210].

Medicines that are presumed to be innovative:

The pharmaceutical company which operates it can, as soon as the marketing authorisation application has been submitted to the EMA and before the positive opinion of the CHMP, submit an application for registration to the Commission. This early submission does not exempt pharmaceutical companies from formally submitting a price and funding application after the marketing authorisation has been granted and notifying the French authorities of the marketing authorisation, which is the starting point of the regulatory period[209].

The Transparency Commission defines a medicinal product as innovative when it fulfils the following three conditions[209]:

1. The medicine represents a new way of treating a disease, either a new therapeutic class or a new mechanism of action.

2. It is likely that, on the basis of the results announced by the pharmaceutical company, the medicinal product will provide clinically relevant progress, relative to the means available, in the treatment of the patients concerned by the indication, either in terms of efficacy, tolerability or access to therapy. This assessment in no way prejudges the Commission's subsequent opinion on the SMRs or ASMRs of this medicinal product.

3. The medicinal product satisfies, in this indication, a need that is not yet covered or poorly covered, in particular if it concerns a specific population, in the absence of an alternative, either by a medicinal product with a marketing authorisation in an indication corresponding to the need, or by any other therapeutic alternative.

The Commission is committed to reply to the laboratory within one month of receipt of the request[209].

Prior submission of a dossier:

This procedure allows the laboratory to submit an application for registration prior to marketing authorisation. For medicinal products examined through the centralised procedure, it is possible to submit the dossier prior to the marketing authorisation and as soon as a favourable opinion is received from the CHMP. This pre-submission does not exempt the company from formally submitting an application for reimbursement after the marketing authorisation[209].

Economic evaluation

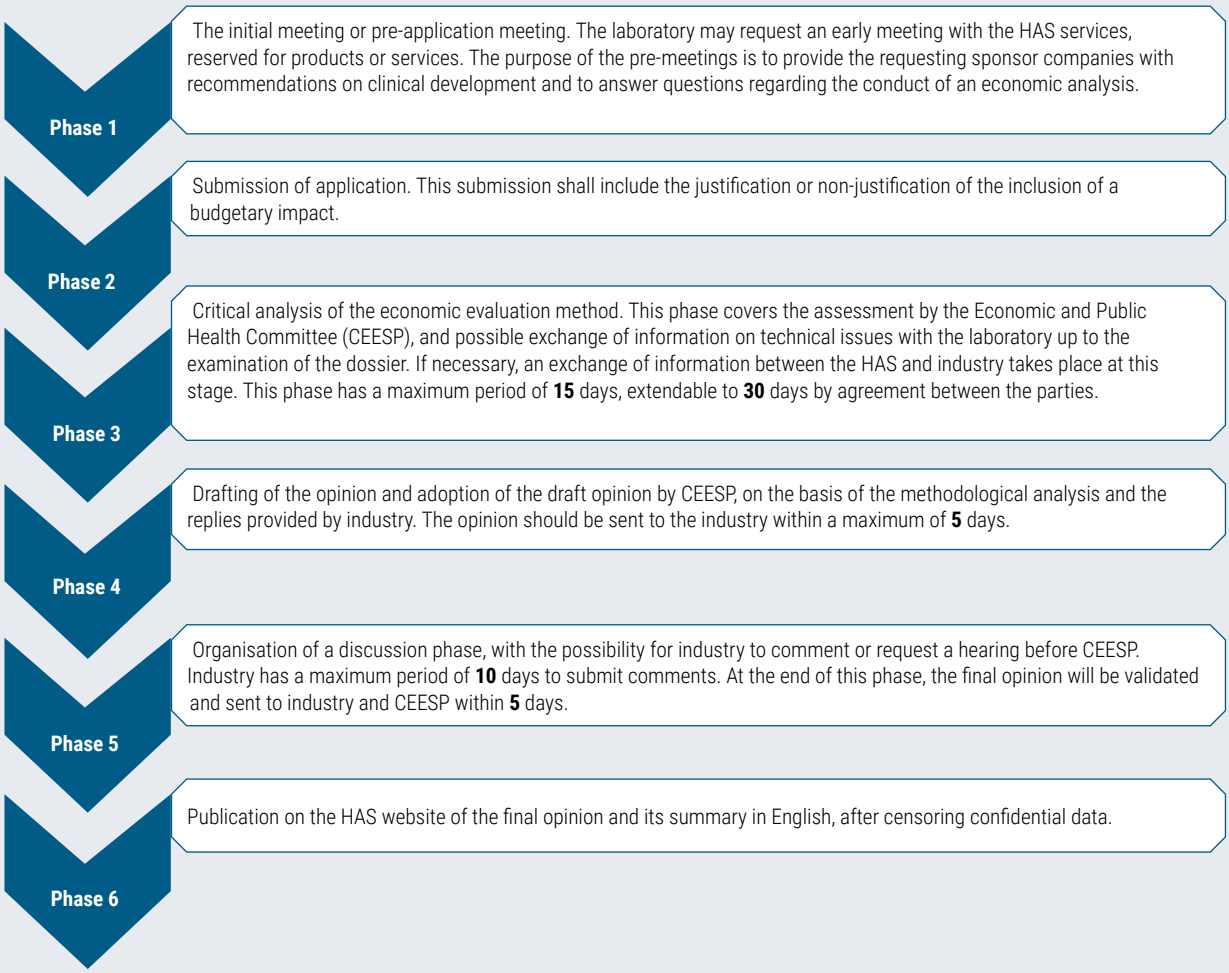
At the same time as the clinical assessment, the sponsor laboratory can submit information on the economic evaluation. In France, the submission of an economic evaluation is mandatory when two cumulative conditions are fulfilled[220]:

a) The claim (or confirmation) of a level I, II or III ASMR.

b) A "*significant impact of the product on health insurance expenditure, taking into account its impact on the organisation of care, professional practices or patient management methods and, where appropriate, its price*". The impact is defined as significant when the manufacturer claims that its product has an impact on the organisation of care, professional practices or patient care conditions or when the annual turnover of the product for all indications combined is greater than or equal to EUR 20 million (taking into account the second full year of marketing).

The economic evaluation process consists of the following phases (**Figure 27**)[221]:

FIGURE 27. Phases of the HAS economic evaluation process in France



Note: HAS: *"Haute Autorité Santé"* (High Health Authority); **CEESP:** Economic and Public Health Committee; **CEPS:** Economic Committee for Health Products

Source: prepared by the authors based on HAS (2020)[221]

The type of evaluation preferred by HAS for economic evaluation is cost-effectiveness if quality of life is not a determinant of the disease and cost-utility if the disease does significantly affect patients' quality of life. If the outcomes of the compared interventions are shown to be equivalent, the benchmark analysis is cost minimisation[211].

If the turnover of the product submitted for economic evaluation in the second year of marketing is EUR **50** million or more, the manufacturer is in turn obliged to submit a budget impact model.

Involvement of patients and scientific societies

Patients' associations are actively involved in the medicines assessment process in France, as three of the members of the TC and the CEESP are patient representatives. Within each committee, two of the patient representatives are full members, with speaking and voting rights, while the other patient representative participates in an advisory capacity, as an alternate[200,202,203].

Patient associations are also involved in the assessment of medicines through questionnaires provided by HAS, which allow patients to express their concerns about their pathology and expectations about treatments[201]. This input is provided by the associations and not by individual patients[222].

P&R decision elements

One of the elements influencing the reimbursement decision in France is the level of SMR obtained for the medicine. The SMR provides the *Union Nationale des Caisses d'Assurance Maladie* (UNCAM) and the System with scientific and clinical information to justify whether or not a medicine should be covered by national solidarity[197]. The relationship between the level of SMR and the reimbursement rate applied to the retail price is shown in **Table 17**[197].

TABLE 17. SMR and reimbursement rate ratio in France

CLINICAL BENEFIT SMR	REIMBURSEMENT RATE
Important	65%
Moderate	30%
Low	15%
Insufficient	Non-refundable

Note: SMR: *"Service Médical Rendu"* (clinical benefit of the medicinal product)
Source: prepared by the authors based on HAS (2017)[197]

Cost-effectiveness threshold

Regarding the use of a cost-effectiveness threshold, although the CEEPS takes into account cost-utility criteria, there is no explicit incremental cost-effectiveness ratio threshold for the approval of medicines in France[223]. However, analysing the drug evaluations conducted between 2014 and 2018 for oncology drugs and ODs, it was observed that, until 2015, the ICER was less than €**100,000**/QALY, while this figure peaked at almost €**600,000**/QALY in 2016 and 2017. This variation stems from the increased entry of medicines that were approved with a particularly high ICER, such as a medicine for spinal muscular atrophy, approved with an ICER of €**930,000** for the type I indication and €**2,660,000** for type II. The HAS assessed this drug with an ASMR of III for both types of the disease[224].

Budgetary impact

Likewise, if sales in the second year of marketing are estimated to be greater than or equal to €**50** million, the manufacturer is required to submit a budget impact model. Medicines that do not reach this figure are not required to present a budget impact, although the HAS recommends it[225]. This information supports the decisions of the CESP and is regulated by the HAS methodological guidelines. These guidelines stipulate that budget impact results should be presented in terms of expenditure per scenario (of the tested medicine and the comparator) and the difference in expenditure between the two scenarios compared.

They should be expressed in monetary units and, if possible, in terms of resources saved (and/or events avoided). The recommended cost perspective is that of compulsory health insurance, with the possibility of using other perspectives, as long as it is duly justified. Likewise, the HAS recommends using a time horizon of between **3** and **5** years. Regarding the target population, the HAS indicates that all indications for the evaluated therapy should be defined in terms of the target population and the population actually reached by the medicine[226].

Support criteria

On the basis of the final pricing decision, and based on the clinical and economic evaluation, the CEPS establishes the price of the medicine taking into account at least one of the following criteria[217]:

a) The age of the registration of the associated product or service

b) The prices of comparable products and services and the discounts applicable to the product or service

c) The purchase price of the products and services registered by health care establishments or wholesale or retail distributors, taking into account discounts, rebates and commercial advantages

d) The net cost of discounts for compulsory health insurance for the product or service in question and other products or services used sequentially

e) The existence of lower tariffs, prices or treatment costs, after deduction of the various discounts or taxes in force, in other European countries with a comparable total market size

f) Expected or recorded sales volumes of products or services

g) Amounts of products or services reimbursed for planned or observed compulsory health insurance

h) The product or service belongs to a class other than the coverage classes

Since 2015, with the signing of a framework agreement, it has been specified that medicines that have been granted an ASMR level I to III, and those that have obtained an ASMR IV against a comparator that has itself recently obtained an ASMR I to III, benefit from the European price guarantee. Initially applied for a period of five years, this guarantee ensures that the nominal price of the manufacturer's product in France is not lower than the lowest price in the four comparable markets in Europe, i.e. Germany, the United Kingdom, Italy and Spain[224].

External reference prices

The final price decision is also influenced by the use of international reference prices. This is done by comparing the price with the price set by four countries: Germany, Italy, Spain and the UK. The funded price must not be lower than the lowest price for that medicine in the reference countries. The price data are not weighted by volume, nor by economic data (such as purchasing power parities).

Financial agreements and their monitoring

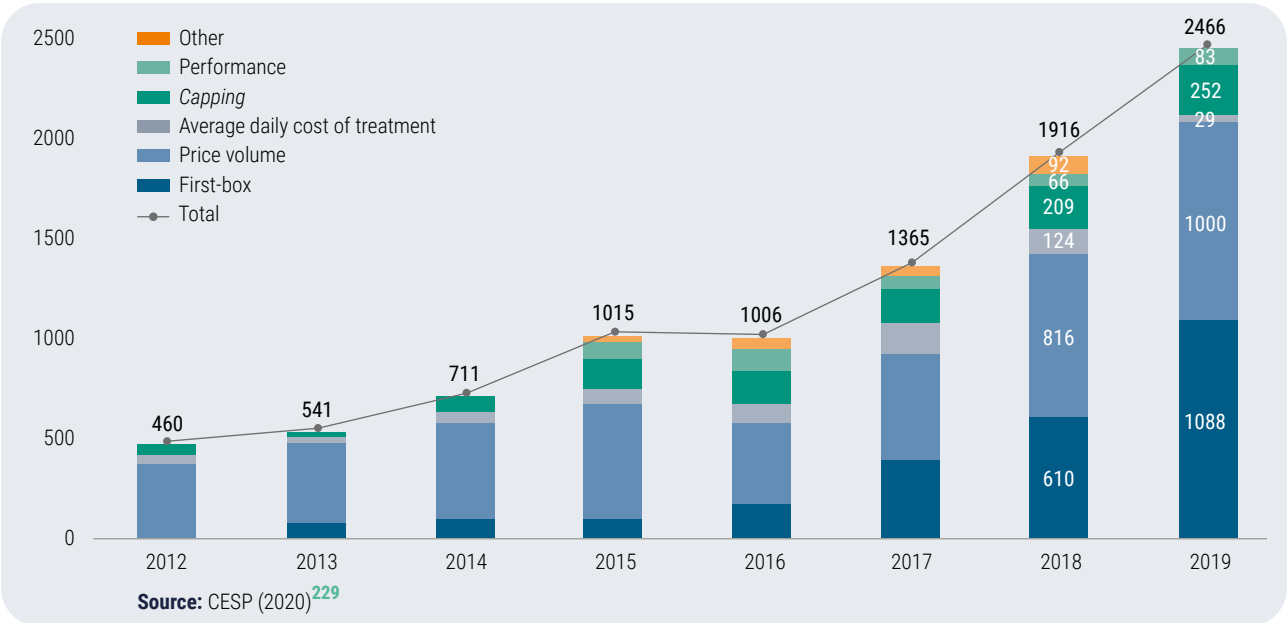
The French system uses different financial formulas for medicines depending on the level of ASMR achieved. The main financial formulas are the fixed rebates and the expenditure ceiling[227,228]. For example, the majority of orphan drugs (ODs) approved up to 2017 were subject to expenditure ceilings (**84%**) and **67%** of oncology drugs were funded under simple rebate agreements[228].

According to the different financial formulas carried out during 2019, **262** therapies were linked to a discount contract. Of these **262** contracts, **70%** resulted in the activation of the discount clause (**185** contracts), the rest did not[229].

Considering the total amount of rebates received by type of agreement, price/volume agreements account for **41%** of the rebates. On the other hand, so-called "first box" discounts account for **44%** of the total. Daily cost of treatment, per dose or limiting the number of units per delivery clauses account for **1%** of the total, and capping agreements account for **10%**. Finally, performance clauses, which aim to confirm the performance obtained during clinical trials through real studies or based on real-life performance indicators, account for **3%** of gross rebates (before deduction of rebate credits) (**Figure 28**)[229].

Since 2012, the structure of discount categories has changed. The weight of first-box discounts has increased from **3%** to **44%** (**+12** points in 2019 compared to 2018), while the weight of volume price clauses has fallen from **80%** to **41%** between 2012 and 2019[229].

FIGURE 28. Gross rebates by type of agreement in millions of euros, France (2019)



Source: CESP (2020)[229]

France does not have any kind of predetermined mechanism for monitoring the various results-based agreements. In signing these agreements, the company and CEPS define the indicators that will allow real-life performance to be assessed, the methods and timeframe for carrying out the assessment, as well as the conditions and limits of price changes in relation to the observed performance. The performance assessment can be based on an observational study or, alternatively, on the monitoring of indicators that can be obtained from registries, market data, medico-administrative databases or any other source deemed appropriate[229].

Examples of the heterogeneity of the databases used to monitor approved therapies through outcome-based agreements can be found in the approval of Sovaldi®, which was monitored using the Hepather database of the "*Agence Nationale de Recherche sur le SIDA et la Hepatitis Virale*" (ANRS)[230], or the approval of Imnovid®, for which an ad hoc study was launched to collect data[231]. Similarly, for other contracts, monitoring has been carried out on the basis of French government databases, such as the *Programme de Medicalisation des Systèmes d'Information* (PMSI)[231]. Under the PMSI, every stay in a health establishment, public or private, is subject to a systematic and minimal collection of administrative and medical information that is mainly used for the financing of health establishments[232].

Finally, France has developed a new action plan on pharmacological innovations in 2020 to promote rapid patient access to the latest innovations, while ensuring the financial capacity of the health system. This new model consists of **6** action measures (**Figure 29**)[233]:

FIGURE 29. HAS action plan for innovation in France

1. **Giving conditional opinions**
   Launch of a temporary conditional reimbursement mechanism for certain medicines. The timeframe for eliminating uncertainties will not exceed **3** years.
2. **Real-life outcome monitoring of medicines**
   Conditional assessments involve extensive monitoring of real-life data. The HAS recommends strengthening the whole process, working with the competent authorities to ensure that the data are systematically archived and used.
3. **Strengthening the agility of the HAS to better support innovation**
   This measure is composed of **4** strands: focusing on high added-value assessments, conducting early meetings to support clinical developments, promoting fast-tracking procedures and improving collective efficiency.
4. **Systematically involve patients and users**
   The involvement of patients in the evaluation is done in two ways: by increasing the voting presence of patients' and users' associations in the TC and by opening up the possibility for them to provide reports to the other members.
5. **Increasing transparency**
   Both in evaluation times, with monitoring indicators on the HAS website, and in the value of real-life studies and their results.
6. **Strengthening European cooperation to share knowledge**
   Increasing investment in the EUnetHTA project that will enable European collaboration in the field of health technology assessment.

Note: EUnetHTA: *European Network for Health Technology Assessment*; TC: Transparency Commission; HAS: *"Haute Autorité Santé"* (High Health Authority). **Source:** prepared by the authors based on HAS (2020)[233]

...TO BE HIGHLIGHTED IN FRANCE

- ✔ *Smooth communication from the beginning of the process with the industry*
- ✔ *Industry participation in the Pricing Committee*
- ✔ *High degree of transparency, with the publication of conflicts of interest of the members of the Committees/Commissions*
- ✔ *Guarantee of a price no lower than the European price if it provides clinical benefit (ASMR of I-III)*
- ✔ *Explicit consideration of MCDA as an approach to decision support*
- ✔ *Obligation to present a budget impact analysis if expected sales in the second year exceed €50M*
- ✔ *The information on the economic evaluation is provided by the companies and reviewed and assessed by the public evaluator*
- ✔ *Development of a guide to clarify the information to be provided in the economic evaluation part*

England

Due to the UK's exit from the European Union in 2020, the Medicines and Healthcare products Regulatory Agency (MHRA) has made a number of reforms to the marketing authorisation process for medicines, unifying previous procedures with new authorisation formulas[169]:

a) **Reliance on EMA-European Commission decisions.** For a period of two years from 1 January 2021, when determining a marketing authorisation application in England, the MHRA may base its approval decision on the decision taken by the EMA-European Commission[234].

b) **Accelerated assessment in 150 days.** The MHRA establishes a new accelerated national assessment route where a marketing application will be assessed across the UK, and an opinion will be reached within 150 days of the submission of a valid application[235].

c) **Continuous review.** This is a new route for marketing authorisation applications, whereby an applicant for a marketing authorisation submits modules of the authorisation dossier incrementally for pre-assessment by the MHRA rather than as part of a complete consolidated dossier. Continuous review is intended to speed up the development of new medicines by providing regular enhanced regulatory interaction and advice to reduce the risk of late-stage failure[236].

d) **Decentralised mutual recognition procedure.** In this procedure the MHRA can rely on the approval of any EU or European Economic Area (EEA) member state under the EU's decentralised and mutual recognition procedures[237].

Once the drug receives marketing authorisation, the holder can market the drug in England, but local authorities are not obliged to fund the drug until the evaluation process is completed[238].

Actors and process

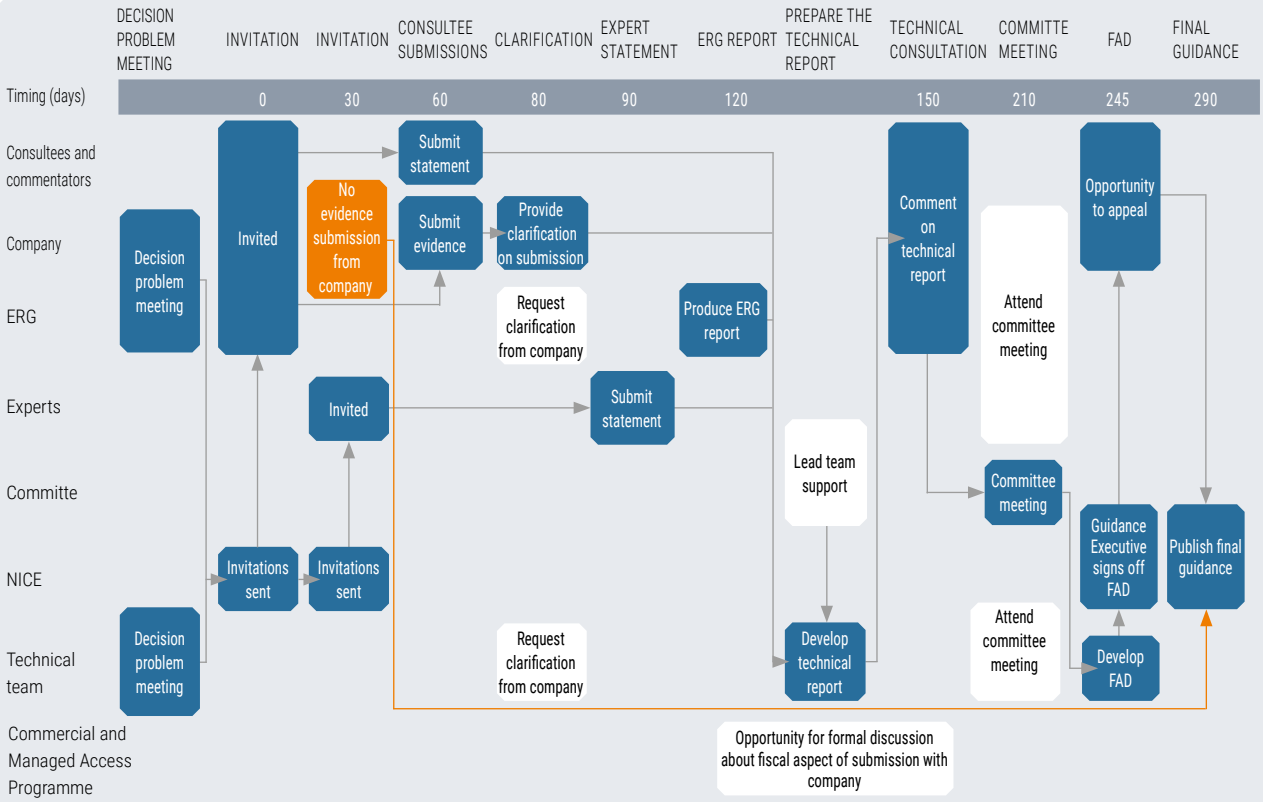
The pricing and reimbursement system in England is a complex process, in which there is no single reimbursement pathway for medicines, nor is there a universal reimbursement list. Primarily, the pricing and reimbursement decision is strongly linked to the recommendations made by the main review body in England, the National Institute for Health and Care Excellence (NICE)[239]. This agency is a non-governmental public body under the UK Department of Health and Social Care, and had a budget for 2019/20 of over €**82** million[240,241]. If NICE makes a positive recommendation, NHS England is obliged to fund the evaluated medicine. In contrast, a negative recommendation by NICE does not make a product ineligible for reimbursement, as the laboratory and the NHS can reach upfront agreements that allow for funding. In this regard, final pricing rests with the NHS and more than **100** clinical commissioning groups[239]. Under the Voluntary Scheme for Branded Medicines Pricing and Access, which came into operation in 2019, NICE automatically reviews all new medicines launched in the UK, or the use of existing medicines for new conditions, unless there is a clear reason not to do so. This is a change from previous practice, where NICE selected which new medicines to review based on their importance to patients and the NHS[242].

NICE has two appraisal processes: the multiple technology appraisal process and the single technology appraisal process (MTA and STA). Although there are differences between the two processes, the principles related to decision-making, assessment methods and decision outcomes are consistent between the two processes[243].

For new medicines, NICE follows a three-stage evaluation process: scoping, assessment and appraisal. In the scoping phase, it determines which specific questions need to be addressed, for example, which diseases and patient groups should be considered and which existing medicines should be used as comparators. In the appraisal phase, NICE assesses the evidence of clinical and cost effectiveness of the available medicine. In the final phase, an appraisal committee decides whether the NHS should fund the new drug, based on factors including the strength of the clinical evidence, the degree of clinical need among patients, the efficiency of the drug (marked by its incremental cost-effectiveness) given its proposed price, and the strength of the economic evaluation[242]. Committee decisions are based on reaching consensus, although if consensus is not reached, a vote is taken and recorded in the minutes of the meeting[244].

In terms of timelines, NICE stipulates that the appraisal process to a final funding decision should not exceed **290** days. The process begins with the identification of new therapies or indications by the National Institute for Health Research (NIHR). The NIHR notifies NICE of new therapies that might be suitable for appraisal. It aims to notify NICE of new medicines in development about **20** months before marketing authorisation and of new indications about **15** months before marketing authorisation. These deadlines are to allow NICE to publish an appraisal (referred to as a "guideline" or "guide" by NICE) as close as possible to the time of product launch (**Figure 30**)[244].

FIGURE 30. Pricing and reimbursement process in England



Note: ERG: Evidence Review Group; FAD: Final Appraisal Document; NICE: National Institute for Health and Care Excellence. **Source:** NICE (2021)[244]

Throughout the whole process, **10** expert groups are involved, whose objectives and composition can be seen in Table 18[244].

TABLE 18. Participants in the evaluation processes in England

Appraisal committee	The appraisal committee considers and discusses the evidence for the therapy to be appraised. NICE recruits committee members through a public call for applications and appoints them for a period of **3** years. The committee consists of **96** members evenly distributed in **4** individual committees. Individual committees usually have **24** voting members, including the chairperson. However, the number may vary depending on the needs of the committee[245]. The committee members are: ● The NHS ● Lay backgrounds (with an understanding of patient and public perspectives on health issues) ● Academia ● Pharmaceutical and medical devices industries Although the committee seeks the views of organisations representing healthcare professionals, patients, carers, companies and government, its advice is independent. Names of committee members are published on the NICE website.
Lead team	A lead team, selected from the committee members at the beginning of each appraisal, assists the NICE team in preparing a technical report to inform the committee. The lead team usually consists of **3** committee members: **1** focuses on clinical effectiveness, **1** on cost-effectiveness and **1** on patient and carer evidence (called the lay lead).

The technical team	The technical team consists of the chair or vice-chair of the committee together with the NICE team, which normally consists of the following: the associate director, the technical adviser and the technical lead. The technical team will be responsible for considering the company evidence submission, Evidence Review Group (ERG) critique and submissions from other consultees and commentators. Its purpose is to identify and explore issues, arrive at preliminary scientific judgements, and advise the appraisal committee in its discussion of the evidence. The technical team will seek input from the lead team, the ERG and experts where appropriate.
Consultees	NICE invites consultees to participate in the appraisal. They include: ● National groups representing patients and carers ● Organisations representing health professionals ● The company that holds, or is expected to hold, the marketing authorisation for medicines, or the equivalent for other therapies ● The department of health and social welfare ● The Welsh Government ● NHS England as the commissioner for specialised services ● Clinical commissioning groups (**2** are randomly selected) Consultees may submit evidence and participate in consultation on the Appraisal Consultation Document (ACD), if produced. All non-company consultees can nominate clinical experts and patient experts to participate in the appraisal. Company consultees can only nominate clinical experts. All consultees have the opportunity to appeal against the final recommendations, or report any factual errors, in the Final Assessment Document (FAD).
Commentators	NICE invites organisations with an interest in the medicine to participate in the appraisal. They include, but are not restricted to: ● Relevant comparator technology companies ● Any relevant National Collaborating Centre (groups commissioned by NICE to develop clinical and social care guidelines) and/or relevant group for public health guidance ● Other related research groups (e.g. Medical Research Council, National Cancer Research Institute) ● Other groups As part of the scoping process, NICE invites commentators to comment on draft remits and draft scopes. Commentators can take part in the consultation on the ACD (if produced), but NICE does not ask them to submit evidence for the appraisal.
Clinical and patient experts	The chair of the appraisal committee selects clinical and patient experts from those nominated by the consultees and commentators. Experts are invited to help clarify questions about the evidence presented and to attend committee meetings. They may be asked to provide advice before, during and after committee meetings.
NHS commissioning experts	NICE invites two NHS commissioning experts from those nominated by NHS England and the clinical commissioning groups to help clarify issues about the submitted evidence. They may be asked to provide advice before, during and after committee meetings about their views and experiences of the technology and the condition from an NHS perspective.
CDF clinical lead	For appraisals of pharmaceutical products for cancer indications, the clinical lead of the Cancer Drugs Fund (CDF) is invited to submit a statement and attend both the public and private parts of appraisal committee meetings.
Evidence Review Group (ERG)	The ERG is an independent (academic) group that reviews the company's evidence submission and may also prepare some additional analysis.
Decision Support Unit (DSU)[246]	Advanced methodological, analytical and other support for NICE and its independent advisory bodies on medicines and medical technology assessment.

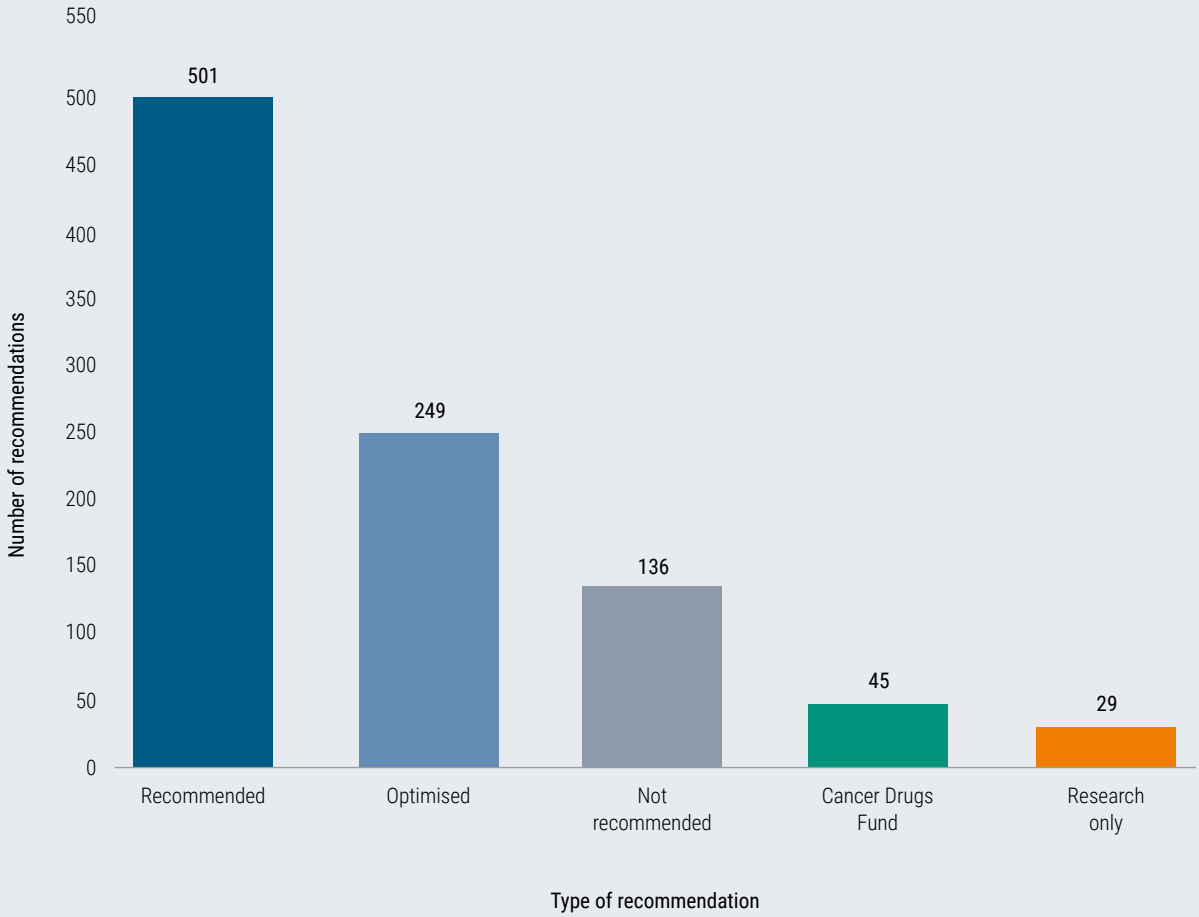
Source: NICE (2021)[247]

Finally, NICE makes a final recommendation for the assessed medicine. Each appraisal may contain more than one recommendation. NICE classifies recommendations at[248]:

- Recommended
- Optimised
- Research only
- Not recommended
- Recommended for use through the Cancer Drugs Fund (CDF)

NICE itself specifies on its website the type of recommendations it has made since 2000, with half of them being simple recommendations (**52%** of the total **960** recommendations made), **26%** optimised recommendations and **14%** non-funding recommendations (**Figure 31**).

FIGURE 31. Recommendations made by NICE's medicines appraisal committees in England (2000-2021)



Source: NICE (2021)[249]

Documentation

With regard to the documentation required for the appraisal, NICE does not directly indicate which comparator is chosen, nor the outcome variables required, nor other elements that are essential when carrying out a clinical appraisal. However, in order to encourage flexibility in the process, and to make it adaptable to the different cases that the appraisal committee will face when assessing new therapies, NICE has created a reference case system, which provides the main specific guidelines that the Institute considers appropriate for the purpose of the appraisal committee (Table 19)[250].

TABLE 19. Summary of the reference case in England

ELEMENT OF HEALTH TECHNOLOGY ASSESSMENT	REFERENCE CASE	DETAILS
Comparator(s)	As indicated in the scoping developed by NICE.	All potentially relevant comparators should be used, taking into account the issues that the Appraisal Committee is likely to consider in selecting the most appropriate comparator.
Perspective on outcomes	All direct health effects, whether for patients or, when relevant, carers.	For the reference case, the perspective on outcomes should be all direct health effects, whether for patients or others. The perspective adopted on costs should be that of the NHS and personal and social services.
Perspective on costs	NHS and PSS.	The reference case perspective on costs is that of the NHS and personal social services. Productivity costs are not included in either the reference or non-reference case analyses.
Type of economic evaluation	Cost-utility analysis with incremental analysis.	For the reference case, cost-effectiveness (specifically cost-utility) analysis is the preferred form of economic evaluation. This seeks to establish whether differences in expected costs between options can be justified in terms of changes in expected health effects. Health effects should be expressed in terms of QALYs.
Time horizon	Long enough to reflect any significant differences in cost or performance between the technologies being compared.	The time horizon for estimating clinical effectiveness should be sufficiently long to reflect all important differences in costs or outcomes between the technologies being compared.
Synthesis of evidence on health effects	Based on systematic review.	Analysis of clinical effectiveness must be based on data from all relevant studies of the best available quality and should consider the range of typical patients, normal clinical circumstances, clinically relevant outcomes, comparison with relevant comparators, and measures of both relative and absolute effectiveness with appropriate measures of uncertainty. NICE has a preference for RCTs that directly compare the intervention with one or more relevant comparators and these should be presented in the reference case analysis if available.
Measuring and valuing health effects	Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of health-related quality of life in adults.	For the reference case, the measurement of changes in health-related quality of life must be reported directly from patients and the usefulness of these changes should be based on public preferences using a choice-based approach. The EQ-5D is the preferred measure of health-related quality of life in adults.
Source of data for measurement of health-related quality of life	Reported directly by patients and/or carers.	Health-related quality of life, or changes in health-related quality of life, should be measured directly by patients. Where it is not possible to obtain measures of health-related quality of life directly from patients, data should be obtained from the person acting as their caregiver, in preference to the healthcare professional.
Source of preference data for valuation of changes in health-related quality of life	Representative sample of the UK population.	The assessment of health-related quality of life measured in patients (or by their carers) should be based on an assessment of the public preferences of a representative sample of the UK population using a choice-based method.

HEALTH TECHNOLOGY ASSESSMENT ELEMENT	REFERENCE CASE	DETAILS
Evidence on resource use and costs	Costs should be related to NHS and PSS resources and should be valued using the relevant prices for the NHS and PSS.	For the reference case, costs should relate to resources under the control of the NHS and personal and social services. These resources should be valued using relevant prices for NHS and personal and social services. Evidence should be provided to demonstrate that data on resource use and costs have been systematically identified.
Discounting	Same annual discount rate (**3.5%**) for both costs and health effects.	Cost-effectiveness results should reflect the present value of the cumulative flow of costs and benefits over the time horizon of the analysis. For the reference case, the same annual discount rate should be used for both costs and benefits (currently **3.5%**).

Note: **QALYs**: quality-adjusted life years; **RCTs**: randomized controlled trials; **EQ-5D:** EuroQol-5D; **NHS:** National Health Service; **PSS:** Personal Social Services

Source: adapted from NICE (2020)[250]

Any of the consulted assessors may submit an appeal which may be considered at an oral hearing or in writing. Consultees have **15** working days to submit an appeal from the day the final draft of the guidance is sent to consultees and commentators. NICE's Vice President reviews the appeals submitted and considers whether they fall within the grounds of appeal. If they do, and are "debatable", the vice-chair will decide whether an oral or written appeal hearing will take place. After this scrutiny process, a panel is convened to hear the appeal. The panel is made up of a group of people approved by the Secretary of State for Health and Social Care to hear appeals. Each appeal panel consists of five members, four of whom are independent of NICE[251].

Clinical assessment

Due to the characteristics of the NICE appraisal process, there is no separate clinical appraisal and economic evaluation, but rather the two go together throughout the entire process.

During the scoping part, NICE identifies the main health outcome measures that will be relevant for the estimation of clinical effectiveness. These measures are appropriate to verify health benefits and adverse effects that are important for patients. Clinical outcome measures are generally quantified through the impact on patients' quality of life or survival, which in turn translates into QALY gains[252].

The assessment of clinical efficacy requires quantification of the effect of therapy and relevant comparators on survival, disease progression and health-related quality of life, so that it can be used to estimate QALYs. This QALY gain is used to assess the cost-effectiveness of therapy, based on the incremental cost-effectiveness ratio (ICER)[253]. In its guidelines for evaluation, the British agency indicates that the EQ-5D is the preferred measure of utilities derived from health-related quality of life[250].

The assessment of health-related quality of life measured in patients (or by their carers) should be based on an assessment of the public preferences of a representative sample of the UK population. In some circumstances, the EQ-5D may not be the most appropriate. To argue that the EQ-5D is inappropriate, qualitative empirical evidence must be provided on the lack of validity of the EQ-5D, demonstrating that key dimensions of health are missing[250].

Orphan drug assessment

When assessing specialised technologies, NICE may deviate from its standard methodology and apply parallel assessment methods, such as Highly Specialised Technology Assessment (HST). These medicines are indicated for rare and very specific diseases.

This assessment process is only available for medicines that meet the following conditions[239]:

- The target patient group is either distinct for clinical reasons or small enough for treatment to be concentrated in a few NHS centres
- The disease is chronic and highly disabling
- The drug has the potential to be used throughout the patient's life

The aim of this type of appraisal is to notify the Department of Health and Social Care of key, new and emerging health technologies that may need to be referred to NICE within the following timeframes[254]:

- New medicines, **20** months after marketing authorisation
- New indications, **15** months after marketing authorisation

Economic evaluation

In England's price and reimbursement system, it is essential that the company concerned submit an economic evaluation in order to be able to make an accurate assessment of the ICER of the therapy being reviewed.

The types of economic analysis most commonly accepted by NICE are[255]:

- Cost minimisation analysis: a determination of the lowest costs among alternatives that are assumed to produce equivalent results.
- Cost-effectiveness analysis (CEA): a comparison of costs in monetary units with outcomes in non-monetary quantitative units (e.g. reduction in mortality or morbidity).
- Cost-utility analysis (CUA): a form of cost-effectiveness analysis that compares costs in monetary units with outcomes in terms of their utility, usually to the patient, measured in QALYs. This type of analysis is the gold standard for NICE, as it establishes whether differences between the costs of the therapy being evaluated and the comparator can be justified in terms of changes in health[250].
- Cost-consequence analysis: a form of cost-effectiveness analysis that presents costs and outcomes in discrete categories, without aggregating or weighting them.
- Cost-benefit analysis (CBA): a comparison of costs and benefits, which are quantified in monetary terms.

Resource impact is considered in terms of additional cost or savings over and above current practice for each of the first **5** years of implementation of the guidance. Resource impact is defined as substantial if it meets any of the following conditions[255]:

- Implementing one of the recommendations in the guidance will cost more than £**1** million (approximately **1.2** million euros) per year in England.
- Implementing all the recommendations in the guidance will cost more than £**5** million (approximately **6** million euros) per year in England.

NICE's final guideline recommendations are based on the balance between the estimated costs of interventions and their expected benefits compared to an alternative (i.e. their cost-effectiveness). However, the cost impact or potential savings of a recommendation should not be the sole reason for the committee's decision[255].

Depending on the health problem that NICE is faced with when assessing a particular medicine, the economic evaluation can be done from a payer perspective or taking into account a societal perspective[255]. NICE states in its reference case that the cost perspective adopted should be that of NHS England and social services[250]. The time horizon should be long enough to reflect all important differences in costs or outcomes between the interventions being compared and QALYs in adults should be measured using the EuroQol-5D questionnaires. Also, the same annual discount rate should be applied to both costs and health effects in the economic evaluations presented (currently **3.5%**)[255].

According to NICE guidance, sensitivity analysis should be used to explore the impact that potential sources of bias and uncertainty could have on the model results. A deterministic analysis should be used to explore the assumptions used in the model. NICE states that such an analysis could be performed in the following cases[255]:

- When there is uncertainty about the most appropriate assumption to use for the extrapolation of costs and effects beyond the follow-up period of the trial.
- When there is uncertainty about how the care pathway is most appropriately represented in the analysis.
- Where there may be economies of scale (e.g. when assessing diagnostic technologies).
- For models of infectious disease transmission.
- To test for any bias resulting from the data sources selected for key model inputs.

Probabilistic sensitivity analysis can be used to account for uncertainty arising from imprecision in model inputs. Any uncertainty must be balanced by a convincing argument in favour of the recommendation[255].

At the end of the appraisal of the therapy, NICE publishes the documentation listed in the following table, in order to promote the transparency of the appraisal process[244]. Similarly, NICE publishes in its guidelines the elements discussed during the meeting and the different contributions made by each expert.

TABLE 20. Documents published by NICE during the appraisal process in England

ASSESSMENT DOCUMENT WITH CONFIDENTIAL INFORMATION DULY REDACTED
List of consultees and commentators
Final scope and terms of reference of the evaluation
Submission of evidence from the company
Statements/presentations by consultees and experts from outside the company
Report of the Evidence Review Group (ERG)
Clarifying questions and answers
Technical report
Comments from consultees, commentators and experts on the NICE technical report and NICE responses
If it is produced, the appraisal consultation document (ACD)
Comments from consultees and commentators and members of the public on ACD, and NICE responses
Final Assessment Document (FAD)

Source: NICE (2018)[244]

Drug assessment reform process

In England, the participation of NICE's external stakeholders in the pricing and reimbursement process is not only limited to sitting on the appraisal committees, but they also participate in the various reforms that NICE carries out on the process of appraising and funding medicines. When the British assessment agency considers it appropriate to carry out reforms to the process, it launches a public consultation so that the different stakeholders can contribute with their vision and knowledge. This public consultation is not a blank sheet of paper, but is based on a series of proposals and questions that NICE launches with the aim of improving the appraisal and funding process. Stakeholders involved in the reform process range from the pharmaceutical industry to patients' associations, as well as experts from different public administrations. The latest consultation, launched in 2019 and currently underway, focuses on three blocks: accelerating patient access to promising new health technologies, supporting better market access and simplifying the health technology assessment process[256].

Involvement of patients and scientific societies

Within the NICE appraisal, the patient voice is represented, as at least two voting members of the Committees are patients, carers or users of the medical service[257]. Also, the technical report has a separate section on patient feedback[244].

NICE also takes into account the views of patient organisations and scientific societies in the appraisal process, giving both parties the opportunity to comment on the draft appraisal report before it is published[244].

Looking to the future, NICE in its reform strategy published in 2021, commits to developing partnerships with organisations across the healthcare system, including patient organisations, to create an information feedback loop for action based on the input received. However, it does not indicate how these partnerships will work, nor how they will be articulated[258].

P&R decision elements

Agreements between industry and payer

In England, medicine prices are influenced by agreements signed between the industry, through the Association of the British Pharmaceutical Industry (ABPI), and the UK Department of Health, represented by the Voluntary Scheme for Branded Medicines Pricing and Access. This voluntary scheme has been running in one form or another since 1957, with the latest coming into force in 2019 and running for five years[259]. The scheme aims to limit spending by the NHS. In the previous plan made in 2014, it was introduced that industry must pay the NHS a fixed percentage of its annual net sales to compensate for anticipated growth above **2%**, a percentage that has been retained in the 2019 agreement[259,260]. The percentages to be paid depend on the difference between the agreed growth rate and projected sales growth, with these percentages being **5.9%** and **5.1%** of net sales for 2020 and 2021, respectively[261]. However, not all member companies have to pay in the same proportion. Small companies (with sales of less than **5** million pounds [approximately **6** million euros]) are exempt from entering the payment scheme. For medium-sized companies, i.e. those with sales between £**5** million and £**25** million (**30** million euros or so) per year, the first £**5** million of sales are exempt from entering the payment scheme[259].

Cost-effectiveness threshold

One aspect that sets NICE's pricing process apart from other European countries is the intensive use of ICER when making judgements about whether or not to fund therapies. Although NICE did not initially state how much it was prepared to pay for a QALY, in 2004 it indicated that drugs with an ICER of less than £**20,000** (approximately €**24,000**) per QALY were likely to be approved[242]. In the latest Voluntary Scheme for Branded Medicines Pricing and Access, this threshold was defined as being in the range of £**20,000** - **30,000** (approximately €**24,000**-**36,000**) per QALY[259].

In 2017, an ICER threshold of up to £**300,000** (approximately €**360,000**) was adopted for medicines targeting ultra-orphan diseases (affecting fewer than **1** in **50,000** people within the HST assessment)[242]. The upper limit of the ICER threshold varies depending on the impact of the therapy on the patient's life, ranging from £**100,000** (approximately €**120,000**) per QALY per year for treatments that provide less than 10 additional QALYs to the patient, to a maximum of £**300,000** for treatments that provide more than **30** additional QALYs to the patient over the patient's lifetime[262–264].

Recently, NICE has introduced a new modifier for the cost-effectiveness threshold, replacing the former "end of life" modifier. This new modifier, called "severity", broadens the previous view to include those medicines indicated for pathologies that have a major impact on the patient's life, whether life-threatening or not.

In order for this modifier to be applied, NICE considers two measures: the proportional deficit and the absolute deficit. The proportional deficit looks at the quality and quantity of life lost due to a disease, using available therapies, relative to the expected quality and quantity of life the patient should have without the disease. This measure has a scale of **0** to **1**. On the other hand, the absolute deficit is the number of QALYs the person loses with the disease, considering also the existing treatment available to the patient. For example, if the patient loses **5** QALYs by contracting a pathology, the absolute deficit is **5**[266]. The sum of these two measures will fall into a classification that will change the threshold for which NICE is willing to pay. This classification is not yet publicly available[266].

Budgetary impact

Since 2017, NICE has included the drug's budget impact analysis in its assessment. If that impact exceeds £**20** million (approximately €**24** million) for the NHS in any of the first three years, NHS England can enter into negotiations with the company on the price of the drug or other commercial elements before healthcare professionals start prescribing it to their patients. If no agreement is reached, the NHS can ask NICE to recommend how the drug should be phased in to reduce the budgetary impact[242].

Financial agreements and their monitoring

In England, the term of the NICE appraisal guidance determines the duration of the contract, but the exact financial agreement reached by both parties must clearly define the terms and conditions of the contract. In case of new indications or changes in the type of scheme, a new submission of a managed agreement is required[267].

In the Voluntary Scheme for Branded Medicines Pricing and Access, the NHS committed to establishing a new commercial framework outlining the purpose and principles on which NHS commercial medicines activity will be based, as well as defining the roles and responsibilities of those involved in commercial medicines activity and describing the commercial flexibilities and circumstances in which they might be considered. Within this new NHS commercial framework for new medicines are the 3 commercial access options available for branded medicines: patient access schemes, commercial access agreements and managed access agreements (PAS, CAA and MAA, respectively)[268].

Patient Access Schemes (PASs)

Patient access schemes are innovative pricing arrangements proposed by pharmaceutical companies. They aim to improve the cost-effectiveness of therapies and enable patients to gain access to high-cost medicines and treatments. Companies can submit a patient access scheme proposal for any technology that is undergoing the NICE appraisal process[269].

Proposals for patient access schemes are assessed according to the principles set out in the Voluntary Scheme for Branded Medicines Pricing and Access[269]. Companies are obliged to propose which financial formulae they want to use. These can be of two types[268,269]:

- **Simple discount schemes**, which basically use the formulae of a fixed price agreement that is lower than the list price of the treatment, and a percentage discount from the list price. As these schemes are less complicated and easier to implement than complex schemes, the review involves a lower level of consultation with the NHS, so the review time is usually within **4** weeks.
- **Complex schemes,** including outcome-based dose limits, price reductions or free up-front stock. The complexity of these schemes involves a high level of consultation with the NHS, so the decision process requires at least **12** weeks.

Commercial Access Agreements (CAAs)

Unlike complex PASs, which are transparent, CAAs are confidential. The agreements typically relate to medicines that are expected to have value propositions at or below the lower end of NICE's standard acceptability threshold range. Examples of such agreements are shown in Table 21[268].

TABLE 21. Examples of formats for commercial access agreements in England

TYPE	DESCRIPTION
Budget ceiling	Maximum budgetary impact of a product (or products) above which a centralised reimbursement is paid.
Price/volume agreement	Agreed price for a certain volume of patients and then staggered reductions depending on the number of additional patients, or the company refunds the full amount (similar to the budget limit).
Cost sharing	The company finances the initial cost of the therapy, e.g. by offering the first month free of charge.
Start/stop criteria	Rules on eligibility criteria for when patients should start/stop therapy.
Results-based agreement/payment by results	Discount or refund applied if a product does not perform as expected or for non-responders.

Source: NHS[268]

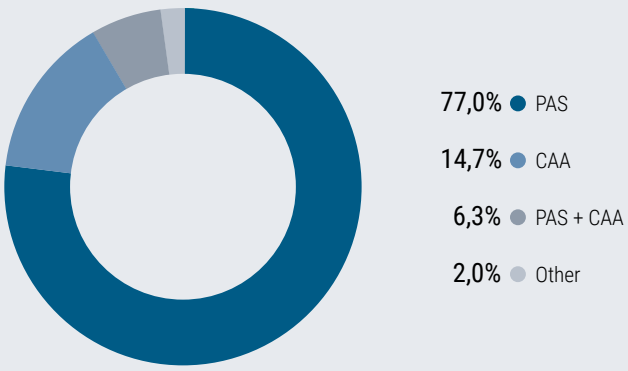
Managed Access Agreements (MAAs)

Finally, managed access agreements are used when the clinical uncertainty associated with the treatment is high, leading to uncertainty about the cost-effectiveness of the medicine. MAAs consist of two key components: a data collection agreement to mitigate clinical uncertainty and a commercial access agreement or PAS[268].

MAAs are interim agreements with a committed future date for reassessment, and are therefore time-limited. To date, MAAs have most often been used in the context of the CDF or HST, where a very small number of patients can lead to significant uncertainty in the clinical evidence presented[268].

NICE currently publishes the patient access agreements reached. During the period 2007-2021, the majority of agreements have been PAS (**77.0%**), followed by CAA (**14.7%**), while **6.3%** are mixed PAS+CAA agreements (Figure 32)[269].

FIGURE 32. Types of managed access arrangements in place by NICE in England (2007-2021)



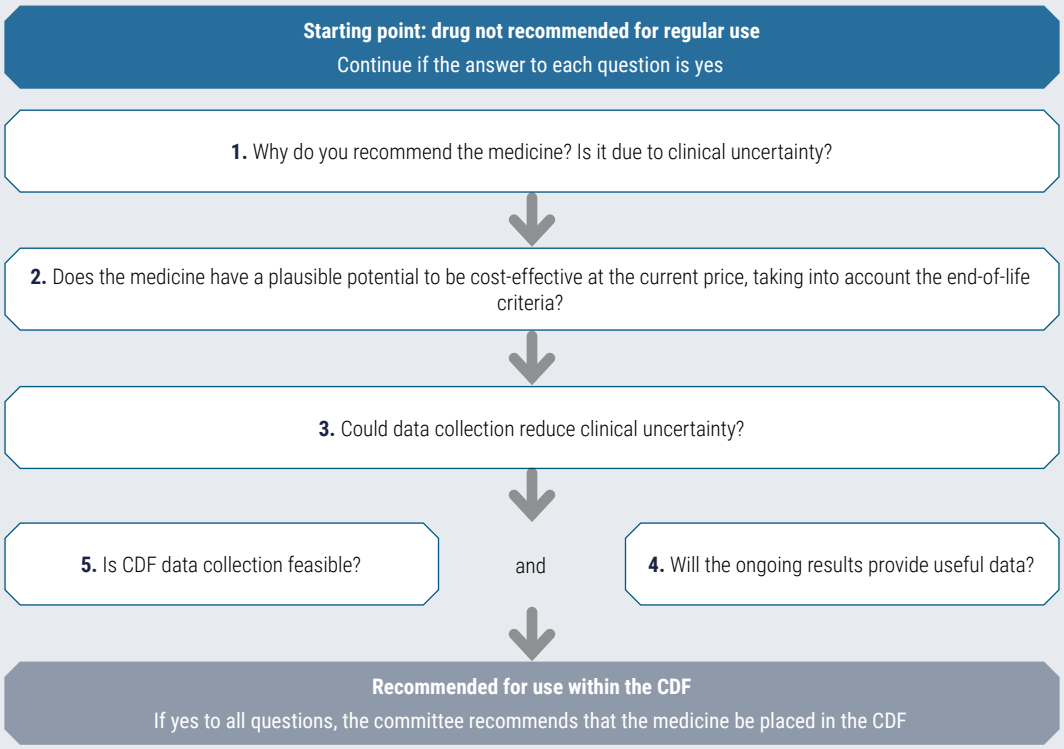
Note: PAS: Patient Access Scheme; CAA: Commercial Access Agreement. **Source:** Prepared by the authors based on NICE (2021)[269]

Recommendation for use under the CDF is made when there is plausible potential for the therapy to meet the criteria for routine procedure, but there is uncertainty about clinical outcomes that requires further investigation through clinical studies or data collection. This pathway involves the signing of a managed entry agreement between the pharmaceutical company and the NHS, which consists of two key components[270]:

- Data collection agreement, which sets out the results to be collected to resolve key areas of clinical uncertainty.
- CDF commercial agreement, which determines the cost of the medicine during the agreement period.

This Cancer Drugs Fund (CDF) provides patients with faster access (up to 8 months faster) to the most promising new cancer treatments, and offers pharmaceutical companies a fast-track to NHS funding[270]. By 2021, this fund has funding of £**340** million (approximately **400** million euros)[271]. In order for a drug to be included in the fund, the following decision algorithm (**Figure 33**) must be followed by the assessment committee[270].

FIGURE 33. Algorithm for CDF decision-making in England



Note: CDF: Cancer Drugs Fund. **Source:** NICE (2021)[270]

In addition to these funds, NICE has introduced one-off funding for life-saving innovative medicines called the Innovative Medicines Fund, which will be funded to the tune of £**340** million (approximately **400** million euros). It will operate in a similar way to the Cancer Drugs Fund and will provide treatments such as breakthrough gene therapies that could offer life-saving benefits and, in particular, help those with less common diseases where data collection on drug efficacy takes longer due to the smaller patient cohort[271].

On multi-indication pricing systems, the NHS stipulates that in the voluntary scheme for pricing and access to branded medicines neither combined pricing nor pricing by indication applies[259].

There is great heterogeneity in the monitoring mechanisms used to reassess outcomes. In some cases, the laboratory must include drug efficacy and use results in privately held databases, such as the UK Cystic Fibrosis Registry[272], ongoing clinical trials[273] or national databases such as the Systemic Cancer Therapy Dataset[274].

The Systemic Anti-Cancer Therapy Dataset (SACT) is a mandatory database for all cancer medicines funded in England. The data collected includes information at the patient and tumour level. The database is designed to link to other data sources to provide a complete picture of cancer patient treatment. Among others, SACT aims to assess adherence to NICE guidelines and provide information for the CDF[274].

SACT data are recorded in the hospitals' electronic prescribing systems. Patient details and prescribed medication are entered during the course of treatment by doctors, nurses, pharmacists and other healthcare providers[274].

...TO BE HIGHLIGHTED IN ENGLAND

- ✔ *Explicit use of ICER to justify funding (or not) of a new therapy: threshold of up to £300,000 (€360,000 approx.)/QALY for ultra-rare therapies*
- ✔ *Transparency on the aspects discussed during the elaboration of the evaluations*
- ✔ *Justification of the criteria taken into account for the approval of funding*
- ✔ *Open participation of all actors involved in the assessment process, as well as in the proposal for its reform*
- ✔ *Free access and free price once marketing authorisation has been received*
- ✔ *Clarity of the process and of the responsibilities of the parties involved*

ITALY

Italy is a country with decentralised health care in its **21** regions. As in the Spanish healthcare system, clinical and economic evaluation is the responsibility of the national body, in this case the *Agenzia Italiana del Farmaco* (AIFA)[275], a body under the Italian Ministry of Health[276]. As in other EU countries, the pricing and funding process in Italy starts with the approval of the drug through the centralised, mutual recognition or national procedures[277].

FIGURE 34. Pricing and funding process in Italy

Source: prepared by the authors

Actors and process

In Italy, the assessment, pricing and reimbursement process starts when the sponsor company submits the documentation required by the current legislation to AIFA. This information is analysed by two committees, the Technical Scientific Commission (CTS), which is in charge of assessing the technical part of the medicine, and the Price and Reimbursement Committee (CPR), which is in charge of the economic part of the evaluation[277].

The Technical Scientific Commission is in charge of analysing the clinical value of the drug and the added therapeutic value compared to the drugs selected as comparator drugs for the indication. During this process, either the CTS or the pharmaceutical company may convene a rapprochement meeting[277]. The CTS decisions are used in an advisory manner on the classification of medicines for reimbursement purposes. In turn, the CTS can introduce limitations on reimbursement if it considers that there have been significant changes between the information submitted and the actual situation[278].

The CTS is composed of **10** members, appointed by decree by the Ministry of Health. Two of them are ex officio members, who are the director general of the Agency and the president of the Higher Institute of Health, while the rest are nominative members, who serve for 3 years, renewable once for another **3** years. Of these **8** positions, **3** are appointed by the Ministry of Health, one of whom acts as chairman of the committee, **1** by the Minister of Health, Economy and Finance, and **4** by the Standing Conference for relations between the State and the Regions. These experts must have a minimum of **5** years of experience in the assessment of medicines in order to be a member of the CTS[278]. Similarly, the CTS may consult and/or invite experts and consultants to participate in its meetings, as well as hold hearings with representatives of applicant pharmaceutical companies, scientific societies, patient associations or evaluation stakeholders[279].

According to the results of the CTS assessment, medicines fall into one of the following three categories, on the basis of which the level of public reimbursement is defined[280]:

- **Class A:** includes essential medicines and medicines for chronic diseases, fully reimbursed by the national health system unless there is an AIFA note, which links reimbursement to specific pathological or therapeutic conditions.

- **Class H:** includes medicines for hospital use only, are fully reimbursed, and can only be used in hospitals or health centres.
- **Class C:** medicines not funded by the State.

After the assessment, the CTS forwards the documentation to the Price and Reimbursement Committee (PRC), which is responsible for negotiating the final price of the therapy. In the event that the CTS assessment does not reveal a clinical superiority of the drug over its comparator, and the company does not propose a cost equal to or lower than that of the comparator, the process is considered negatively concluded[277].

The composition of the CPR is analogous to that of the CTS and is composed of members with sector expertise in drug pricing methodology, health economics and pharmaco-economics, as well as experts in health and health law related organisations[278].

Documentation

Over the last year, AIFA has been working on reshaping the criteria to be taken into account in the pricing and reimbursement decision. This reshaping has included the establishment of new rules on the preparation of the dossier submitted by the pharmaceutical company to AIFA, the application of which started on 1 March 2021[281]. According to this new decree, the dossier must include the following information[277]:

a) Scientific documentation inferring the potential added therapeutic value of the medicine compared to the main treatments with which the medicine is compared. This comparison takes into consideration the therapeutic alternatives used in Italian clinical practice, providing evaluative and cognitive elements indicating the main treatments with which the medicine can be compared. To allow for a subsequent evaluation of the costs of alternative treatments, the dosing regimen and duration of treatments should be explained.

b) Economic evaluation of the drug.

c) Self-certified information elements on the medicine in question, the negotiation of marketing, consumption and reimbursement in other countries and, if so, under what price and reimbursement conditions, including any other negotiation agreements.

d) The expected annual market shares over the next **36** months in the specific market segment.

e) Self-certification of the company's production capacity and management of possible unforeseen events that could compromise production standards, as well as the activities that will be implemented in order to guarantee the adequate supply of the medicine.

f) Forecast and evolution of NHS expenditure resulting from the proposed prices.

g) Quantification of public contributions and incentives for research and development programmes for the assessed medicine.

h) Quantification of the economic and financial impact on the National Health Service and related consumption resulting from possible inclusion in early access programmes.

i) Quantification of the economic and financial impact and related consumption resulting from the marketing of the medicine in the country.

j) Any other information that may be useful for the purpose of the negotiation, including the patent status of the medicine.

If the medicine does not demonstrate any therapeutic advantage, either in efficacy or safety compared to comparators, the pharmaceutical company should provide other elements of interest in terms of economic advantage to the National Health Service[277].

Clinical assessment

In the clinical assessment, the medicine is compared against therapeutic alternatives used in the Italian healthcare context for the target population and on the results recognised as clinically relevant and validated for the disease by national guidelines, with particular reference to those published in the Italian national system. In the absence of national guidelines, AIFA suggests consulting updated European and international guidelines, indicating the differences with respect to the comparators used in national clinical practice. The therapeutic alternatives used in clinical practice represent the comparator(s) with which the medicine is to be compared for the purposes of this negotiation: specifically, it is required to identify the comparator(s) taking into account the indications of the treatment, the same target population and subpopulations and efficacy, tolerability and safety profiles[282].

When performing the clinical assessment, AIFA takes into account the unmet needs in the pathology for which the drug is intended and the added therapeutic value compared to standard clinical practice. To make this comparison, AIFA subdivides these two categories into **5** different levels (Table 22)[282].

TABLA 22. Criteria for the clinical assessment of medicines in Italy

CRITERIA	LEVELS	DESCRIPTION
Unmet medical needs	Maximum	Lack of therapeutic options for that specific disease.
	Important	Availability of therapeutic alternatives, but no impact on relevant and validated outcomes.
	Moderate	Availability of therapeutic alternatives, with limited measurable impact on clinically recognised outcomes and/or with an uncertain or not entirely satisfactory safety profile.
	Scarce	Availability of one or more therapeutic alternatives, with a high measurable impact on outcomes, recognised as clinically relevant, and with a favourable safety profile.
	Absence	Availability of alternative treatments capable of modifying the natural course of the disease, with a favourable safety profile.
Added therapeutic value[i]	Maximum	Demonstrated greater efficacy in clinically relevant outcomes over alternatives. The drug is able to cure the disease or at least significantly alter its natural course.
	Important	Greater efficacy in relevant outcomes, or ability to reduce the risk of serious complications, improve the benefit/risk ratio or avoid the use of risky clinical procedures. The medicine modifies the natural course in certain patients, or represents a relevant advantage.
	Moderate	Moderately superior efficacy, demonstrated in some patient subpopulations or surrogate outcomes, and with limited effects on quality of life.
	Scarce	Slightly superior effectiveness or in terms of clinically insignificant outcomes. Lower benefits than alternatives (more favourable route).
	Absence	No added clinical benefit over available alternatives.

Fuente: AIFA (2017)[282]

i For anticancer drugs, the measure to be used is overall survival (OS). The lack of OS data must be adequately justified and, in relation to the type of malignancy and therapeutic setting, Progression Free Survival (PFS), Disease Free Survival (DFS), duration of complete response or other surrogate outcomes whose predictive value of clinical benefit is recognised, also depending on the magnitude of the effect, may be considered[283].

One of the differentiating aspects of the transalpine country is that it has a defined system for assessing drug innovation. To assess innovation, AIFA adds the category of quality of evidence to unmet medical need and added therapeutic value.

TABLE 23. Levels of quality of evidence taken into account by AIFA to assess innovation in Italy

CRITERIA	LEVELS	DESCRIPTION
Quality of evidence	High	≥ 4 points in the GRADE methodology.
	Moderate	3 points in the GRADE methodology.
	Low	2 points in the GRADE methodology.
	Very low	≤ 1 point in the GRADE methodology.

Note: GRADE: Grading of Recommendations Assessment, Development and Evaluation
Fuente: AIFA (2017)[283]

The quality of evidence is divided into **4** different levels (Table 23), based on the score obtained using the GRADE methodology, which encompasses **5** different categories (Table 24)[284].

TABLE 24. GRADE methodology for assessing the quality of evidence in Italy

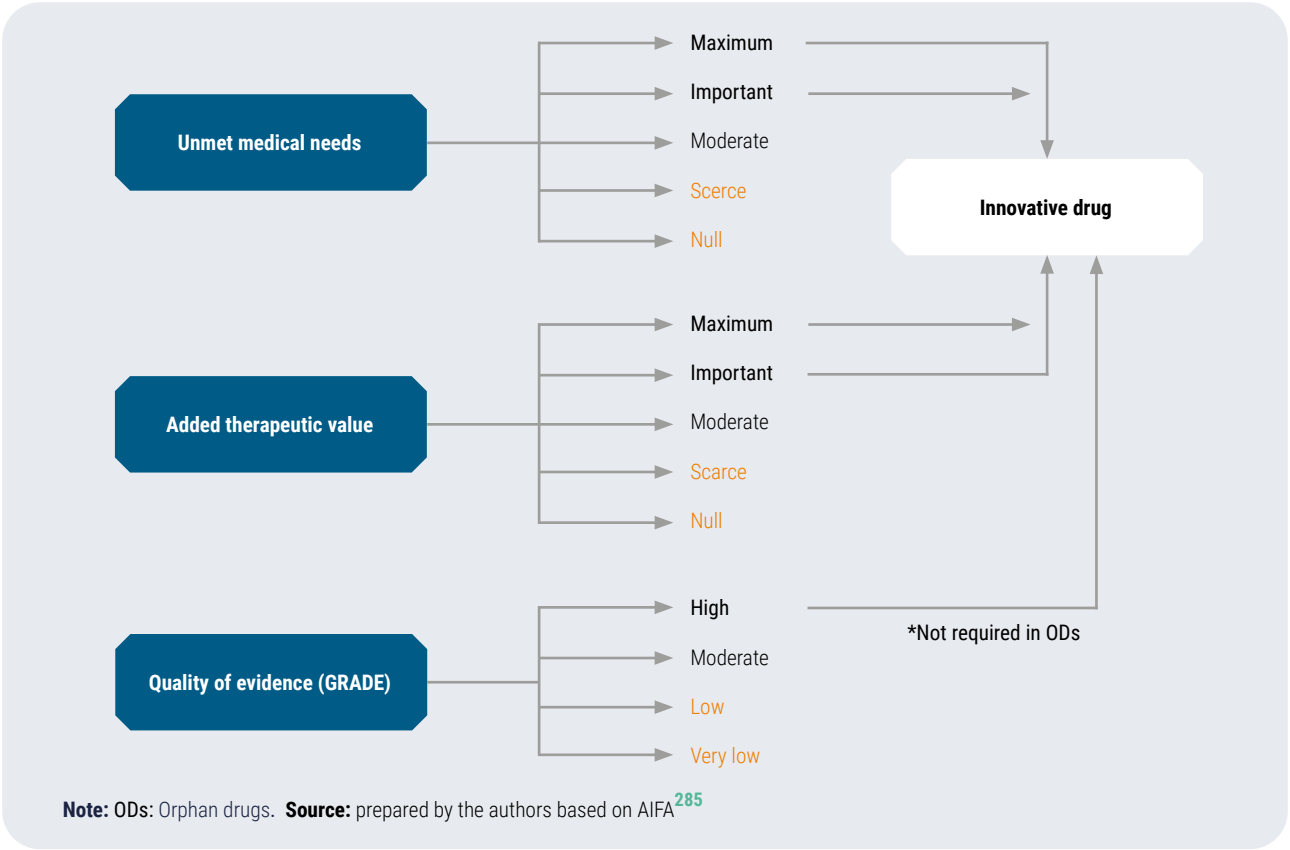
CATEGORY	POINTS	DESCRIPTION
Type of evidence	+4	Randomised clinical trials/systematic reviews ± other types of evidence.
	+2	Observational evidence.
Methodological quality	0	No problems.
	-1	Problem in 1 element.
	-2	Problem in 2 elements.
	-3	Problem in 3 or more elements.
Consistency	+1	Evidence of dose-response between studies.
	0	Similar results in all studies.
	-1	Lack of agreement between studies.
Applicability	0	Population and generalisable results.
	-1	Problem with 1 element.
	-2	Problem with 2 elements.
Magnitude of effect	0	Not all effect sizes >2 or <0.5 and significant or HR/OD not significant.
	+1	Magnitude of effect >2 or <0.5 for all studies and significant.
	+2	Magnitude of effect >5 or <0.2 for all studies and significant.

Note: HR: Hazard Rate Ratio; OD: Odds ratio.
Surce: Elaboración propia a partir de GRADE[284]

Since 2017, pharmaceutical companies can apply to AIFA for a medicine to be considered as innovative in order to benefit from the innovative medicines funds proposed by the Ministry of Health. For a medicine to be classified as innovative, its unmet medical need and added therapeutic value must be recognised as "Highest" or "Important", and the quality of evidence must be "High". Innovativeness cannot be recognised, on the other hand, in the presence of a therapeutic need and/or added therapeutic value judged as "Low" or "Absent", or a quality of evidence judged as "Low" or "Very Low". In the intermediate situations, the CTS takes into account the weight of

each of the following elements to make a decision. In the case of medicines targeting RDs, the assessment of the quality of evidence takes into account the objective difficulty of conducting adequately powered landmark clinical trials (Figure 35)[285].

FIGURE 35. Criteria and levels of the innovation algorithm in italy



Note: ODs: Orphan drugs. **Source:** prepared by the authors based on AIFA[285]

Based on the results of the clinical assessment, whether for medicines that have applied for special innovative status or not, the CTS issues a decision, which can be found at[285]:

- Recognition of the innovative character, which will be associated with inclusion in the Innovative Medicines Fund, or in the Fund for Innovative Oncological Medicines.
- Recognition of conditional (or potential) innovation.
- Non-recognition of innovative capacity.

In view of this resolution, the company may submit additional information within the following 10 days. When the process is concluded, both the final result and the assessment leading to it are made public on the AIFA website, and the company may request the exclusion of sensitive data[285].

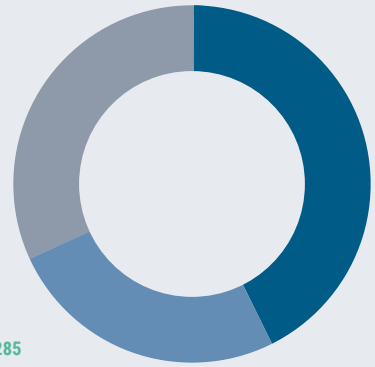
The status of "innovative medicine" lasts for a maximum of **36** months, not exempt from reassessment if evidence comes to light that justifies it. If evidence is found that contradicts the justification for recognition as an innovative medicine, the benefits linked to such recognition are automatically lost and a new price and financing negotiation is initiated. In the case of conditional innovation recognition, a reassessment is mandatory after **18** months[285].

Orphan drug assessment

Since 2012, with the entry into force of the Balduzzi Law, it has been established that the pharmaceutical company holding a marketing authorisation for an orphan drug may submit an application for pricing and reimbursement to AIFA as soon as the positive opinion of the CHMP is issued, i.e. before the European Commission issues the marketing authorisation. In turn, this law establishes that AIFA will assess as a priority, for the purposes of classification and reimbursement by the National Health Service, orphan drugs and medicines of exceptional therapeutic importance for which an application has been submitted. In this case, the assessment period is reduced to **100** days[286].

In the 2017-2020 period in Italy, a total of **118** drug assessments have been carried out, with the majority of them (**63%**) falling into the category of innovative medicines or medicines with a conditional innovation (Figure 36)[285].

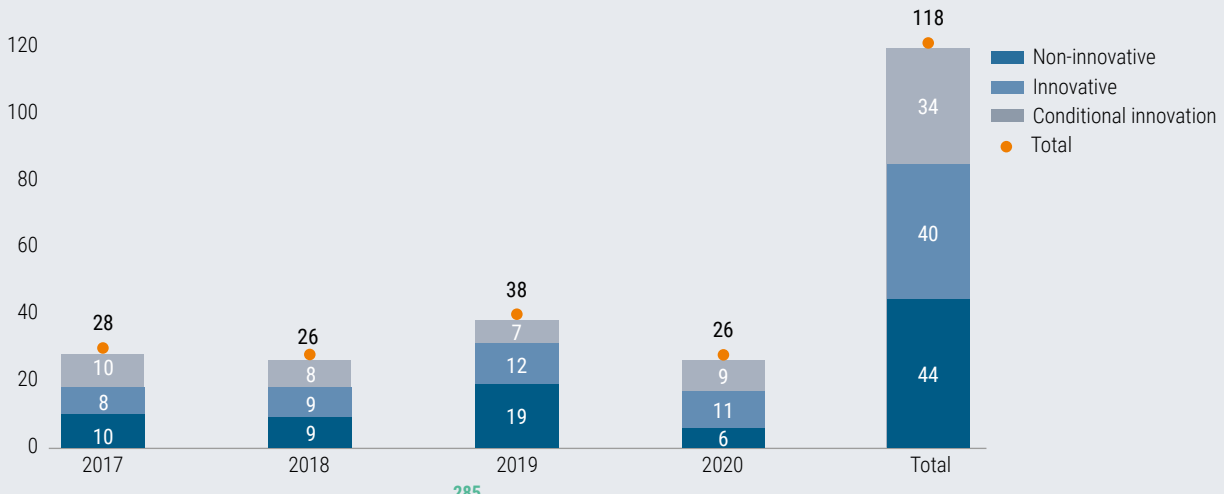
FIGURE 36. Percentage of medicines classified as innovative, non-innovative and conditional innovation in Italy (2017-2020)



Source: prepared by the authors based on AIFA[285]

Specifically, 2019 saw the highest number of medicines assessed in the indicated four-year period, with **38** assessments in total (Figure 37)[285].

FIGURE 37. Medicines classified as innovative, non-innovative and conditional innovation in each year in Italy (2017-2020)



Source: prepared by the authors based on AIFA[285]

Economic evaluation

To negotiate the price, CPR examines the proposals made by the pharmaceutical company, while taking into account the assessments and opinions expressed by the CTS, with particular reference to the judgement on the added value of the medicine and the costs of the therapy compared to available pharmacological therapies. Similarly, the assessment is also carried out taking into account the prices charged to National Health Service bodies and the number of treatments envisaged, following the possible limiting conditions defined by the CTS. Therefore, the CPR does not carry out economic evaluations per se, but its decisions are based on the CTS opinions and the economic evaluations submitted by the laboratory.

The activity of the CPR comprises the following actions[287]:

a) Critical assessment of the pharmaco-economic studies presented by pharmaceutical companies in the dossier

b) Revision of the pharmacoeconomic model when provided by the company in open and editable format

c) Literature review to identify additional published pharmacoeconomic studies related to the national or international context

d) Identification of recommendations and decisions taken in other countries with regard to the the medicine in question

e) Analysis of treatment costs in relation to therapeutic alternatives

f) Economic and Financial Impact Assessment

The economic evaluation submitted by the pharmaceutical company must comply, inter alia, with the following guidelines[282]:

1. Type of evaluation used: cost-effectiveness, cost-utility, cost-benefit and cost minimisation[288].
2. Perspective: the evaluation will be carried out from the point of view of the Italian National Health System, with the possibility of an additional evaluation from the perspective of society.
3. Time horizon: the time horizon chosen should be the lifetime of the patient, or at least a period long enough to capture all differences between the alternatives being compared, also presenting incremental costs and outcomes **5** and **10** years after the start of the comparison between alternatives. Time horizons other than those explicitly requested may be considered.
4. Discount rate: if the time horizon of the analysis is longer than one year, the discount rate to be used in the base case is **3%** for both costs and benefits.
5. Sensitivity analysis: a description of the methods and results of sensitivity analyses performed to explore the uncertainty of the parameters of effectiveness, safety, resource use, cost and utility and to check the robustness of the model used is requested. The univariate deterministic sensitivity analysis should be presented using a tornado diagram, while the results of the probabilistic sensitivity analysis should preferably be presented both at the cost-effectiveness level and using the cost-effectiveness acceptability curve.

The time limit for the price negotiation and reimbursement procedure may not exceed **180** days. This time limit may be interrupted once at the request of AIFA, for the request of new documents or information that it deems necessary for the assessment. In the same way, the company may also request a suspension, once, to submit new information that it considers relevant for the negotiation. This suspension period cannot last longer than **90** days after which, if the process has not been reactivated, the negotiation period ends without agreement and the drug falls under class C[277].

Involvement of patients and scientific societies

Within the Italian assessment and pricing processes, patients' associations and scientific societies participate as advisory elements in the deliberations at the STS meetings, but without voting rights[279].

Similarly, the scientific societies collaborate with AIFA in the preparation of scientific and technical reports based on the monitoring data of the therapies designated in Italy[289].

P&R decision elements

Support criteria

Once the medicine has passed the evaluation of both committees, and to finalise the price and reimbursement negotiation procedure, the following considerations are taken into account, in addition to the documentation provided by the company (see section: DOCUMENTATION), for setting the price and reimbursement[277]:

- **a)** Sales volumes
- **b)** Product availability for the national health service
- **c)** Discounts on supplies to national health service entities
- **d)** Public contributions to drug development and research programmes

Agreements between industry and payer

In the agreements between the industry and AIFA, the pharmaceutical company is obliged to report on sales data, turnover, marketing costs and patent status of the drug in Italy and on any deviation between the information provided for the approval of the drug and the actual situation. In addition, AIFA opens the possibility to consider a price increase only in the exceptional case that the pharmaceutical company encounters difficulties in finding the raw materials necessary for the manufacture of the drug, and only for low-cost drugs[277].

During the price negotiation phase, AIFA takes into account, in addition to the foreseeable consumption data, the financial constraints provided for by the current regulations on pharmaceutical expenditure[277].

Budgetary impact

In addition, the CPR also takes into account the economic-financial impact of the new therapy in the context of the Italian National Health System. To this end, AIFA asks the company to present a budgetary impact comparing the set of treatments present in the current scenario (in the absence of the assessed medicine), with the new treatment scenario, in which the medicine is progressively introduced on the market, with complementary or substitutive effect with respect to the existing set. Scenario 1, without the medicine, should reflect the treatments currently used in the Italian healthcare setting for each indication demanded. In the absence of treatments, the

"no treatments" scenario can be considered. Scenario 2, with the assessed medicine, should reflect the expected change in the existing set of treatments as a consequence of the introduction of the new therapy, relative to the assumed market penetration data. When describing the treatments in scenarios 1 and 2, the possible evolution of the combination over time (e.g. if a medicine goes off-patent or a new competitor is expected within the time horizon considered) should also be taken into account[282].

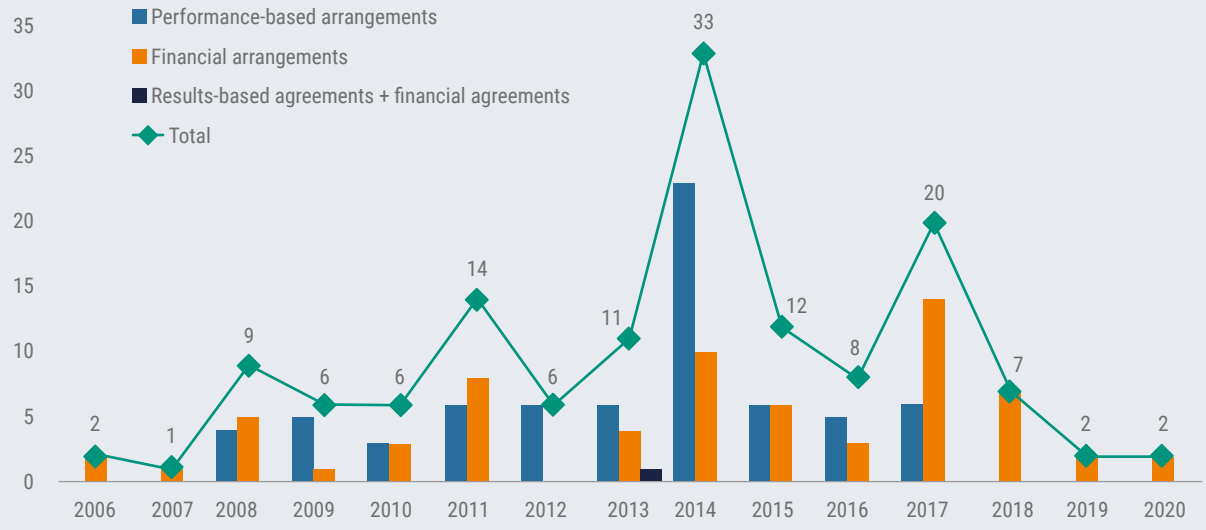
The perspective used in the budgetary impact has to be that of the Italian NHS, leaving open the possibility for the pharmaceutical company to present another budgetary impact from the societal perspective, including health and non-health costs and indirect costs. The time horizon should be at least two years, with the possibility of considering a longer time horizon to capture the overall impact of the assessed medicine on the NHS[282].

Financial agreements and their monitoring

Italy is one of the most experienced European countries in terms of innovative financial formulae. The main financial models used by AIFA fall into two main groups: outcome-based risk-sharing agreements and financial agreements. These managed entry agreements apply to both innovative and non-innovative medicines.

Analysing the information provided by AIFA, a total of **137** managed entry agreements (for **79** drugs) were approved in Italy during the period 2006-2020, of which **69** were outcome-based agreements, **67** were financial agreements, and one was a mixed agreement comprising both types. The year 2014 was when the most financial formulas were approved, with more than **30** (Figure 38)[290].

FIGURE 38. Evolution of the types of managed entry agreements in Italy (2006-2020)



Note: the date of commencement of the agreement has been used to determine the date of the agreement
Source: prepared by the authors based on AIFA[290]

Overall pharmaceutical expenditure ceiling

Since 2011, Italy has limited the budget for pharmaceuticals, distinguishing between drugs for hospital use and those dispensed in pharmacies. Since 2017, this expenditure is limited to **14.85%** of public health expenditure, with the following two budget caps[291,292]:

- **6.89%** of NHS expenditure is allocated to expenditure on pharmaceuticals purchased directly from manufacturers (mainly by hospitals).
- **7.96%** is allocated to regional expenditure on pharmaceuticals purchased in pharmacies. This expenditure is controlled by the integrated information system called "*Sistema Tesserasanitaria*"[293].

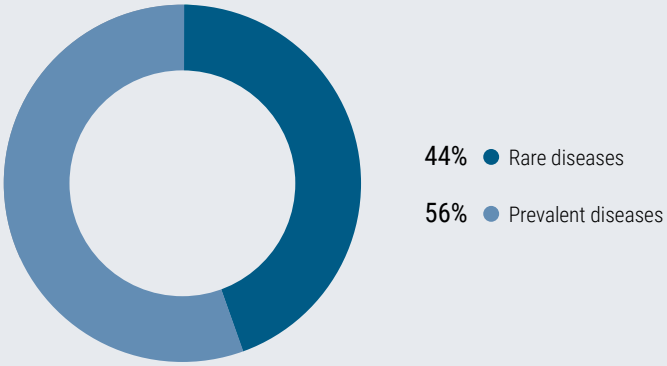
If the "direct purchase budget" is exceeded, pharmaceutical companies and regions are asked to cover the shortfall (**50%** each). If the "retail budget" is exceeded, the pharmaceutical industry and distributors must pay back the difference[291].

Specific funds

Another of the differentiating aspects in Italy on the funding of therapies is the establishment of specific funds for innovative medicines. If a medicine is recognised as innovative for a specific therapeutic indication, it can be included in the innovative medicines fund and, in the case of a cancer medicine, it can be included in the fund for innovative cancer medicines. These funds have a budget of **1** billion euros per year, split **50/50** between the two funds. If one fund exceeds its limit, while the other fund does not reach its limit, the unused funding from the latter can be used by the former[294]. The lists of innovative medicines, according to art. 1, Law 11/12/2016, nº 232 (Budget Law 2017, represent the set of medicines accessing the aforementioned funds. The reference to the list of medicines is published in the Official Gazette for each individual speciality in relation to its therapeutic indication and the reimbursement class of the National Health Service[295].

The innovative medicines fund (non-oncology) funded **9** drugs between 2018 and 2020. Four of them (**44%**) were directed to the treatment of rare diseases (haemophilia A, neurotrophic keratitis, hereditary dystrophy and neuronal ceroidolipofuscinosis type 2), and the remaining **56%** to prevalent diseases such as atopic dermatitis (2 drugs), multiple sclerosis, chronic hepatitis C virus infection and cytomegalovirus reactivation (**Figure 39**). Between January and July 2021, 3 drugs have been approved for funding under this fund, all of them targeting different rare diseases, such as acute hepatic porphyria (AHP), hereditary dystrophy and spinal muscular atrophy (SMA)[295].

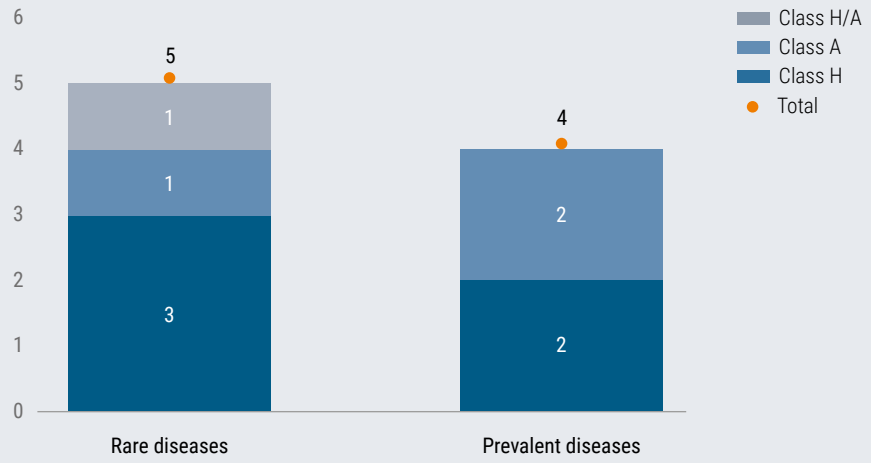
FIGURE 39. Distribution of the fund for the purchase of innovative (non-oncological) medicines in Italy (2018-2020)



Source: prepared by the authors based on AIFA[295]

Five of these drugs are for hospital use (class H) and **3** for chronic diseases (class A) (**Figure 40**)[295].

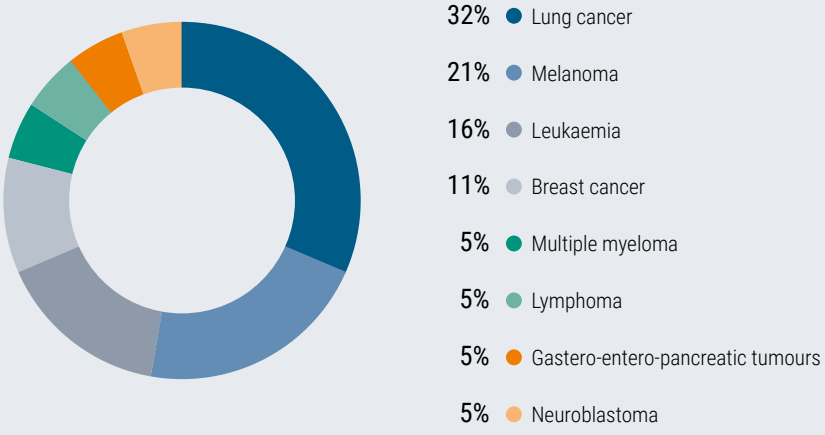
FIGURE 40. Reimbursement class of drugs included in the fund for innovative (non-oncological) medicines in Italy (2018-2020)



Source: prepared by the authors based on AIFA[295]

Between 2018 and 2020, a total of **19** drugs were funded under the innovative cancer medicines fund, all of which were reimbursed by hospitals. Most of these drugs (**32%**) are indicated for non-small-cell lung cancer (NSCLC), followed by those indicated for melanoma (**21%**). Other cancers targeted by this fund include multiple myeloma, breast cancer and various types of leukaemia and lymphomas, among others (**Figure 41**)[295]. Between January and July 2021, a single drug targeting multiple myeloma has been included in this fund.

FIGURE 41. Diseases included in the fund for innovative cancer medicines in Italy (2018-2020)



Source: prepared by the authors based on AIFA[295]

In 2020, the fund for innovative cancer medicines was exceeded for the first time, with a deficit of **464.2** million, reaching a total expenditure of **964.2** million euros. In contrast, the fund for innovative non-oncology medicines recorded a surplus of **193** million, which does not offset the deficit of its twin fund[296].

On the other hand, Italy also has a fund for the use of ODs or medicines that represent a therapeutic hope that are pending commercialisation, for serious and specific diseases (neoplasms, nephropathies, mental illnesses, thalassaemia and neoplasms. This fund is called the "AIFA National Fund" and is made up of **50%** of the contribution that pharmaceutical companies pay annually to AIFA, which corresponds to **5%** of the annual expenses for promotional activities that the pharmaceutical companies allocate to doctors297. By 2021, this fund has resources of 10.5 million euros[298].

Monitoring mechanisms

In Italy, a large part of the established financial formulae have been linked to the assessment of real-life health outcomes, which has led to an advanced network of monitoring mechanisms to check whether medicines are achieving the desired results. AIFA's monitoring registry platform is a computerised system that allows for homogenous monitoring across the country. The system, co-managed with the regions, also allows the planning and use of medicines subject to monitoring in each area, controlling their expenditure. The monitoring registers have a multiplicity of functions, but are essentially a form of administrative control that cannot interfere with patient care[299]. The register includes medicines with additional monitoring for safety issues, all medicines that depend on a managed entry financial agreement (and thus innovators) and those of "prescriptive appropriateness", which comprise medicines that require appropriate use according to AIFA, such as those indicated to prevent cardiovascular risks, depression, broad spectrum antibiotics, etc.[300,301].

The inclusion of a medicine in a monitoring register takes place after marketing authorisation, or after authorisation of an extension of its therapeutic indications (with the possibility to differentiate between approved indications). In some particular cases, the registers also monitor medicines reimbursed by the Italian national health system for those medicines not authorised in Italy, or prior to their marketing[299].

The AIFA registers attribute a very important role to the regions in the management of the supporting infrastructure, allowing intervention also in the authorisation system of prescribing centres. In fact, the health directors of the centres are authorised to use the platform and, in turn, authorise doctors and pharmacists to use it[299].

The registration platform is managed by a network comprising approximately **3,500** health structures, **52** regional managers, **963** health directors, **32,857** doctors (**25%** of hospital doctors[302] and **2,318** pharmacists. This network enables the regions to regulate the organisation of pharmaceutical care throughout the territory. Currently, **49** pharmaceutical companies have at least one monitoring register managed by the AIFA platform. The companies interact with pharmacies through a profile defined on the platform, which provides for compliance with conditional reimbursement agreements, stipulated during negotiation[299].

In an exercise of transparency, AIFA publishes technical-scientific monitoring reports specific to each drug and therapeutic indication(s) that are monitored. The reports contain the descriptive analysis of the data collected by the individual registries, usually after their closure. The format of the published reports is developed in full collaboration and exchange with the relevant scientific societies in the specific therapeutic area[289].

…TO BE HIGHLIGHTED IN ITALY

- ✔ *Pharmaceutical innovation algorithm based on unmet medical needs, added therapeutic value and quality of evidence*
- ✔ *Specific funds to fund innovative and/or oncological medicines*
- ✔ *Innovative financial agreements linked to mandatory monitoring mechanisms*
- ✔ *Open publication of the technical-scientific monitoring reports on funded medicines*
- ✔ *Major development in medicines information and monitoring system*

JAPAN

The Pharmaceuticals and Medical Devices Agency (PMDA) is the Japanese regulatory authority that ensures the safety, efficacy and quality of medicines. For marketing approval of a new medicine, the PMDA conducts a scientific review of the product's application in accordance with Japanese law. Following PMDA approval, the Ministry of Health, Labour and Welfare (MHLW) administratively grants marketing authorisation for the product based on the PMDA review report[303]. Once marketing approval is received, the medicine is available for marketing in the country, following a model similar to the pharmaceutical market in Germany, where the assessment is subsequent to the entry of the medicine into the funding[304].

Actors and process

In Japan, companies cannot freely set the prices of medicines and medical devices provided by public health insurance. The price is decided by the MHLW and the main actor in the evaluation is the "Central Medical Council of Social Insurance (*Chuikyo*)", which reports to the MHLW[305]. Japan does not assess all its medicines, but establishes five categories based on a set of criteria (**Table 25**). Generally, medicines are included in public health insurance within **60** days of marketing authorisation, with a maximum period of **90** days[306].

TABLE 25. Categories of selection criteria in an assessment of cost-effectiveness in Japan

Ranking	Name	Selection criteria
Products newly included in the funding	H1	Estimated maximum annual sales in excess of €76 million.
	H2	Estimated maximum annual sales between €38 million and €76 million.
	H3	Refers to products with notably high prices* and products that require reassessment because there is strong new evidence with a significant impact on the assessment.
Products already included in the funding	H4	Annual sales of €758 million. Products with significantly high prices*. Products requiring reassessment because there is strong new evidence with a significant impact on the assessment.
Similar products	H5	Products whose prices are calculated comparatively with those classified in classifications H1 to H4.

Note: * Remarkably high price is not explicitly defined. **Source:** Hasegawa (2020)[306]

Japan has established a standard timeframe for conducting the assessment process. First, manufacturers are requested to complete their analysis within **9** months after the start of the assessment, including pre-consultation. A pre-consultation regarding the analytical framework (e.g. scope, data selection) is carried out with external academic groups. After submissions, the *Chuikyo* expert committee determines the analytical framework and the manufacturers start their analysis against the framework. After submitting this information, the academic groups determined by the MHLW and the Center for Outcomes Research and Economic Evaluation for Health (C2H) review the submitted information within **3** months. If this review shows that the manufacturers' analyses are scientifically questionable, a further **3**-month deadline for modification is given; thus, the review and reassessment process takes a maximum of **6** months. After the academic analysis, the assessment and price adjustment is completed within **3** months. Consequently, the duration of the process ranges between **15** and **18** months from selection to final price adjustment (**Figure 42**)[306].

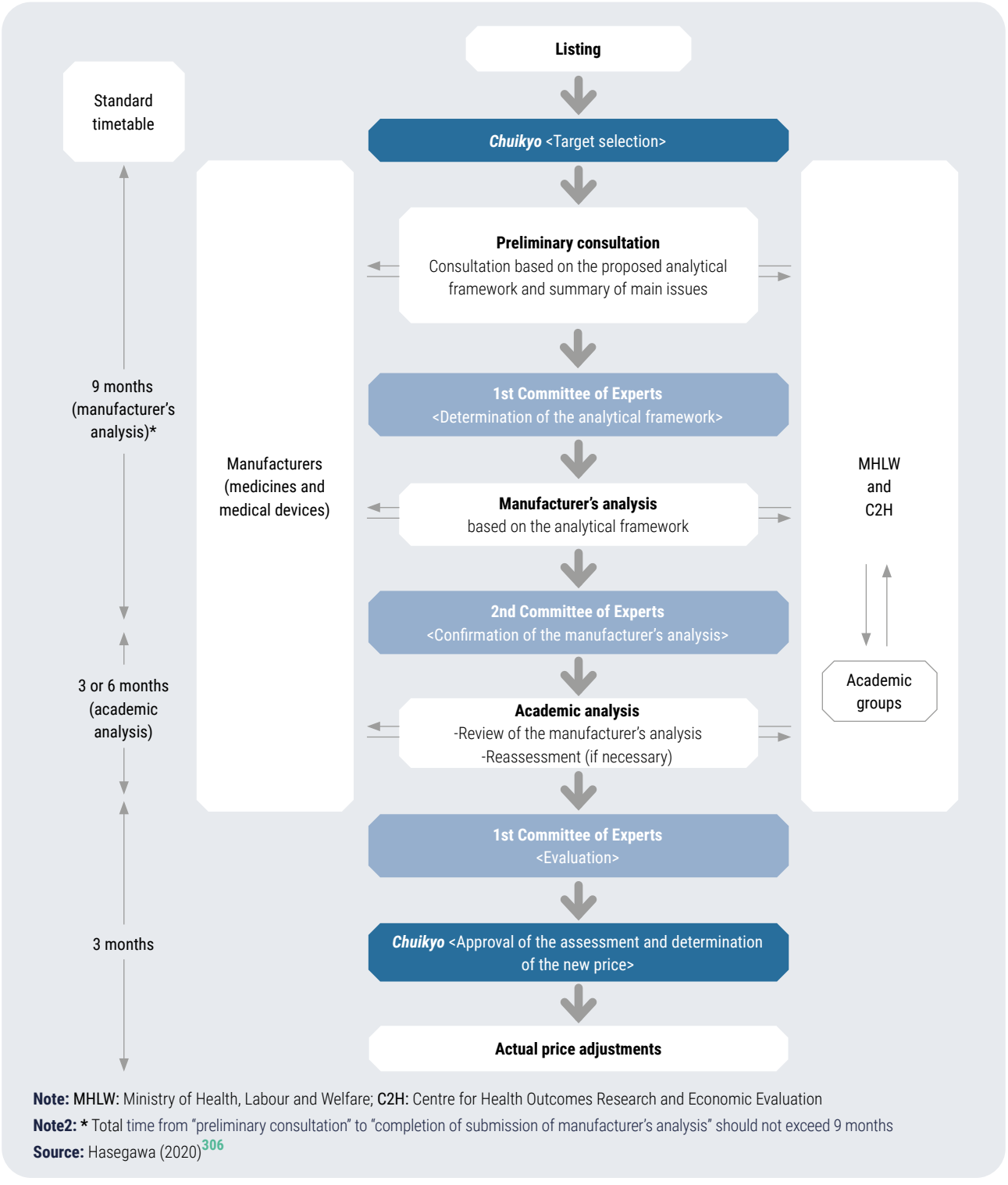
During this analytical process, the expert committee meets three times: first to determine the analytical framework for the cost-effectiveness study; then to evaluate the submitted manufacturer's dossier; and finally to evaluate the report produced by the academic group. The main participants in the assessment process are listed in **Table 26**.

TABLE 26. Composition and roles of organisations involved in the assessment of medicines in Japan

Organisation	Central Medical Council of Social Insurance (*Chuikyo*)	Subcommittee of experts on economic evaluation	Academic think tanks
Membership composition	Health care payers (n=7) Health care providers (n=7) Third members of the public (academics and researchers) (n =6). Specialists (n=10).	Health care payers (n=6) Health care providers (n=6). Third members of the public (academics and researchers) (n= 4) Specialists (n=4). Non-voting members (n=2).	Economic medical specialist. Clinical specialist. Specialist in medical statistics. Specialist in medical ethics.
Type of meetings	Public	Public	Private
Role	Development of guidelines for cost-benefit assessment. Selection of items and final decision on price adjustments.	Evaluation of findings of independent specialised organisations.	Confirmation of the pre-analysis consultation and determination of the framework of the cost-benefit analysis presented and reassessment of the cost-benefit analysis, if necessary.

Source: Kamae (2020)[307]

FIGURE 42. Diagram of the drug assessment process in Japan



Note: MHLW: Ministry of Health, Labour and Welfare; C2H: Centre for Health Outcomes Research and Economic Evaluation
Note2: * Total time from "preliminary consultation" to "completion of submission of manufacturer's analysis" should not exceed 9 months
Source: Hasegawa (2020)[306]

Documentation

Following the 2016 reform, a sub-committee of the *Chuikyo*, funded by the MHLW, developed a methodological guide, in which companies were asked to provide information on the following **14** points for the submission of an assessment[308,309]:

1. Perspective of the analysis used
2. Target population
3. Comparator (en)
4. Additional benefit in effectiveness and safety
5. Chosen method of analysis
6. Time horizon
7. Selected outcome measure
8. Sources of clinical data
9. Costing
10. Long-term care costs and lost productivity
11. Discount used
12. Chosen decision model
13. Study of uncertainty
14. Reports/publication with details of confidential data to be censored

Clinical assessment

Since the reform, *Chuikyo* conducts assessments of medicines on the basis of their incremental cost-effectiveness against the comparator(s), similar to the process conducted in England by NICE, i.e. without separating the clinical assessment from the economic evaluation. The comparator(s) should be selected primarily from among the therapies reimbursed by public health insurance that are expected to be substituted by the assessed medicine. In general, therapies that are widely used in clinical practice and produce a better outcome for patients should be selected. In the case where a single comparator cannot be determined, the comparator(s) should be selected taking into account comparators from the randomised controlled trials provided, the therapy referred to when determining cost-effectiveness, and other factors, based on consultations between the laboratory and *Chuikyo*[310].

When measuring the outcome, the *Chuikyo* stipulates that, as a general rule, data should be in the form of QALYs. Where this is not possible, other outcome measures may be used, subject to agreement between the laboratory and the Japanese entity. When calculating QALY, the quality of life score should be consistent with the general population in Japan, (using the preference-based measure or direct preference methods such as the standard gamble or the Time Trade-Off method). The *Chuikyo* states that data should be reported directly by the patient, and responses from a person close to the patient (family member or caregiver) can only be used when the patient is unable to respond by his or her own means[310].

As a first step before determining the cost-effectiveness of a therapy, the additional benefit of the selected therapy relative to the comparator(s) should be assessed. The *Chuikyo* stipulates that assessments of additional benefit should be made on the basis of a systematic review of randomised clinical trials. Clinical trial data should be directly compared with the selected comparator technology. Results from unpublished clinical studies/trials may also be included in the systematic review if deemed appropriate by the company[310].

When conducting a systematic review, clinical questions should be clearly presented. For example, a definition of clinical questions structured according to the PICO method (P: patient, I: intervention, C: comparator, O: outcome) can be provided. The Japanese evaluator states that the most appropriate clinical outcomes should be used to evaluate the therapy in terms of clinical efficacy, safety and health-related quality of life (HRQoL). *Chuikyo* takes into account the inclusion/exclusion criteria, the databases used, the search algorithm and the selection process of the studies provided by the company in accordance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement[310].

If the test facility does not provide sufficient data, or sufficient studies are not available, the *Chuikyo* may assess additional clinical benefit through comparative studies based on non-randomised clinical trials. In this case, the laboratory must sufficiently explain the study design provided, the methods of statistical analysis used and the sample size of the studies, among other issues[310]. In the event that no clinical trial information is provided using the comparator chosen for the assessment, the *Chuikyo* may use indirect comparisons, subject to agreement between the organisation and the test facility. In these cases, the assessment of additional benefit takes into account a number of factors such as the characteristics of the therapy and/or disease, the background of the participants, and the quality of the studies. If the results shown by the tested medicine are inferior to those of the comparator(s), the cost-effectiveness analysis is not performed[310].

Orphan drug assessment

Japan has an orphan drug designation and approval system similar to that practised by the European Medicines Agency. This system is aimed at medicines indicated for diseases with a prevalence of less than **1/50,000** in the country, for which no other alternatives are available, or for which the new medicine is expected to be significantly more effective and safer than medicines available in the country. When a drug is designated as an orphan drug, it receives a research grant, priority counselling by the PMDA, tax incentives and priority for approval[311].

In addition, these medicines receive a price premium of **5-20%** over the initial price set by the MHLW[312].

Economic evaluation

Chuikyo determines that a cost-effectiveness analysis should be used. If the clinical data shown indicate an additional benefit of the assessed medicine, the ICER should be calculated from the expected cost and effectiveness in each treatment group. In cases where the technology is equivalent or superior in terms of effectiveness (non-negative incremental effectiveness) and lower in terms of cost relative to the comparator, the technology is considered "dominant" without the need to calculate the ICER. If the new medicine does not demonstrate additional benefit, a cost comparison should be performed following a cost-minimisation analysis. If a cost-effectiveness analysis of the assessed medicine is available and published in an academic journal or has been evaluated by an international public health technology assessment body, it should also be submitted to the Japanese authority.

The standard perspective to be used is that of the public health payer, including costs, comparators and target populations within Japan's public health insurance system. In addition, analyses from other perspectives may be presented. If the introduction of an assessed therapy has a direct influence on productivity, the *Chuikyo* considers it acceptable to conduct a broader analysis that considers these costs and computes the productivity loss[310].

In addition, to predict the prognosis and future treatment costs, the *Chuikyo* stipulates that decision analytic models, such as Markov models, should be used and an analysis of the internal and external validity of the model should be presented. The assumption used to build the model should also be clearly specified and the parameters and data sources used to complete the model should be shown[310]. The base model should not include long-term public care costs, nor productivity losses due to incapacity for work. If included in other models, they can only be estimated from Japanese data.

The time horizon of the presented assessment should be long enough to assess the influence of the new therapy in terms of demonstrated efficacy and cost, justifying the choice of the new therapy[310]. Costs and health outcomes should be discounted at a discount rate of **2%** per year. This discount rate should be modified to between **0%** and **4%** in the sensitivity analysis for both costs and health outcomes[310].

When assessing model uncertainty, the *Chuikyo* indicates that a parametric sensitivity analysis should be performed. For situations where the time horizon is long, sensitivity analysis should be performed with a shorter time horizon, using the same period for which clinical trial data are available. Sensitivity analyses are necessary for parameters with larger variations and for data that are based on assumptions, if actual data are not available or there is possible heterogeneity between Japanese and international data. The *Chuikyo* states that a **95%** confidence interval should be used to account for the variance of the estimator. In addition, it indicates that the use of probabilistic sensitivity analyses is desirable, in which the distribution used in the analyses, scatter plots of the cost-effectiveness plane, as well as cost-effectiveness acceptability curves[310] should be presented.

Involvement of patients and scientific societies

Patients and scientific societies are not actively involved in decisions on the assessment, pricing and reimbursement of medicines in Japan. Patients are involved in a limited and indirect way in the evaluation of therapies because the Japanese evaluation system takes into account patient-reported outcomes when calculating the QALYs contributed by the evaluated therapy.

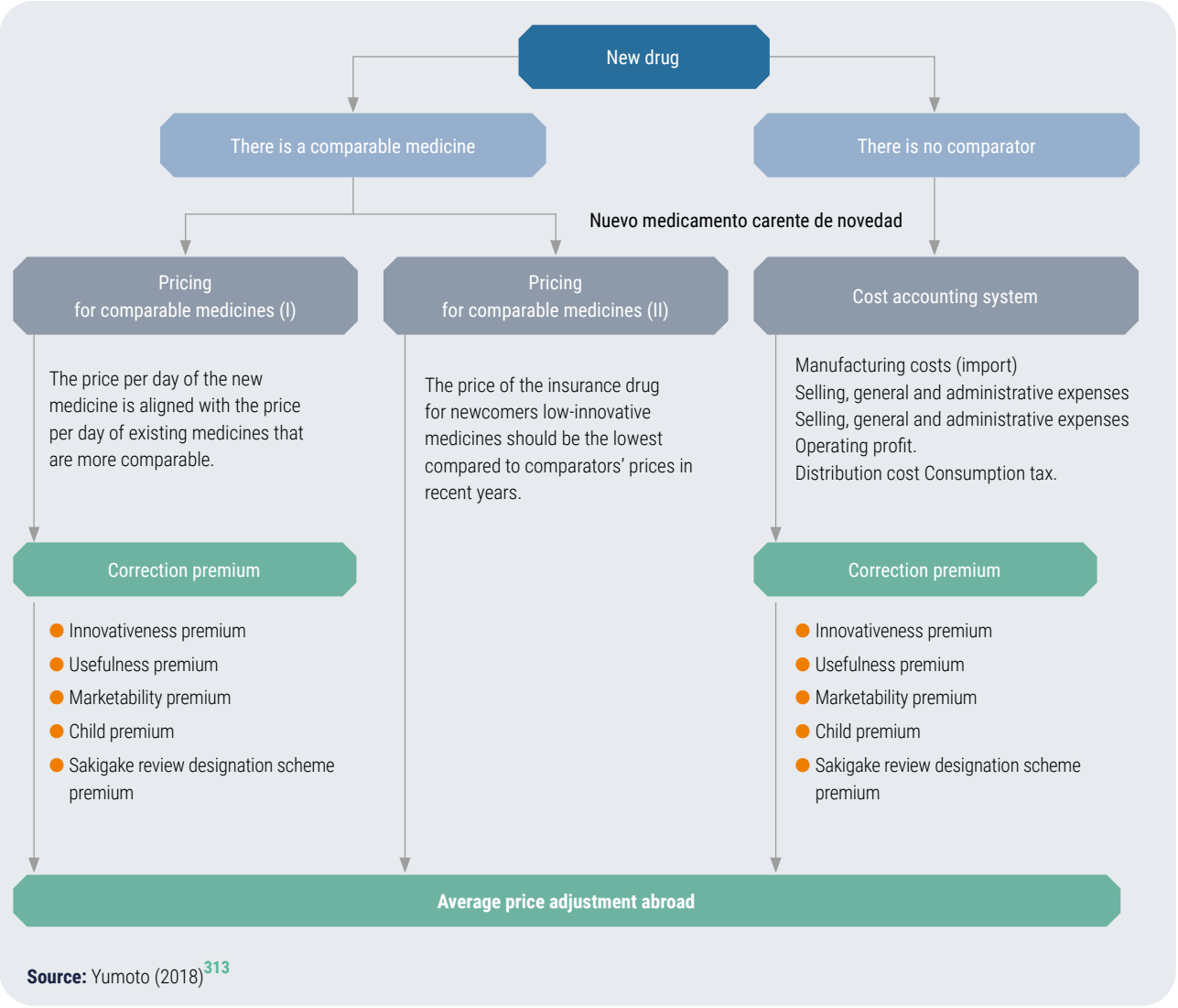
P&R decision elements

Japan uses a complex system to determine the price of medicines based primarily on the distinction between comparable and non-comparable therapies, followed by a series of price corrections and/or price premiums. Finally, the price is adjusted by taking into account prices in other countries (see section on reference prices) (**Figure 43**).

If there is a comparable medicine to the new therapy, the price is decided on the basis of the price of the "similar" medicine already on the Japanese market. If the new medicine does not offer any improvement over the comparator, the price will be the same as the price of the already available therapy. However, if it offers any additional improvement, the Japanese system offers a price premium of between **5%** and **120%** over the price of the comparator, depending on various parameters, such as degree of innovation, paediatric use, indication in RRD, or whether it has *Sakigake* designation (which implies that the approval of the drug was obtained in Japan before other countries and that the first human clinical trial or proof of concept was conducted in Japan) (**Figure 44**)[305].

On the other hand, if the new medicine is considered to be a disruptive therapy and not comparable to other therapies available in the country, the price is set using the cost accounting system. Under this method, the cost of manufacturing and distribution of the medicine, as well as other operational costs, are calculated, while adding a percentage of profit for the sponsor company. This system is also influenced by the premium system[305].

FIGURE 43. Method of drug pricing in Japan



Source: Yumoto (2018)[313]

FIGURE 44. Price correction through premium system in Japan

Bonus	Bonus percentage	Description of the improvement
Innovativeness premium	70-120%	New mechanism of action, more effective or safety, improved treatment method
Usefulness premium	5-60%	Increased effectiveness or safety, improved method of treatment
Marketability premium	5%, 10-20%	Medicines for rare diseases or specific, etc.
Child premium	5-20%	The dosage and usage is specifically designed to for children, etc.
Sakigake review designation scheme premium	10-20%	Approval of the drug was obtained in Japan earlier than in other countries, etc.

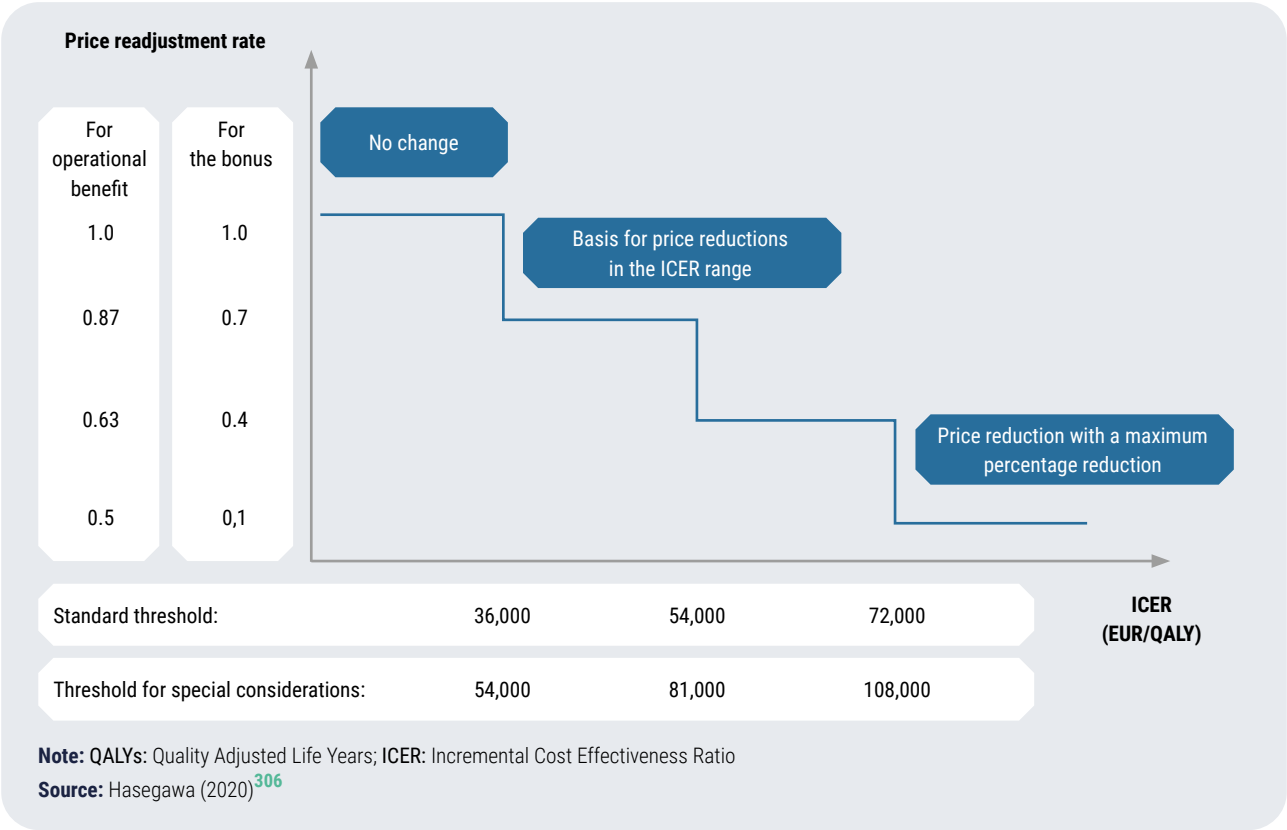
Source: ICEX (2020)[314]

Cost-effectiveness threshold

In Japan, there is a system of explicit cost-effectiveness thresholds that introduces a final price adjustment based on the ICER of the evaluated medicine. In general terms, a base threshold of €**38,000**/QALY, below which the price of the drug should not be adjusted. If the ICER is between €**38,000-58,000**/QALY If the price is calculated using the cost accounting method, the price is reduced at a rate of between **0.7** and **0.4** of the innovation premium or between **0.87** and **0.63** of the company's operating profit when the price is calculated using the cost accounting method. Finally, if the ICER exceeds **€76,000**/QALY, the price must be reduced at a rate of up to **0.1** of the innovation premium or **0.5** of the company's operating profit (**Figure 45**). In any case, the final price after such adjustments should not fall below the price corresponding to an ICER of €**38,000**/QALY (or €**58,000**/QALY in the case of products with special considerations)[306].

In addition, the Japanese system allows higher thresholds for so-called "special consideration" medicines, which refers to those indicated for rare diseases, paediatric use or certain cancer medicines. The expert subcommittee is in charge of judging whether a medicine qualifies for these special consideration thresholds[306].

FIGURE 45. Price adjustment rate as a function of threshold in Japan



Note: QALYs: Quality Adjusted Life Years; **ICER:** Incremental Cost Effectiveness Ratio
Source: Hasegawa (2020)[306]

Finally, in cases where a product has multiple indications or heterogeneous target population groups, a price adjustment rate is first determined for each sub-population, based on the calculated ICER for these groups. Then, the weighted average of the calculated price adjustments is estimated, based on the population size of each group, rather than a weighted average of the ICERs obtained for each population[306].

International reference prices

For the pricing of medicines, the MHLW uses external reference prices to adjust prices that deviate by more than **25%** from the prices set in the US, UK, Germany and France[315]. That is, the price receives a downward correction if it is **1.25** times or more the average foreign price. Conversely, if the price of the medicine is **0.75** times or less the average foreign price, it receives a bonus[316].

Financial agreements and their monitoring

When it comes to negotiating drug funding, in Japan there are no agreements between the government and pharmaceutical companies, either financial or performance-based[317].

In 2016, a national registry-driven clinical research project was initiated, leading to the establishment of the Clinical Innovation Network (CIN). This platform is funded by the Japan Medical Research and Development Agency and aims to establish an appropriate registration infrastructure for the efficient clinical development of new medicines. The development of this platform is supported by a working group consisting of MHLW and PMDA staff for the design of the platform and its use for the assessment of marketing approval applications for pharmaceuticals[318,319]. The CIN currently consists of 6 databases on different pathologies such as muscular dystrophy, rare diseases in adults, rare and chronic diseases in children, stroke, cognitive impairment and patients with rare cancers in the country, and in the future isexpected to serve as a starting point for assessing medicines based on real practice data[318,320].

...TO BE HIGHLIGHTED IN JAPAN

- ✔ *Premium system to define the price of therapy, depending on different parameters*
- ✔ *System of explicit cost-effectiveness thresholds, where the price is modulated according to the ICER, with higher thresholds for medicines of special consideration*
- ✔ *Price premium for medicines with R&D carried out in Japan and approved in Japan before those approved in other countries (Sakigake)*
- ✔ *National clinical trial data monitoring system to support new drug entry*

NETHERLANDS

In the Netherlands, access to medicines is governed by the Health Insurance Act, enacted in 2006. The dynamics are determined by three main actors. On the one hand, the government determines a "basic health package" (including medicines and other services) to which all citizens must have access. On the other hand, citizens over the age of 18 are obliged to purchase basic health insurance, and are free to choose and change insurance companies. Risk premiums are the same for all insured persons, and are not affected by their state of health, age or background. Finally, insurers are obliged to accept anyone on their policy, regardless of their health status, and to ensure that the services of the government-determined "basic health package" are included in their policy[321].

Actors and process

The Dutch government has developed a process, with the aim of assessing medicines, deciding which medicines are to be funded (included in the "basic health package") and monitoring their use in actual clinical practice[322], which distinguishes outpatient medicines (dispensed in pharmacies) from inpatient medicines[323].

Outpatient medicines

The process of assessment and reimbursement of outpatient medicines starts with an application for inclusion of the drug in the "Drug Reimbursement System" ("*Geneesmiddelenvergoedingssysteem*", GVS) by the pharmaceutical companies to the Ministry of Health[324].

The National Institute of Health ("*Zorginstituut*", ZIN), an independent body that advises the Dutch Minister of Public Health, Welfare and Sport and responds to conflicts between health insurers and clients, carries out the assessment of these medicines, determining their therapeutic value, budgetary impact and cost-effectiveness. For this, it draws on the information and advice of the Scientific Advisory Committee ("*Wetenschappelijke Adviesraad*", WAR), composed of a Medicines Committee ("*Commissie Geneesmiddelen*", CG) and other independent experts with different profiles. In addition, throughout the process, marketing authorisation holders, as well as representatives of patient organisations, healthcare professionals and insurers, have the possibility to comment on the draft reports[323,324].

After the assessment has been carried out, the ZIN Steering Board issues its conclusions which, in most cases, are based on the WAR's recommendations. In some situations, the assessment process is followed by an "administrative phase", which aims to identify the social consequences of the conclusions issued by the ZIN. This phase, which may include advice from the Advisory Committee on issues related to the "*Adviescommissie Pakket*" (ACP), does not discuss fundamental aspects of the assessment conducted, but legal, policy and/or social aspects[324].

The final step is the decision by the Ministry of Health on the inclusion of a medicine in the GVS, in one of the three possible lists:

- **List 1A:** consists of groups of interchangeable medicines, i.e. with similar indications, dosage forms and target population. This group of medicines is subject to maximum fundable prices, above which the citizen must pay a co-payment for the amount exceeding this limit.
- **List 1B:** includes non-interchangeable medicines, for which no maximum fundable prices are set.

- **Schedule 2:** for medicines not included in Schedules 1A and 1B, which implies that their reimbursement is subject to special conditions, e.g. to a pre-determined population[325].

Hospital medicines

Unlike outpatient medicines, inpatient medicines are part of an open system, which means that they are automatically included in the "basic health package" as long as they meet criteria established by clinical research and practice, in other words, they have been previously demonstrated to be effective, or they have a marketing authorisation from the EMA[323,326].

Only medicines that pose a high financial risk to the system go through a formal review process. During this process, these medicines are temporarily excluded from the "basic health package" through the application of the *lock procedure*, a regulatory instrument implemented since 2015[326].

The selection of candidate medicines for the lock procedure is based on the analysis of the costs of medicines that could be introduced in the country in the next **2** years, as they are under evaluation by the EMA (Horizon Scan). The criteria for inclusion of a medicine in the lock procedure are: (i) the annual costs of introducing this medicine are ≥ €**40** million; or (ii) the annual cost of treating each patient is ≥ €**50,000** and the estimated total annual cost of treating the entire target population in the country is ≥ €**10** million[326].

The assessment procedure for hospital drugs consists of a preliminary (optional) step, followed by the assessment per se, and the possibility of a discussion on the social consequences of the recommendations (**Figure 46**)[326].

In the preliminary stage, the manufacturer has the right to request a prior consultation with the ZIN about its assessment process, allowing ambiguities, flaws or problems in its documentation to be detected at an early stage. In turn, at this same stage, the ZIN can consult with different professionals in the sector regarding doubts about the process, such as relevant variables, target population, or the positioning of the drug in the treatment algorithm, among others. Finally, this phase can also be used by the manufacturer to request scientific advice from the ZIN in relation to the approach to be used for the preparation of its documentation[326].

Following submission of the dossier by the manufacturer, the process of clinical assessment, budget impact estimation and, if necessary, a cost-effectiveness analysis (including calculation of the burden of disease) is initiated by the ZIN. Once this step is completed, the ZIN meets with the WAR to receive advice on the results, and the conclusions of this meeting are reflected in a new draft assessment report. The ZIN conducts a public consultation on the quality of the evidence used and the assessment conducted. This consultation involves the manufacturer, representatives of healthcare professionals, patient associations and insurers. The draft report with the new comments is discussed in a second meeting between the ZIN and the WAR. The next step is the production of a final report by the ZIN[326].

FIGURE 46. Assessment process and funding of hospital medicines in the Netherlands

Nota: ACP: Package Advisory Committee; **BIA:** Budget impact analysis; **FT:** Pharmaco-therapeutic; **CEA:** Cost-effectiveness analysis; **SW&P:** Established medical science and medical practice; **WAR- CG:** Scientific Advisory Council – committee on Medicinal Products; **ZIN:** National Health Care Institute.

Fuente: Ophuis and Diemer (2020)[326]

In case the outcome of the assessment is negative, i.e. it concludes that the medicine does not meet the criteria for research or clinical practice, the ZIN issues a recommendation for non-inclusion in the "basic health package". For drugs that meet the criteria, the ZIN issues a positive report[326].

Based on this (positive) report, the ZIN receives advice from the ACP on the social consequences of this assessment. At this meeting, the other actors previously involved in the process also participate. The ACP advises the ZIN Board on whether it believes the drug should be included in the "basic health package", based on four criteria (need, effectiveness, cost-effectiveness and feasibility)[326].

The last step is a final recommendation by the ZIN to the Ministry of Health on the inclusion (or not) of the drug in the "basic health package". At this stage, the ZIN may also advise the Ministry of Health on the need to initiate a negotiation or a financial agreement, based on the assessments and discussion of the social consequences. The final decision rests with the Ministry of Health. In the case of a negative conclusion of the ZIN about the medicine, the Ministry cannot include it in the "basic health package"[326].

For the assessment process of hospital medicines, the manufacturer can submit the required documentation according to a timeframe that suits him/her best. Within **2** weeks after receipt of the documentation, ZIN checks whether the required information is complete and, if so, the formal assessment process is initiated, with a deadline of **4** months[326].

Actual assessment times are longer than stipulated. For outpatient drugs in Schedule 1A, the average time between the submission of the documentation by the manufacturer and the reimbursement decision is **162** *days, while for drugs in Schedule 1B it is* **194** *days. For hospital medicines, the average delay is* **257** *days*[327].

In May 2019, the Netherlands started a pilot programme with the aim of streamlining the timelines related to the funding decision for medicines considered innovative[328] , which consists of conducting the assessment and funding process in parallel to the process of obtaining centralised marketing authorisation from the EMA[329]. Six cases were registered under this pilot programme, three of which had been completed by September 2021. In two of the completed cases (Rybelsius® and Evrenzo®), the reimbursement decision was published one week after the publication of the marketing authorisation by the EMA, while in the third case (Arikayce®), the reimbursement decision was published one month after the marketing authorisation[329].

Ministry of Health, Welfare and Sports (VWS)

The VWS ("*Ministerie van Volksgezondheid, Welzijn en Sport*") is responsible for drug policy, decisions on maximum prices for outpatient drugs, and the content of the "basic health package". It is also responsible for budgetary control, or to whom it is delegated (insurers, hospitals), and for centralised financial agreements, among other functions[323].

National Institute of Health (ZIN)

"The ZIN is responsible for the management of the ""basic health package"" and for carrying out the assessment and recommendation processes for funding and reimbursement, coordinating its advice through"

consultations with different actors involved in the process (manufacturers, insurers, patients, healthcare professionals and the advisory committees - WAR-CG and ACP). It is also responsible for conducting the Horizon Scan, and for suggesting candidates for the l*ock procedure*[323].

Scientific Advisory Committee (WAR)

The WAR provides scientific advice on the management of "basic health packages". It is composed of up to **50** independent experts, including physicians, scientists, researchers, health economists, pharmacists and policy advisors from the health sector. Within the WAR, there are **4** independent working committees, the most important of which is the Medicines Committee (MC), which is composed of **20** members from different backgrounds (general and specialised medicine, health economists, pharmacists and ZIN consultants), meets monthly with the WAR and is involved in all evaluation processes, as the main technical advisor on medicines-related issues[330].

Advisory Committee on the "Basic Health Package" (ACP)

The ACP advises the ZIN board on the proposed recommendations of the "basic health package". It analyses these recommendations on the basis of four criteria (need, effectiveness, cost-effectiveness, and feasibility) and certain cost-effectiveness thresholds, determined (see economic evaluation), determining whether the results of the ZIN evaluation will be socially desirable from the perspective of the various stakeholders in the sector[331].

It is composed of **11** members with expertise in the field of social security, health care and insurance, ethics, health decision-making, health technology assessment, public administration and the patient perspective[332].

Netherlands Health Authority (NZa)

The NZa ("*Nederlandse Zorgautoriteit*") has the task of regulating the market and supervising health insurers and providers, through various activities, such as ensuring that all insurers accept any citizen, regardless of age, health status or background; or that insurers offer the "basic health package" to their policyholders[333].

Dutch Authority for Consumers and Markets (ACM)

The ACM ("*Authority for Consumers and Markets*") is in charge of the supervision of competition in the Dutch market, and one of its responsibilities includes the health sector, for which the institution has a specific department. Part of the work related to this supervision consists of publishing working papers and conducting sector enquiries, indicating possible imbalances in the pricing system (excessive pricing), or reporting on the possibility of cost reductions through collective purchasing of medicines, among others[323,334].

Documentation

The documentation required for the evaluation and decision-making on the inclusion of medicines in the "basic health package" depends on the type of application, but generally includes a clinical analysis, an economic evaluation (in cases where the medicine demonstrates clinical superiority over comparators), and an estimate of the budgetary impact[335]. The following is a detailed description of what is required in each of these analyses.

Clinic

The clinical analysis document should include data related to the drug, the disease, and efficacy and safety outcomes[336]:

- Description of the drug: name, indication, current registration and funding status
- Introduction: cause, symptoms, prevalence, severity and treatment of the disease
- Methodology: comparator, literature search, relevant clinical trials
- Therapeutic value
  - Chosen variables
  - Excluded variables
  - Effectiveness results: primary and secondary variables
  - Safety findings: adverse effects
  - Outcomes of routine clinical practice
  - Applicability: target groups, contraindications, interactions, warnings and precautions
  - Convenience: frequency, timing and form of administration, packaging
- Conclusion

Economic

The economic analysis should include information on pricing and reimbursement decisions in other countries, a methodological section, followed by the results and conclusions of the analysis[337]:

- Introduction: indication, epidemiology (including subgroups), evaluations in other countries, purpose of the analysis
- Methodology
  - Population
  - Intervention
  - Comparator
  - Outcome variables
  - Time horizon
  - Assumptions: outlook, discount rates, etc.

- Literature review
- Model and parameters: structure (Markov, decision tree), parameters (costs, utility, probabilities)
- Internal / external validation
- Sensitivity analysis

- Results
  - Burden of disease
  - Incremental effectiveness
  - Incremental cost
  - Incremental cost-effectiveness ratio
  - Results of the sensitivity analysis
- Discussion and conclusion

Clinical assessment

Clinical assessment is based on whether a medicine meets the criteria established by research and clinical practice. Only medicines that are considered effective can be included in the "basic health package". The following are the main elements considered in these assessments[338].

Relative effectiveness

To determine whether a drug meets the criteria established by research and clinical practice, the ZIN assesses whether the risk-benefit ratio of a new treatment generates added value for the patient compared to the standard treatment. In other words, it asks whether the net benefit of the new treatment is relevant and sufficiently high compared to other treatments, and whether they can be sufficiently confident that this value will actually be generated in clinical practice[338].

Evidence-based medicine (EBM)

The ZIN analyses the quality of the evidence and the structure used in the generation of evidence[338].

- **Integrated assessment of research and clinical practice elements**: not only scientific aspects are used in the assessment (e.g. clinical trials), but also the experience of patients and healthcare professionals in clinical practice (users). Therefore, they consult with all these actors in all value-determination processes.
- **Appropriate evidence**: when determining the value of the analysis, they prioritise the most relevant and valid evidence, such as randomised trials versus observational studies.

- **Structure of the analysis**:
  - Determination of PICOT: population, intervention, comparator, relevant variables and minimum follow-up time required.
  - Determination of the minimum clinically relevant differences required.
  - Determination of the appropriate evidence profile for the analysis.
  - Assessment of the quality of the evidence, for each variable, through the GRADE methodology, where"high quality" represents a high degree of confidence in the estimates of intervention outcomes.
  - Making recommendations and conclusions, i.e. whether the drug has equal or greater added value than the comparator, and presenting arguments based on **4** blocks: (1) risk-benefit of the intervention; (2) quality of evidence; (3) appropriate approach to evidence generation; (4) opinions of professionals and patients.

Criteria

The criteria used in the clinical assessment are as follows[339]:

- **Therapeutic benefits**: based on clinically relevant variables (with preference given to endpoints over intermediates), compared to existing treatments in the same populations (direct comparisons are preferable).
- **Adverse events**: serious, common, unexpected adverse events and treatment discontinuations. The degree of laxity applied to the assessment of adverse events correlates with the severity of the disease.
- **Clinical practice**: medicines that have been used for more than **3** years, in more than **20,000** patients/years (chronic diseases), or that have been prescribed more than **100,000** times (non-chronic diseases) can provide data from routine clinical practice, thus increasing confidence in relation to the results observed in clinical trials.
- **Applicability**: The applicability of a medicine is limited if it cannot be administered to a relevant group of patients suffering from a disease. The applicability of the intervention is compared with the comparator, with preference given to those with greater applicability.
- **Convenience**: For this criterion to be considered, advantages in convenience (frequency, route of administration, time of administration, taste, packaging, etc.) have to be considered as significant clinical improvements.

Economic evaluation

All economic evaluations must comply with at least what is called the 'reference case', to allow comparability between different analyses carried out in the Netherlands. Deviations from the "reference case" are allowed, as long as they are well explained and substantiated (e.g. use of cost-effectiveness), however, alternative analyses are not allowed as a substitute for the "reference case". The parameters included in the "reference case" of the economic evaluations are detailed below[340]:

- **Time horizon**: prioritise the use of the patient's entire lifetime. The use of other time horizons is allowed, provided that the reason is justified.
- **Perspective**: societal, however, results can be disaggregated based on other perspectives, such as health sector, patient, etc.
- **PICOT** (patients, intervention, comparators, outcome variables, time horizon): preference for analyses whose PICOT is determined on the basis of consultations with relevant actors in the system. In cases where the ZIN requests the economic evaluation, it is mandatory to define the PICOT together with the ZIN.
- **Type of economic evaluation**: cost-utility, as it allows comparisons of outcomes in different types of disease.
- **Costs**: The methodology developed by Drummond (2015)[341], which includes all direct (health and non-health) and indirect costs, is required. To quantify productivity losses, the friction cost methodology should be used.
- **Efficacy**: For empirical studies, data from clinical trials should be used. For model-based studies, data collection should be based on a systematic review of the literature, prioritising randomised clinical trials and direct comparisons.
- **Utility**: measured through Quality Adjusted Life Years (QALYs). As a minimum, use of the EQ-5D-5l with normative values based on the Dutch population is expected.
- **Discount rates**: for costs, 4% is used, and for health outcomes, 1.5% is used.
- **Presentation of results**: total and incremental costs and health outcomes, as well as the incremental cost-utility ratio, should be presented.
- **Uncertainty and sensitivity analysis**: univariate sensitivity analysis (Tornado Diagram), probabilistic sensitivity analysis (cost-effectiveness plane and cost-effectiveness acceptability curve) and scenario analysis (tables) should be used.

Involvement of patients and scientific societies

In addition to the aforementioned participation in the bodies, patients and scientific societies have a limited role in the medicines assessment process, which is established on the basis of the comments made by both parties on the draft reports of the different evaluation committees, both for inpatient and outpatient medicines.

P&R decision elements

Criteria considered

Decisions to include medicines in the "basic health package" are based on the following four main criteria[342]:

- **Effectiveness**: this is a key criterion in the analysis, because if the medicine is not considered effective, none of the three additional criteria are assessed. Considering whether there is sufficient evidence on the effectiveness of the treatment is not always a straightforward process, as in many cases the minimum required evidence is not available, for example in the case of rare diseases.

- **Need**: consider whether the disease is severe, based on burden of disease and QALYs lost.
- **Cost-effectiveness**: they consider whether the cost-benefit ratio of the treatment is reasonable or acceptable. They argue that one of the consequences of funding non-cost-effective drugs is the opportunity cost of not funding other treatments.
- **Feasibility**: considers whether the inclusion of the medicine is feasible in practice, i.e. it measures whether the costs of the intervention are beyond the reach of the individual, but within the reach of society. Effectively, it establishes where the state's solidarity with an individual begins and ends.

The integration of social arguments

In the phase related to the discussion of the social consequences of a recommendation between the ZIN and the ACP, a process integrating multi-criteria decision analysis (MCDA) and accountability for reasonableness is used[343]. In this process, the arguments obtained from the previous phases (preliminary assessment and formal assessment) are weighted, and the contribution of each argument within the ZIN assessment context is determined. Starting from an initial situation (favourable/unfavourable), each argument can contribute positively or negatively, and be considered as a strong or not so strong argument. Some of these arguments are related to justice, fairness and equality[342].

This is done in order to structure the social debate and to frame it in a transparent way in the formal evaluation process. Furthermore, it serves to prioritise, in a systematic way, the criteria that are in conflict with each other, indicating the existing consensus among the parties involved, and focusing the discussion on the arguments for which there is no consensus among the participants of the evaluation process[342].

International reference price system

The Dutch Medicines Prices Act determines the maximum prices allowed in the Netherlands based on the arithmetic mean of the price of four countries: Norway, Belgium, France and the United Kingdom. Initially, Germany was one of these 4 reference countries, but was replaced by Norway in 2019, as the Ministry of Health considered the prices applied in Germany to be too high[323,344].

Cost-utility threshold

The cost-utility thresholds used as parameters for drug inclusion decisions are not prescriptive, so there may be situations where drugs with unfavourable cost-effectiveness results are included in the "basic health package", and situations where drugs with favourable results are not included. The official reference cost-utility thresholds used in the decision process are based on the following disease burden ranges (**Table 27**)[345].

TABLE 27. Cost-utility thresholds used in drug inclusion decision processes in the Netherlands

BURDEN OF DISEASE*	COST-EFFECTIVENESS THRESHOLDS
From 0.10 to 0.40	Up to 20,000€ per QALY earned.
Between 0.41 and 0.70	Up to 50,000€ per QALY earned.
Between 0.71 and 1.00	Up to 80,000€ per QALY earned.

Notes: QALYs: Quality Adjusted Life Years.

Note2: (*) calculated according to the proportional shortfall method, which divides the QALYs of a patient with the disease by the total QALYs of a healthy person in the same age group[346].

Source: Zwaap (2015)[345]

Budgetary impact

When pricing medicines in the Netherlands, the financial impact of the entry of the medicine into the country is taken into account. The budget impact dossier submitted by the company for the evaluation of the medicine should include the following elements[347]:

- **Introduction:** indication and positioning in the treatment algorithm, based on Dutch clinical practice guidelines.
- **Basis for analysis**: number of current and **3**-year patients, expected market penetration, risk of off-label use, current treatments, data to estimate annual cost per patient (frequency, adherence, etc.), main assumptions used.
- **Budget impact analysis**: estimation of the **3**-year financial consequences of drug implementation (annual breakdown), based on the costs of current treatments, the new drug and the difference in costs.
- **Conclusions**

Financial agreements and their monitoring

Between 2006 and 2012, the Netherlands implemented a systematic payment-by-results funding process for medicines considered to have a high financial impact, which included **4** years of funding based on mandatory additional evidence development by manufacturers. Medicines included in this process had to meet **3** criteria: (1) have a budgetary impact of more than €**2.5** million/year; (2) demonstrate therapeutic value superior to existing alternatives; and (3) have a well-defined set of relevant variables to demonstrate their appropriate use and cost-effectiveness in routine clinical practice[348].

After these 4 years, the ZIN reassessed the drug on its efficacy, cost-effectiveness and budgetary impact and, as a final part of the process, the ACP and the ZIN conducted an evaluation based on the four funding criteria used (necessity, effectiveness, cost-effectiveness and feasibility) and on the social consequences of keeping this drug in the "basic health package"[348].

In that period, **49** medicines were considered for participation in the process, of which **24** were excluded in the initial assessment because they did not meet one of the **3** necessary criteria. Of the **25** medicines included, information on the end of the process is only available for **12** of them. Five medicines (**40%** of the **12**) did not report sufficient scientific evidence to draw conclusions about their cost-effectiveness. For **4** of the **7** medicines with sufficient information, the incremental cost-effectiveness ratios exceeded the threshold of €**80,000** per QALY[348].

Currently, the main financial formula used by the Dutch government appears to be negotiations with suppliers on agreed price discounts, with the aim of balancing the budget, or keeping the included medicines within the cost-effectiveness thresholds. One such example is Yescarta® , for which the ZIN recommendation was to negotiate a **5%** price discount in order to keep it within the €**80,000** per QALY threshold, following evaluation of its results in routine clinical practice **51** months after inclusion[349].

The ZIN can also recommend to the Ministry of Health the implementation of outcome-based agreements, depending on the level of evidence presented and the certainty of the cost-effectiveness results. This is the case for Zynteglo® , whose recommendation includes both a **35%** discount to be considered cost-effective and an outcome-based agreement, with a reassessment of its cost-effectiveness in real clinical practice after a period of **5** years[350].

Conditional funding

Some medicines can be included in the conditional funding process as long as they meet five criteria: (1) they have received conditional or exceptional marketing authorisation from the EMA, or orphan drug designation; (2) the treatment is indicated for an unmet need; (3) the company applying for funding is the marketing authorisation holder, and the institutions co-applying for the application are independent; (4) the ZIN considers it plausible that the data provided by the study included in the dossier can demonstrate that the medicine can be included in the "basic health package"; and (5) the ZIN considers that, in the next **7** to **14** years, the medicine included can provide sufficient data to allow a definitive inclusion in the "basic health package"[351].

Marketing authorisation holders can apply for funding before the regular ZIN funding process starts, or following a refusal of an assessment process by the ZIN. In 2019, the government made €**24.2** million of budget available for the funding of drugs in this category. Once this amount was reached, applicants were put on a waiting list. The fund for these drugs was €**25.5** million in 2020 and €**26.8** million in 2021. Through this mechanism, the government expects to be able to include **2-3** drugs annually in the "basic health package"[352].

ZIN developed a programme called "appropriate health care" to assess the extent of utilisation of medicines, services and health products included in the "basic health package", identifying and reducing inefficiencies in the system, improving the quality of care, increasing health gains and reducing unnecessary costs. This assessment is carried out systematically for some diseases[353].

The process is carried out in four phases: selection, in-depth analysis, implementation and monitoring/evaluation. In the selection phase, the healthcare process of any selected disease is analysed, indicating which variables are to be included in the next phase (in-depth analysis), in which points for improvement in this care are identified, based on additional analyses of outcomes in routine clinical practice systematic reviews or new published clinical trials. The third phase is the implementation of these improvements by healthcare providers. In the fourth phase of monitoring or evaluation, the results of these changes are assessed, proposing further modifications where it is considered that there is room for improvement [353].

The elements used in the evaluation of appropriate health care are knowledge about care, its application in routine clinical practice, the outcome variables necessary for the evaluation of processes, the effectiveness of a treatment, its cost-effectiveness, and whether it meets the criteria of necessity and feasibility. The data sources used in these evaluations are, in general, insurance company databases ("claimdata") and registries[353].

In this respect, it is useful to give an overview of existing and developing health registrations in the country[354]:

- The Netherlands Clinical Audit Institute is an organisation responsible for the development and maintenance of **22** disease registries.
- PHARMO, an independent Dutch research organisation, maintains a network of databases containing information on more than **4** million (**25%**) of the population, and **10** years.
- The *Health RI* Foundation is developing, in collaboration with more than **70** organisations, a nationwide data infrastructure, with the aim of becoming a single platform for health data.
- ZIN is developing a project called "Control of Registrations of High Cost Medicines", which consists of the elaboration of a standard methodology for the implementation of health registrations.

...TO BE HIGHLIGHTED IN THE NETHERLANDS

- ✔ *Systematic integration of social elements into decisions*
- ✔ *Involvement of relevant actors throughout the process*
- ✔ *Development of a pilot system to speed up access to innovative therapies through parallel screening*
- ✔ *Transparency in the process and in the criteria used for decisions*
- ✔ *Use of cost-utility thresholds according to disease burden*
- ✔ *Use of a process integrating MCDA and accountability for reasonableness in the social impact assessment phase*
- ✔ *Implementation of a systematic programme to reassess the efficiency of the health system (including medicines)*

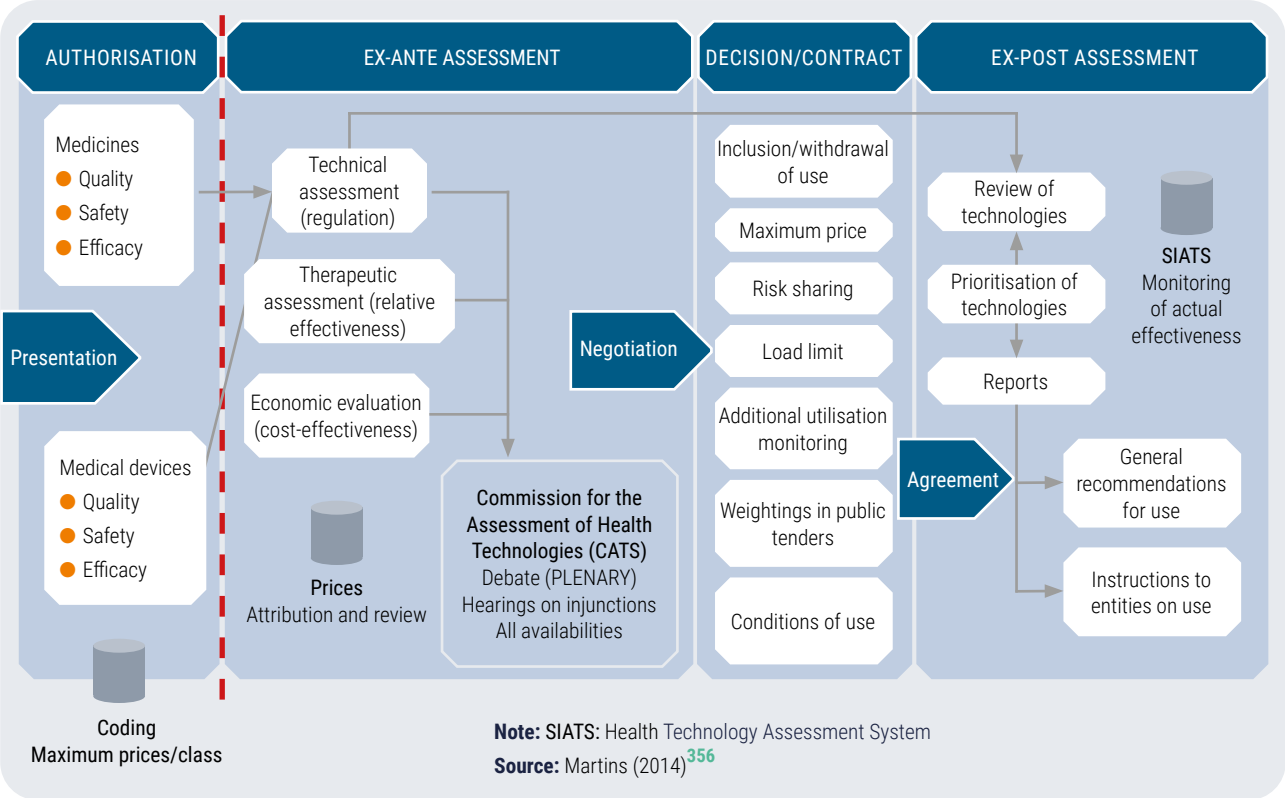
PORTUGAL

In Portugal, the assessment and funding processes of medicines are governed by the rules of the National Health Technology Assessment System (SiNATS), created in 2015 through Decree Law Nº 97/2015 of 1 June[355]. The entire management of SiNATS is carried out by the National Authority for Medicines and Health Products (INFARMED), which is subordinate to the Ministry of Health[355]. The process of funding any medicine in Portugal starts with obtaining a marketing authorisation from INFARMED or the European Commission. In order to obtain this authorisation, quality, efficacy and safety criteria are taken into account[356].

Actors and process

According to the standards set by SiNATS, the determination of the value of medicines should be done throughout their life cycle and not only at the time of market introduction. This life cycle is reflected in three stages, which are the "ex-ante assessment", the "funding/contract decision" and the "ex-post assessment" (**Figure 47**)[356].

FIGURE 47. The process of health technology assessment and funding in Portugal



Note: SIATS: Health Technology Assessment System
Source: Martins (2014)[356]

The *ex ante* assessment consists of four elements, namely the technical assessment, the clinical assessment, the economic assessment and the discussion between the sponsors and the Health Technology Assessment Committee[356]. The clinical and economic (ex-ante) assessments are carried out by the Health Technology Assessment Committee (CATS), which is an independent advisory body to INFARMED, and by INFARMED's Directorate for Health Technology Assessment (DATS)[356].

In the next stage (funding/contract) decisions are made about funding/non-funding (in the case of medicines dispensed in pharmacies) or utilisation/non-utilisation (in the case of medicines for hospital use), which is

followed by a process of negotiation and contract development, which may include conditions such as maximum prices, spending limits for the NHS, risk sharing based on data from routine clinical practice, conditions of use (indication, population, etc.), and monitoring or additional studies after market introduction[356]. Funding negotiations and recommendations are made by the INFARMED Board of Directors (BoD), together with the DATS. The funding decision is made by the Ministry of Health[356].

The monitoring of the risk-benefit ratio in actual clinical practice (ex-post stage) is carried out through the Health Technology Assessment Information System (SIATS), which collects the information necessary for cost-effectiveness reassessments related to the financing of medicines (dispensed in pharmacies) or their use (hospital medication), subsequent to their funding[356]. Reassessments and recommendations are made by CATS/DATS, and decisions are taken by the Ministry of Health[356].

Below, we detail the competences of the three main actors involved in the assessment and funding processes of medicines in Portugal (CATS, DATS and BoD).

Committee on Health Technology Assessment (CATS)

CATS is a specialised committee generally responsible for issuing opinions and recommendations, reviewing economic evaluation studies and proposing measures appropriate to the interests of public health and the National Health Service in relation to technologies, within the scope of SiNATS. It is a scientific body that does not depend on INFARMED, and liaises with the DATS in the pharmacotherapeutic and pharmacoeconomic evaluation of reimbursement processes. It is made up of a president, two vice-presidents and more than **150** members, who have a consultative role, adding value to the assessments through their profiles as clinicians from different specialties, economists, pharmacists and researchers[357–360].

INFARMED's Directorate for Health Technology Assessment (DATS)

The main attributions of INFARMED's DATS are (i) to ensure the management of SiNATS and SIATS; (ii) to manage the process of assessment, funding and decision on the price and reimbursement of health technologies; (iii) carry out prospective identification of health technology innovations and assess their potential impact on public health and the National Health Service (Horizon Scanning); (iv) ensure the implementation of policies for the control and evaluation of the health technology market, with special emphasis on subsidised technologies; (v) conduct periodic evaluations of the performance of the health technology assessment system; (vi) monitor the evolution of health technology prices; and (vii) collaborate in scientific and policy advisory activities. DATS is currently composed of a director (a pharmacist, with a PhD in public health and a specialisation in health economics) and about **25** members[361].

INFARMED Board of Directors (BoD)

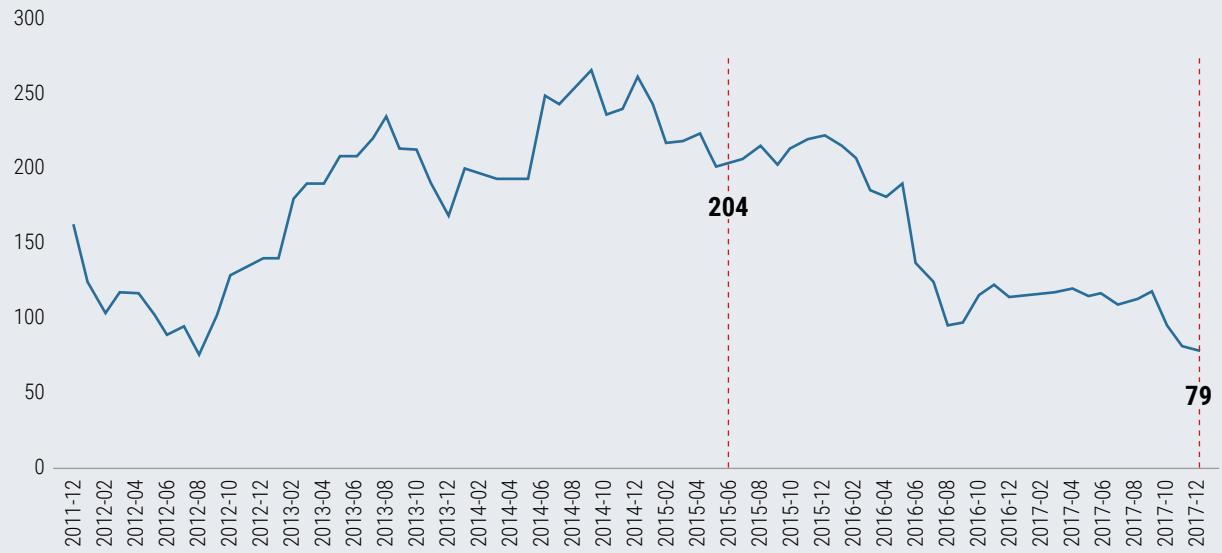
INFARMED's BoD is responsible, among other functions, for (i) regulating, supervising and monitoring the activities of the entities participating in SiNATS; (ii) regulating and authorising the prices of medicines funded by the SNS; (iii) authorising clinical trials with medicines and verifying compliance with good clinical practice; (iv) ordering the withdrawal of medicines from the market; and (v) deciding on requests for ex-ante assessment of the therapeutic and economic value of medicines. It is composed of a chairman, a vice-chairman and a member[362].

Following the request to initiate the funding process, INFARMED will have **20** days to request additional information it deems necessary for the process. In this case, the applicant has 10 days to send additional documentation or clarifications[363,364].

The deadlines established for a funding decision, by article 11 of Portaria Nº 195-A/2015, of 30 June, and amended by Portaria Nº 270/2017, of 12 September, are **30** days for generic and biosimilar medicines; **75** days for new indications of non-generic medicines already funded by the system, and **180** days for non-generic medicines that do not yet have funding[364,365].

The Ministry of Health's transparency portal discloses data up to 2017 on the average times for a funding decision[366]. Since the establishment of the maximum time limits in the process, the average time for a funding decision decreased by **60%** (Figure 48). The proportion of generics increased from **99%** in 2012 to **88%** in 2014, and ranged from **86%** to **88%** in 2015-2016.

FIGURE 48. Timing of drug funding decisions in Portugal, 12-month average



Source: Ministry of Health of Portugal (2021)[366]

Reports with activity indicators are also published on the INFARMED website[367]. The latest report published for the full year (2019) tracks compliance with the established deadlines, indicating that for biosimilar and generic medicines, **80-85%** of the indicated deadlines were met, while for new indications of the same medicine, only **50%** of the deadlines were met, and for new medicines, **38%** of the established deadlines[368].

Documentation

The elements included in the documentation required from the sponsor laboratory depend on the "initial proposal" made by the Evidence Assessment Group assigned by CATS for each process, and are therefore not preset. In

the proposal, the CATS shall include which efficacy and safety measures are necessary, the sub-populations and sub-indications requiring evidence; the comparators to be included; and the statistical analyses required[369].

Clinical assessment

The clinical assessment of the medicine is performed at national (centralised) level by the CATS Evidence Assessment Group, and takes into account the following criteria[369]:

1. Efficacy and safety measures
   a. Efficacy: mortality, morbidity, clinical effect
   b. Life expectancy
   c. Health-related quality of life
   d. Average duration of illness
   e. Safety measures (adverse effects, etc.)
   f. Other measures (use of resources, such as hospitalisations and medical visits)
2. Uncertainty about the outcomes presented (outcomes in subgroups or other indications, etc.)
3. Relationship between the outcomes presented and the probability that these are also demonstrated in routine clinical practice (heterogeneity of the population in routine clinical practice vs. the clinical trial population, e.g. presence of comorbidities, factors such as gender, age)
4. Benefit-risk assessment (based on measures of efficacy and safety)
   a. In the case of surrogate variables, their possible relationship with the final outcome should be presented, based, if possible, on systematic reviews and meta-analyses
   b. The results presented for adverse events should focus on those that are relevant, such as those that may have an important influence on the benefit-risk ratio; include mortality, serious morbidity, or a notable difference in quality of life; vary substantially between drugs with the same benefit, etc.
5. Assessment of the quality of the evidence for each outcome variable, using the GRADE methodology

Determination of clinical value versus existing alternatives

The clinical assessment report issued by CATS, which serves as the basis for the funding decision, includes, on the one hand, whether the medicine provides an additional clinical benefit, and on the other hand, the extent of this benefit, always in relation to the existing risk. This is done for each variable analysed[369].

In determining existing value, these are classified into: (i) evidence, indication or suggestion of added value relative to the comparator; (ii) evidence, indication or suggestion of equivalence relative to the comparator; (iii) evidence, indication or suggestion of inferiority relative to the comparator, where evidence refers to the highest possible level of evidence; and suggestion, to the lowest possible level[369].

The extent of therapeutic value is classified into four categories: (i) "major" therapeutic value added; (ii) "moderate" therapeutic value added; (iii) "minor" therapeutic value added; (iv) "unquantifiable" therapeutic value added[369].

The outcome of the clinical evaluation is published together with the outcome of the economic evaluation and the funding decision on the INFARMED website, and includes data related to the epidemiology, existing technologies, the comparators selected in the evaluation, the main data from the clinical and economic evaluation and the conclusions[370,371].

Economic evaluation

For situations where there is a technical-scientific demonstration of added value or equivalence for the indications, the application for funding requires an economic evaluation, which follows the principles described below[372,373]:

- **Evaluation principles**: Identify outcomes in terms of economic benefits of health technologies, to inform the pricing and reimbursement decision process. Economic evidence is evaluated in terms of its appropriateness, scope and quality.
- **Comparators**: The economic evaluation should compare the new technology with all other relevant options for the treatment of the disease, as defined within the pharmacotherapeutic evaluation and contained in the CATS pharmacotherapeutic recommendation.
- **Population and subgroups**: The economic evaluation should analyse the use of the new technology in the entire target population and relevant subgroups, defined in the scope of the pharmacotherapeutic evaluation and included in the CATS pharmacotherapeutic recommendation.
- **Therapeutic effect**: The economic evaluation should be based on an assessment of all measures of efficacy contained in the CATS pharmacotherapeutic recommendation. However, additional methods and requirements may be needed to assess the economic advantage of the technology.
- **Time horizon**: The time horizon used in the cost-effectiveness model should be long enough to include all important differences in the technologies being compared, in terms of costs and consequences.
- **Techniques of analysis**: It is recommended that cost-effectiveness studies be conducted with consequences expressed in terms of Quality Adjusted Life Years (QALYs). Health consequences should not be expressed in monetary terms. Cost minimisation is allowed when the therapeutic outcomes of comparators are equivalent[372].
- **Perspective**: The cost perspective should be that of the NHS. The consequences perspective should consider all health effects on current patients.
- **Identification, measurement and valuation of costs**: All health resources relevant to the analysis should be identified. Separate and detailed information should be provided on the health resources used (measured in physical units) and how they are valued (unit prices or costs).
- **Measurement and assessment of health effects**: The EQ-5D-5L is the preferred instrument for assessing health-related quality of life.

- **Study design and models used in the studies**: The study should include a full description of how the model used reflects the natural course of the disease and the impact of treatment(s) on disease, health outcomes and costs. The approach chosen for modelling should always be justified. If it is possible and reasonable to apply different approaches, it is preferable to implement the simplest one.

- **Evidence and assumptions related to other aspects of the model**: The evidence underlying the parameters and assumptions should be identified through a systematic and explicit process, taking into account the quality of each source and its appropriateness to the healthcare context in Portugal.

- **Information based on expert opinion**: When there is no empirical evidence on a parameter of interest, or its representativeness in the context of the target population is questionable, expert opinion should be used.

- **Quantitative analysis of primary data to support modelling**: Statistical analyses performed to support model parameters that are not fully published in the peer-reviewed literature should be documented in a statistical annex.

- **Decision uncertainty and identification of the need for additional evidence**: Parameterised and non-parameterised uncertainties should be systematically assessed and explicitly characterised, using sensitivity analysis and scenario analysis.

- **Validation**: Validation should focus on all elements of model development and elucidate the method of transposing and generalising model predictions to the Portuguese context.

- **Discount rate**: All costs and consequences should be discounted at a discount rate of **4%**.

- **Cost-effectiveness presentation and results**: Interventions should be evaluated through a full incremental analysis.

- **Uncertainty and additional evidence gathering to support decision-making on aspects to be reassessed**: The results of the uncertainty analyses should form the basis of a prioritised list of additional evidence needs, which will aim to support formal requests for evidence gathering, to be submitted in the reassessment phase.

- **Budget impact analysis**: The budget impact analysis should take a NHS perspective and consider the costs related to the comparators selected in the economic evaluation.

- **Ethical aspects**: A full list of authors and their institutional affiliation, a list of the funding body(ies) and a statement of the contribution of each body and each author to the study must be provided.

The economic study is reviewed by a CATS expert, and the CATS Executive Committee draws up a recommendation with the conclusions of the pharmacoeconomic evaluation. The outcome of the assessment is published, as well as the clinical assessment, together with the funding decision resolution, on the INFARMED website[370,371].

Involvement of patients and scientific societies

Patients and experts may be invited to participate in the medicines assessment process. For patients, this is done at the stage of drafting the "initial proposal" documentation required by CATS. More specifically, patient associations registered with INFARMED, and which have undergone a training course, can participate in the development of this proposal by contributing their knowledge regarding the target population, currently existing comparators and, above all, patient-reported outcomes[374].

P&R decision elements

External reference pricing

Portugal uses an external reference pricing system for non-generic hospital medicines and for medicines dispensed in community pharmacies. Prices are determined on the basis of prices published in other countries for the same or similar medicines. The maximum prices cannot exceed the maximum prices of the reference countries, taking into account the production or import phases. The choice of reference countries is made annually, taking into account EU members with a GDP similar to that of Portugal. These reference countries are used both for the pricing of new medicines and for the annual price review carried out in the country[356]. The reference countries chosen for 2021 were Spain, France, Italy and Slovenia[375].

In the case of hospital generic medicines, prices must be at least **30%** lower than the maximum prices applied to reference (originator) medicines, with the same dosage and presentation. In case the reference medicine has different dosages, the maximum price of the dosage closest to the one being evaluated with the generic is applied[376].

Hospital medicines may be subject to the notified price regime[377]. These medicines may have a notified MVP higher than the maximum reimbursed MVP. The notified RRP may be increased annually by up to **10%** above the reported RRP, with a maximum limit of €**2.50** per year[378].

Maximum price regime

Medicines are subject to a ceiling price regime, which are the Retail Price (RRP), authorised by INFARMED or, in the case of funded medicines dispensed in pharmacies, defined through the co-payment system[379]. As an alternative to the price cap regime, notified price regimes may be established. The practice of rebates is allowed throughout the entire medicine circuit, from the manufacturer to the point of dispensing[355].

Price revisions

As part of the annual review process of the maximum PVP for each non-generic medicine, AIM holders must submit, by 15 December of each year, the price lists to be applied, which come into effect on 1 January of the following year. The revision is made on the basis of the average of the international reference prices applied on the first day of the month prior to the month in which the revision is made. Only downward PVP revisions are made, with the exception of medicines with maximum prices of €**5.00**, which may be upward[377].

The maximum price of a medicine may be revised exceptionally, for reasons of public interest or at the initiative of the AIM holder. Such a review can only occur in the third year from the approval of the initial market launch price. The criteria for deciding on these revisions are: (i) whether or not it is essential in the therapeutic arsenal;

(ii) its productive and economic viability; (iii) the cost of production; (iv) the budgetary impact for the NHS; (v) the price of existing alternatives; and (vi) its relative efficiency[377,380].

Support criteria

According to Article 25 of Decree-Law Nº 97/2015, the two criteria used for the decision to fund medicines for hospital use are: (i) technical-scientific criteria that demonstrate the existence of therapeutic innovation, or therapeutic equivalence; and (ii) economic advantage[355]. In cases of therapeutic equivalence, the maximum price established for medicines for hospital use is **10%** lower than the existing alternative, or a **5%** reduction in the maximum price of the medicine evaluated, together with a reduction in the prices of the existing alternatives that, added together, amount to a zero budgetary impact for the NHS[355].

Cost-effectiveness threshold

Portugal's official methodological guidelines state that, to support negotiations, all economic analyses provided by pharmaceutical companies for their health interventions should calculate the opportunity cost, using ranges for the cost-effectiveness threshold of between **10,000** euros and **100,000** euros per QALY gained[381].

Financial agreements and their monitoring

Innovative formulas

Data related to the implementation of innovative financial formulas (risk-sharing arrangements, payment by results, etc.) in Portugal are scarce[382]. In a 2013 survey of selected European countries, **84** risk-sharing arrangements were identified in Portugal, of which **74** (**88.1%**) were financial, **2** (**2.4%**) were performance-based, and the rest (**9.5%**) were a combination of both[383].

According to a review by Gonçalves (2018), expenditure ceilings have been implemented for all medicines for hospital use, and other types of risk-sharing agreements have been announced, including full cost per patient treated agreements, and others based on outcomes[382]. However, the authors of this study only identified **5** such agreements, published between 2013 and 2018[384–388], concluding that this is an underestimated list, as it is based on public INFARMED assessment reports, and excludes risk-sharing agreements established in the context of pharmacy dispensed medicines or other confidential agreements[382]. INFARMED publishes all assessment reports it produces, specifying whether or not a risk-sharing agreement has been made, but without information on the details.

The assessment of technologies in the post-marketing stage (reassessment), based on data from actual clinical practice, was one of the main modifications introduced by Decree-Law Nº 97/2015[355]. There are currently **4** registries developed by INFARMED (hepatitis C, spinal muscular atrophy, lysosomal depot diseases and minimum registry for biological medicines), **2** registries created between INFARMED and other public entities (national oncology registry and AIDS information system) and **1** registry resulting from collaboration between INFARMED and medical societies (national registry of rheumatic patients)[389].

The reassessment procedure for medicines can lead to different decisions on their funding by the NHS. In one of them, medicines are excluded from public co-payment funding if they do not demonstrate efficacy or effectiveness; if they are priced 20% higher than non-generic therapeutic alternatives under the same co-payment regime, and with the same therapeutic purpose; or if they present a lower added therapeutic value compared to

similar non-generic medicines. In other cases of reassessment, price corrections can be made, budget limits on use can be set, or additional forms of monitoring and control can be established[389].

For its part, INFARMED publishes monthly data related to consumption and expenditure on medicines, in order to identify areas of strategic interest and draw up proposals for intervention to ensure the sustainability of the system[390].

...TO BE HIGHLIGHTED IN PORTUGAL

- ✔ *Centralised clinical and economic evaluation body (INFARMED)*
- ✔ *Transparency, albeit partial, of the process and results of clinical and economic evaluation, with monitoring indicators*
- ✔ *Well-defined methodological guidelines in terms of required documentation, clinical and economic evaluation implementation*
- ✔ *Systematic reassessment of medicines post-funding*

SWEDEN

Sweden has a universal, decentralised national health care system with three separate levels of government: national, regional and municipal. The budgets and provision of health services (including medicines) are provided by the autonomous regions, which fund them mostly through taxation of citizens. Patients make co-payments of a maximum of €**115** per year for hospital services (including medicines), and €**230** for medicines purchased in community pharmacies, which are included in the Benefit Scheme[391].

Actors and process

The funding and reimbursement processes for medicines are different for outpatient and inpatient medicines.

Outpatient medicines

In 2020, the market for outpatient medicines corresponded to €**4.2** billion, of which, **3.4** billion (**80%**) is public funding (part of the *Benefit Scheme*) and the remainder is divided between prescription medicines not included in the Benefit Scheme (**7%**) and non-prescription medicines (**13%**), which are not funded[391,392].

The decision on the price of outpatient medicines and their inclusion in the reimbursement system is made by the Dental and Pharmaceutical Benefits Agency ("*Tandvårds- och läkemedelsförmånsverket*", TLV) under the Swedish Ministry of Social Affairs. The process begins with an application from the pharmaceutical company to the TLV, indicating its price proposal and including the required clinical and financial documentation. Based on this information, the TLV board can grant two types of reimbursement, general and restricted. The former implies that the reimbursement applies to the entire indicated population, while the latter includes restrictions regarding indications/populations or implies that the manufacturer must provide additional evidence to be included in the reimbursement system[391,393–395].

In some cases, TLV may take a negative decision, indicating its non-conformity with the price requested. In these situations, the manufacturer may reapply for reimbursement, proposing a reduction in the price initially requested. On the other hand, some drugs may be withdrawn from the market after their introduction, either because they lose their marketing authorisation ("*deregistered*"), because the manufacturers request exclusion from the reimbursement system, or because the TLV reassess the drug, considering that the reimbursement is not adequate[391,393–395].

Hospital medicines

In 2020, the market for hospital medicines was estimated at €**1.1** billion[391,392]. The funding and pricing of hospital medicines is done at regional level, through public procurement procedures. The regions have a list of preferred medicines to be considered as first line of treatment, where possible. The economic evaluations used by the regions for decision-making on price, reimbursement and first-line treatments are based on economic evaluations carried out by TLV[391].

These studies are commissioned by the regional authorities, through the Committee for New Therapies ("*Nya läkemedelsterapier*", NLT). In 2020, TLV conducted a total of **14** economic evaluations for NLTs, compared to **12** in 2019 and **11** in 2018. This increase is explained by the intention to prepare for the expected entry of new advanced therapies in the coming years[396].

Below are the main actors involved in the pricing and reimbursement process for medicines in Sweden.

Ministry of Health and Social Affairs

Overall and legislative responsibility for the health sector lies at national level with the Ministry of Health and Social Affairs ("*Socialdepartementet*"). The National Board of Health and Welfare ("*Socialstyrelsen*"), a public authority within this ministry, has a supervisory role over the regional councils, acting as the government's central advisory and supervisory body for health and social services. The Ministry of Health and the National Board of Health and Welfare collaborate with central government bodies, in addition to the Medicinal Products Agency ("*Läkemedelsverket*", LV), the Swedish Board of Health Technology Assessment ("*Statens beredning för medicinsk och social utvärdering*", SBU), the TLV, and the Swedish Public Health Agency ("*Folkhälsomyndigheten*"), among others[391].

Dental and Pharmacological Benefits Agency (TLV)

The TLV is a government agency under the Ministry of Health and Social Affairs, responsible for pricing and reimbursement decisions for outpatient medicines. Specifically, these decisions are made by the Pharmaceutical Benefits Steering Board, which consists of a group of experts within the agency. The

government is responsible for the appointment of the Steering Board, which consists of seven members with expertise from regional councils, universities/centres with expertise in health economics and user groups/ patient organisations[391].

The director general may participate in meetings of the Pharmaceutical Benefits Board, but does not make decisions about reimbursement. Other responsibilities of TLV also include determining the margins for state-subsidised pharmaceuticals for all pharmacies in Sweden, regulating drug substitution in pharmacies and supervising certain areas of the pharmaceutical market[391].

Regional authorities

In Sweden there are **21** regional/local authorities, which are responsible for the management of most health care units, such as hospitals and primary care centres. The regional councils are grouped into six health care regions to facilitate cooperation in specialised health care. The principles of resource allocation vary between regions. Most regions have decentralised much of the financial responsibility to the health districts through centralised budgets, but budgets related to medicines (outpatient and inpatient) remain the responsibility of the regional authorities. For outpatient medicines, the regions receive an annual grant from the central government (the "*Benefit Scheme*", which had €**3.4** billion in 2020). Hospital medicines, on the other hand, are funded through fees and taxes by the regional authorities[391].

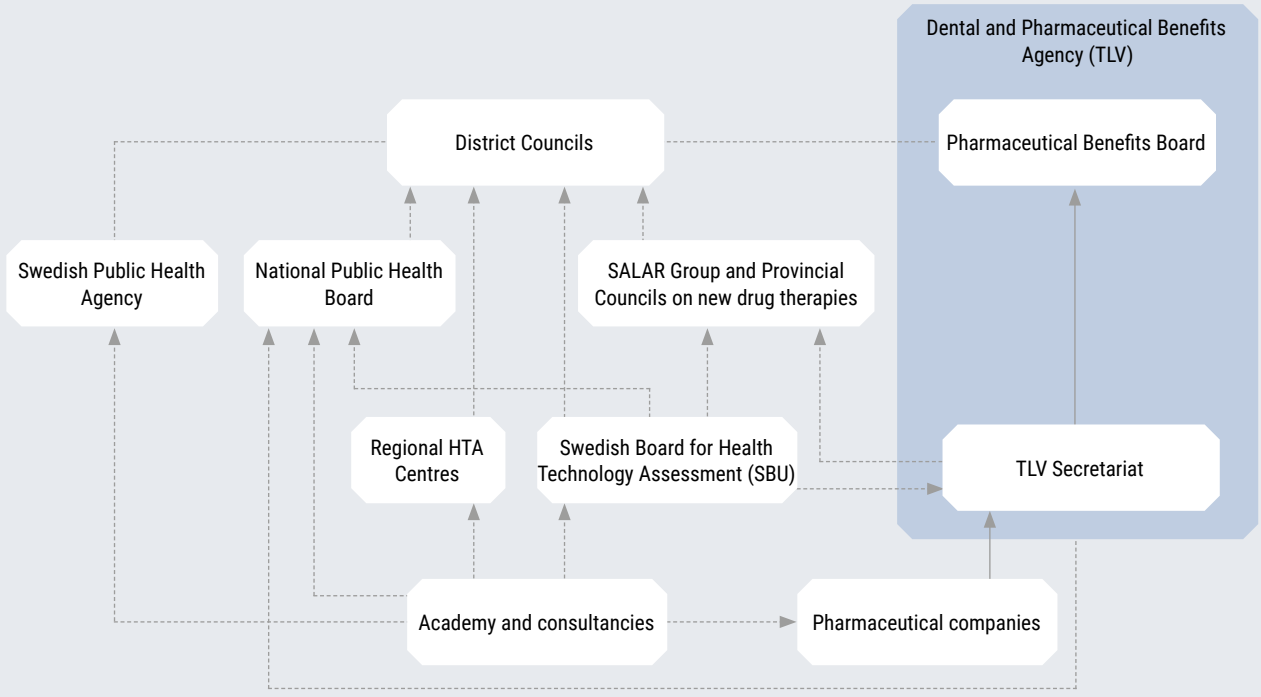
In each of the **21** regional authorities, there is at least one pharmacotherapeutic committee, which supports clinicians in their treatment decisions through the annual publication of recommended first-line drugs. The regional authorities have also appointed a group of experts called the New Therapeutics Steering Board (NLT), who are responsible for requesting studies and economic evaluations from the TLV, in order to make recommendations on treatment options[391].

The regional authorities have the right to deliberate with TLV before the Pharmaceutical Benefits Steering Board takes any decisions, as its decisions directly affect the financial situation of the regions[391].

Other actors

There are several organisations involved in the assessment, pricing and reimbursement processes for medicines. The two decision-making bodies are the TLV and the regional authorities, whose functions and composition are detailed in the previous section. The roles of other organisations involved in the processes, which are generally advisory in nature, are detailed below (**Figure 49**)[397]:

FIGURE 49. Organisations carrying out, reviewing or making decisions based on cost-effectiveness evaluations in Sweden



Note: HTA: Health Technology Assessment. **Source:** Heintz (2014)[397]

National level

- **The National Council on Health and Welfare**: Government agency that, among other functions, issues guidelines related to disease treatment and social services. These guidelines contain scales from **1** to **10** related to recommendations for interventions for certain pathologies (where 1 represents the maximum level of recommendation). Criteria of disease severity and cost-effectiveness are used in the development of these guidelines.

- **Swedish Board for Health Technology Assessment (SBU)**: The SBU is a national, independent body that carries out, on behalf of various stakeholders, assessments in the healthcare field, including clinical, economic, ethical and social aspects.

- **Swedish Public Health Agency**: Has national responsibility for public health issues. For some of the projects for which it is responsible, it carries out health technology assessments, for which it has a department of epidemiology and health economics.

Regional and local level

- **Regional Assessment Agencies**: Their objective is to support regional authorities with health technology assessments. To avoid duplication of assessments and to increase the impact of each report, the SBU setup a network of health technology assessments (HTA network), encouraging regular meetings.

- **New Therapeutics Steering Board (NLT)**: The NLT decides which medicines should be formally evaluated, with the TLV commissioning the evaluations. The NLT is mandated by the regions to issue recommendations on the use of these medicines. In some cases, the NLT negotiates prices, discounts and financial agreements with pharmaceutical companies before issuing its recommendation.

- **Swedish Association of Local and Regional Authorities ("*Sveriges Kommuner och Regioner*", SKR)**: SKR supports regional and local authorities with documentation, recommendations and advice.

According to the Pharmaceutical Benefits Regulation, the time between the manufacturer's application for reimbursement and the TLV's pricing and reimbursement decision on new medicines may not exceed **180** days[391,398]. These timelines are systematically monitored and published in the TLV's annual reports. According to the 2020 report, the actual decision timelines were **101**, **115** and **121** days in 2018, 2019 and 2020, respectively[396].

Documentation

The documentation required by TLV in the application for assessment, pricing and reimbursement is as follows[399]:

- **Applicant's details**: company name, address and registration number
- **Contact details**: name, phone, email and fax
- **Product data**: name, description, quantity per pack / carton, unit price
- **Patients**: target population, estimated number of patients
- **Average daily cost, per patient** (including supporting documentation for calculation)
- **Estimated annual sales**: based on the entire target population and the selling price to the pharmacy.
- **Comparators**: alternatives to existing drugs or treatments (including supporting documentation)
- **Clinical assessment** (TLV or EMA)
- **Marketing authorisation** (TLV or EMA)
- **Economic evaluation**
- **Domestic price comparison** (alternatives)

In general, the documentation requested by the different regions for the assessment of hospital medicines is similar to that required by the TLV, as the economic assessments of hospital medicines prepared by the regions are based on the assessments carried out by the TLV.

Clinical assessment

Based on the analysis of recent economic evaluation reports (including clinical data), the clinical assessment is based on the following information[400–402]:

- **Description of the disease**: prevalence, incidence, mortality, morbidity, quality of life
- **Description of the medicine**: indication, mechanism of action, method and frequency of administration
- **Treatment**: current diagnostic and treatment recommendations (guidelines), comparators used
- **Efficacy and safety results**: clinical trial used, number of patients included, primary and secondary variables, results by subgroups, adverse events (serious, most common, total, etc.)
- **Systematic reviews, meta-analyses or indirect comparisons**
- **Comments or conclusions of the assessment carried out by the EMA**

The TLV assesses aspects such as the relevance of the variables included, the degree of certainty of the results obtained, the quality of the evidence provided and the magnitude of the results.

Economic evaluation

The TLV publishes the official methodological guidance to be used by pharmaceutical companies when submitting an economic evaluation[397]. It should be used as a supporting tool (not as a manual) when submitting an assessment or study. The main guidelines are detailed below[397,403]:

- **Perspective**: Economic evaluation should be carried out from a social perspective.
- **Comparator**: The treatment should be compared with the most appropriate alternative treatment in Sweden (e.g. the most commonly used). The comparator treatment can be a medicine, another treatment or no treatment.
- **Technique of analysis**: In general, the use of Quality Adjusted Life Years (QALYs) is recommended. For treatments that primarily affect survival, both costs per QALY and costs per Life Years Gained (LYG) can be presented. If the use of QALYs is not practically feasible (e.g. diseases that produce severe pain for a short period of time), a cost-benefit analysis based on willingness to pay can be presented. In cases of medicines with equal therapeutic value, a cost comparison may be sufficient.
- **Time horizon**: The time frame should be sufficient to cover the entire period affected by changes in health outcomes and costs. For treatments that affect survival, the patient's entire lifetime should be used to calculate QALYs.
- **Costs**: all relevant costs must be included, calculated and evaluated. Unit costs and resource consumption should be presented separately. The loss of labour productivity associated with the treatment should be included, using the human capital methodology.
- **Quality of life**: standard gamble (SG) and time trade-off (TTO) methodologies should be used to calculate QALYs. As a second option, the *rating scale* methodology can be used. Indirect methods, such as the application of the EQ-5D questionnaire, are also allowed.
- **Modelling techniques**: Models should, as far as possible, be internally and externally validated. They are considered useful for improving external validity in clinical trials (adjusting for differences between trials and clinical practice), or for adapting clinical trials conducted in another country to Swedish conditions.
- **Discount rates**: A discount rate of 3% should be used for both health outcomes and costs.

- **Sensitivity analysis**: Scenarios with discount rates of **0%** and **5%** should be used. In addition, a scenario where **3%** rates are applied for costs and **0%** for health outcomes should be used. The performance of the sensitivity analysis is considered an important aspect.

- **Quality of evidence**: for economic evaluations not published in international journals, greater transparency and quality of the evidence presented will be demanded.

Involvement of patients and scientific societies

Patients are represented on various TLV committees, including the Pharmaceutical Benefits Committee. Their participation mainly includes providing feedback during the reporting process and, in many cases, attending specific meetings organised by TLV on a particular medicine. In addition, TLV organises a patient dialogue forum twice a year to identify improvements in various aspects of healthcare[404].

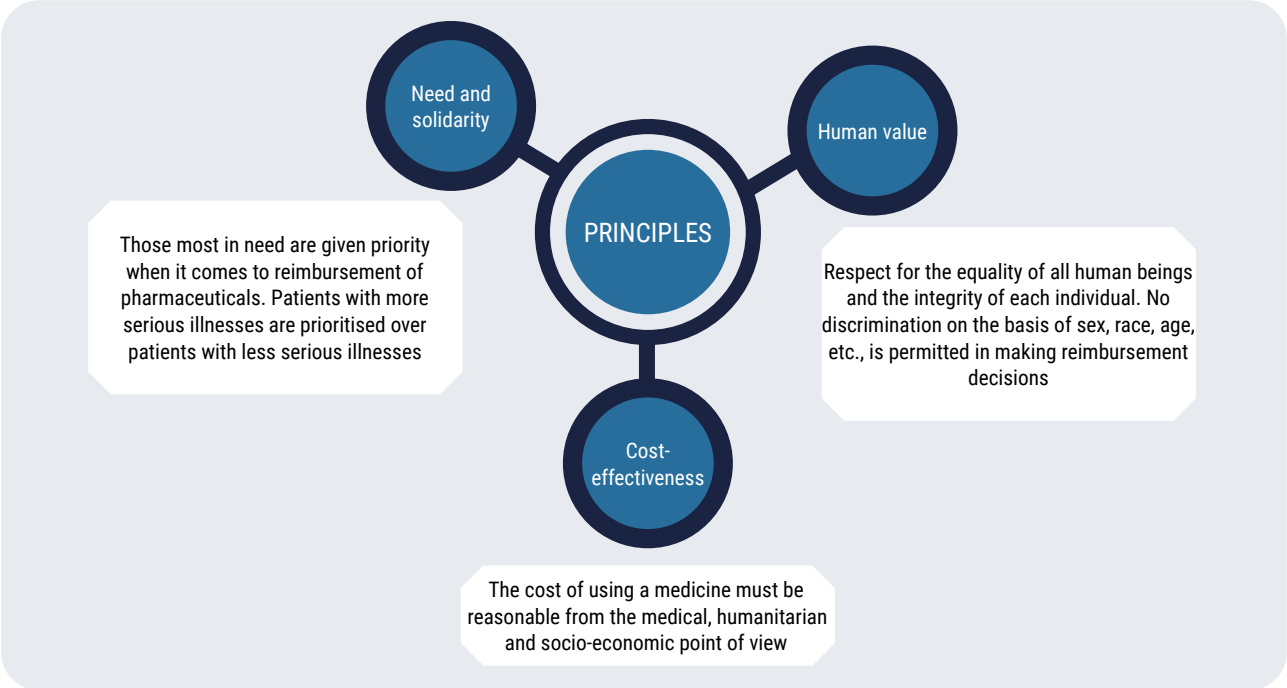
P&R decision elements

In 2002, Sweden abandoned the internal reference pricing system as the basis for the pricing and reimbursement processes used in the country since 1990, and implemented a value-based pricing scheme, the main feature of which is the use of the cost-effectiveness criterion for the funding of medicines[405,406].

Criteria for pricing

The pricing and funding decisions made by TLV are based on an ethical platform for prioritisation of public funds, stipulated in the Health and Medical Services Act 1982 (updated in 2017) and the Pharmaceutical Benefits Act 2002[407–409]. The three principles of this platform are as follows (Figure 50)[391]:

FIGURE 50. Summary of the three main criteria for price setting in Sweden



Cost-effectiveness threshold

Sweden does not set specific cost-effectiveness thresholds for decision-making and does not include budget impact as a formal criterion for pricing and reimbursement decisions[410–412]. In actual practice, according to an analysis of treatments funded in Sweden between 2005 and 2011, the probability of a positive funding decision was **50%** for medicines with incremental cost-effectiveness ratios between €**79,400** (non-severe diseases) and €**111,700** (severe diseases)[413].

Financial agreements and their monitoring

Risk-sharing agreements

Since 2014, risk-sharing agreements (RSAs) between regional authorities and pharmaceutical companies have been incentivised through the return of part of the sales by pharmaceutical companies in cases where the established cost-effectiveness criteria are not met[414].

In 2019, there were a total of **52** RSAs in force in the country, of which **15** (**27%**) were for cancer, **12** (**23%**) for haemophilia, **9** (**17%**) for psoriasis, **6** (**11%**) for hepatitis C and the rest (**22%**) for other pathologies. The total amount repaid by pharma companies as part of these agreements in 2019 was €**310** million of euros versus €**270** million in 2018, €**93** million in 2017, €**71** million in 2016, €**25** million in 2015 and €**300,000** in 2014[415].

In 2017, the total amount of contracts included in RSAs was €**394** million (**15%** of the total medicines in the Benefit Package). The reimbursement made by pharmacists that year (€**93** million) represented almost **25%** of the total cost[414].

Discount after 15 years on the market

In January 2014, a scheme was introduced whereby a **7.5%** price discount is applied to medicines with more than **15** years on the market, with little or no generic competition[391]. Discount decisions are made twice a year (on 1 June and 1 December), and are published on the TLV website. The decision process, which lasts **6** months, starts with a preliminary publication of the rebate candidates, and continues with rounds of reviews and comments by manufacturers, until the publication of the final decision[416].

The pharmaceutical market is monitored on an ongoing basis, both at national and regional level. As an example, TLV systematically monitors the **7.5** per cent price cut on products older than **15** years, the result of which is published annually. The savings generated by this mechanism were €**140** million between 2014 and 2019, in line with expectations[391,415].

In addition, the TLV monitors the medicines included in the reimbursement system, with the aim of determining whether these medicines will remain in the reimbursement system and on the basis of what price or condition, ensuring that publicly funded medicines are cost-effective. The decision on which medicines to reassess is based on dialogues between TLV and the regional authorities[417]. All reassessment processes carried out since 2005 are available on TLV's website[418]. For example, there are currently **11** tumour necrosis factor (TNF) inhibitors in the reassessment process[419].

To a large extent, this monitoring is possible thanks to the existence of a comprehensive, coordinated and population-based registry system, which was created by an agreement between the State, regions and municipalities, with an initial investment of €**58** million between 2012-2016 to promote its creation and integration[420].

Thus, Sweden has more than **100** national registers, which are integrated into clinical processes and have the capacity to generate real-time data, as they are based on individual data on diagnosis, interventions and outcomes after each treatment, within the entire health production chain. Each registry undergoes annual review and funding approval by an Executive Committee[421].

These registers are managed by a group of seven members, of which **2** are national (Board of Health and Welfare and Swedish Research Council), **4** regional and **1** from the SKR. The development of these registers is done through a Collaborators Group (**9** representatives from centres of competence, national representatives and specific register managers), which functions as the main support group for the management function, and is supported by an Expert Group (**5-7** members) that assesses the quality of existing registers, and registers candidates for new registers based on stipulated guidelines and criteria[421].

In addition, **6** centres of competence have been created for these national registries. In these centres, several registries share staff and systems costs that a single registry would not be able to bear, such as those related to analytical work, the use of data to support clinical practice, and the support needed to make data available for the benefit of different users[421,422].

A follow-up report on these registries is published annually, including the strategy, funding, collaborations, quality, patient participation and results. As an example, the number of scientific publications based on these registries was **589** in 2019 (compared to **121** in 2009 and **203** in 2012, when the creation of these registries was promoted in a coordinated manner and with specific funding)[423].

...TO BE HIGHLIGHTED IN SWEDEN

- ✔ *One of the pioneer countries in the implementation of health technology assessment processess*
- ✔ *It does not use international reference price systems*
- ✔ *Inclusion of social criteria in decisions, such as human value and necessity*
- ✔ *Economic evaluation from a social perspective, using the human capital approach to quantify labour productivity losses*
- ✔ *Compliance with the deadlines stipulated in the evaluation process*
- ✔ *Conducting risk-sharing arrangements in a structured and performance-informed manner*
- ✔ *Comprehensive, integrated, population-based system of records, enabling real-time data generation*

2.1. Comparative tables

In order to facilitate the reader's understanding of some of the key aspects of the assessment and pricing processes for medicines listed above, this section provides an easy overview of the main differences that exist in the selected countries for each item.

- Most countries separate the assessment process from the pricing and funding decision. The actors most frequently represented in both parts of the process are technicians from health administrations, health professionals and health economists (**Table 28**).
- The maximum regulated times for the overall process range from **126** days in Scotland to **540** days in Japan, with an average of **229** days. France, England and Italy have fast-track procedures (**Table 29**).
- All the countries analysed base economic evaluation on cost-utility analysis, except Austria and Germany (**Table 30**). All the countries analysed, with the exception of France, Sweden and the Netherlands, preferentially use the perspective of the funder of health services. Among them, Canada, South Korea and Portugal do not allow the use of the social perspective. In contrast, Sweden only allows the social perspective in the economic evaluation. The discount rate used varies between **1.5%** and **5%** (**Tabla 31**).
- Only Scotland, England, the Netherlands and Portugal use explicit efficiency thresholds. In others, such as Spain, Australia, South Korea, France and Sweden, health authorities do not define explicit thresholds, although some scientific literature has determined under which (implicit) cost-effectiveness thresholds funding decisions for health interventions have been made in the past. Four countries use higher thresholds for rare or end-of-life diseases (**Table 32**).
- Germany, Austria and England are characterised by free pricing at entry of the medicine into the country, at least for the first year (**Table 33**). The number of countries included in the external price reference basket ranges from **4** to **27** (**Table 34**).
- The criteria used to set the price include humanistic, clinical and economic aspects. All countries rely on clinical aspects (predominantly therapeutic value, although this concept is open to different interpretations) and economic aspects (especially cost-effectiveness and budget impact). Only Sweden, Australia and the Netherlands explicitly use humanistic aspects or social criteria (**Table 35**).
- Scotland, England, Italy and the Netherlands have specific funds for the funding of certain medicines, ranging from**10.5** to **1** billion euros per year (**Table 36**).

TABLE 28. Participation of different actors in assessing and funding the price of medicines at the national level, by country

Countries	Phases	Health professionals			Patients			Industry		Health administration	Other Adm.	SSCC	Health insurance	Health economists	Other
		Primary care	Specialised care	Pharmacists	Pathology patients	Patient representatives of the pathology	General representatives/ health consumers	General	Of the medicinal product						
Germany	CA-EE		✔			✔✔			✔✔	✔		✔✔	✔		-Representatives of hospitals and dentists.
	P&R												✔		
Australia	CA-EE-P&R	✔	✔	✔		✔✔	✔	✔		✔				✔	-Any interested organisation.
Austria	CA-EE		✔								-Federal provinces.		✔		-Federal Chambers: Commerce, Labour and Pharmacy. -Austrian Medical Association.
	P&R		✔✔							✔	Ministries: -Digitisation and economic location. -Finance. -Sustainability and Tourism.		✔		-Federal Chambers: Economy, and Labour.
Canada	CA-EE	✔	✔	✔	✔✔		✔			✔				✔	-Specialist in bioethics.
	P&R	✔		✔						✔				✔	-Specialists in administrative and health law.
South Korea	CA-EE	✔	✔	✔		✔	✔			✔		✔		✔	-Statistics. -Evaluation specialists. -Representatives of the hospital society.
	P&R	n.a.													
Scotland	CA-EE-P&R	✔	✔	✔		✔✔	✔	✔		✔				✔✔	As support. -Nursing. - Network of clinical experts. -Statistics.
Spain	CA-EE		✔			✔✔			✔✔	✔		✔✔			
	P&R									✔	-Ministries: Economy, Industry, Finance. -Territorial. representatives.				

Countries	Phases	Health professionals			Patients			Industry		Health administration	Other Adm.	SSCC	Health insurance	Health economists	Other
		Primary care	Specialised care	Pharmacists	Pathology patients	Patient representatives of the pathology	General representatives/ health consumers	General	Of the medicinal product						
France	CA	✔	✔	✔		✔✔	✔						✔✔		-Biostatistics.
	EE	✔	✔	✔		✔✔	✔						✔✔	✔	
	P&R									✔	Ministries: -Economy, Finance and Recovery. -Work, Employment and Integration. -Solidarity and Health.		✔		
England	CA-EE	✔	✔	✔		✔✔	✔	✔	✔✔	✔	-Welsh Government.	✔✔		✔	-Nursing. -Statistics. -In support. -Public research institutes. -Relevant comparator companies.
	P&R	n.a.													
Italy	CA-EE		✔	✔		✔✔			✔✔	✔		✔✔			
	P&R	✔	✔	✔		✔✔			✔✔	✔	-Territorial representatives.	✔✔		✔	
Japan	CA-EE-P&R	✔	✔	✔						✔			✔	✔	-Academics. -Researchers.
The Netherlands	CA-EE-P&R	✔	✔	✔		✔✔			✔✔	✔		✔✔	✔✔		
Portugal	CA-EE	✔	✔	✔		✔✔				✔				✔	
	P&R	✔	✔	✔						✔				✔	

Note: Sweden is not included in this table due to the great heterogeneity of its evaluation committees. ✔ Participation with decision-making power; ✔ ✔ Participation in a supportive capacity (speaking but not voting); **Adm:** administration; **CA**: clinical assessment; **EE:** economic evaluation; **n.a.**: not available; **SSCC**: scientific societies; **P&R**: price and reimbursement.

TABLE 29. Maximum regulated times for the different phases of the assessment and funding processes in the countries studied (days)

Country	Clinical assessment	Economic evaluation	Price negotiation	The whole process	Existence of fast-track process (duration)
Germany*	90		180	360	
Australia				140-154	
Austria	No data available				
Canada				186-201	
South Korea	120-150		90	240-360	
Scotland				126	
Spain	20	10		180	
France	90		90	180	✔ (not specified)
England*				290	✔ (150)
Italy				180	✔ (100)
Japan*	360-450		90	450-540	
The Netherlands				162-257	
Portugal				180	
Sweden				180	

Note: * Entry times in these two countries are not comparable with the others, because in Germany, England and Japan, the medicine is available in the country from the time of marketing authorisation and does not require assessment by the agencies in those countries.

TABLE 30. Type of economic evaluations permitted in the countries studied

Country	Cost-effectiveness	Cost-utility	Cost-benefit	Cost minimisation	Comments
Germany					Efficiency frontier.
Australia	✔	✔	✔✔	✔	
Austria			✔	✔	
Canada		✔		✔	
South Korea	✔	✔		✔	
Scotland		✔		✔	
Spain	✔	✔		✔	
France		✔		✔	
England	✔	✔	✔	✔	
Italy	✔	✔	✔	✔	
Japan		✔		✔	
The Netherlands	✔✔	✔		✔	
Portugal		✔		✔	
Sweden	✔✔	✔	✔✔	✔	

Nota: ✔ Primary evaluation ✔✔ Secondary evaluation

TABLE 31. Characteristics of economic evaluation in the countries studied

Country	Selected comparator	Evaluation perspective		Time horizon	Discount rate		Sensitivity analysis	Comments
		Funder	Social		Costs	Results		
Germany	Treatment used in routine practice.	✔	✔	As extensive as possible. At a minimum, average CTs time.	3%		✔	Efficiency frontier. Use of four perspectives.
Australia	Therapy it replaces.	✔	✔✔	The patient's entire life if the disease is fatal. Otherwise not specified.	5%		✔	
Austria	Treatment used in routine practice.	n.a.					✔	
Canada	Treatment used in routine practice.	✔		Sufficiently extensive to see the effect of the therapy.	1.5%		✔	
South Korea		✔		Sufficiently extensive to see the effect of the therapy.	n.d.		✔	
Scotland	Treatment used in routine practice.	✔	✔✔	Sufficiently extensive to see the effect of the therapy.	3.5%		✔	
Spain	Treatment used in routine practice and used in CTs.	✔	✔✔	Sufficiently extensive to see the effect of the therapy.	3%		✔	
France	Clinically relevant.	✔✔	✔*	The patient's entire life.	1.5% - 2.5%		✔	Cost-consequence analysis.
England	All potentially relevant.	✔	✔✔	Sufficiently extensive to see the effect of the therapy.	3.5%		✔	
Italy	Treatment used in routine practice.	✔	✔✔	The patient's entire life.	3%		✔	
Japan	Therapy it replaces.	✔	✔✔	Sufficiently long to see the effect of therapy or the same period as CTs data.	2%		✔	Incorporation of analytical decision models (e.g. Markov).
The Netherlands	Treatment used in routine practice.	✔✔	✔	The patient's entire life.	4%	1.5%	✔	PICOT analysis.
Portugal	All potentially relevant.	✔		Sufficiently extensive to see the effect of the therapy.	4%		✔	
Sweden	Treatment used in routine practice.		✔	The patient's entire life or that allows the health effect to be seen.	3%		✔	

Nota: ✔ Main perspective; ✔ ✔ Additional perspective; **n.a.:** not available.

***** France uses a type of perspective called collective perspective, which mixes components of the health perspective with a broader perspective.

CTs: clinical trials

TABLE 32. Cost-effectiveness thresholds used in the countries studied

Country	Existence of cost-effectiveness threshold		Threshold amount (€/QALY)	Existence of different thresholds (€/QALY)		Comments
	Explicit	Implicit		Rare diseases	End on life	
Germany						It does not use cost-effectiveness, but efficiency frontier.
Australia		✔				**32,000**€/QALY according to the Donovan[98] and Lybrand studies[99].
Austria	n.a.					
Canada	✔			✔ (**105,000-140,000**)		It uses a cost-effectiveness threshold to set a maximum price.
South Korea		✔				It depends on GDP per capita. **17,000**€/QALY according to the Bae study[163].
Scotland	✔		**23,500-35,200**		✔	The upper threshold can be exceeded only if certain criteria are criteria are met.
Spain		✔				**22,000-25,000** €/QALY according to the Vallejo-Torres study[24].
France		✔				**100,000**€/QALY only for ODs and oncology according to the Forest study[224].
England	✔		**23,000-35,000**	✔ (**360,000**)	✔	
Italy	n.a.					
Japan			**38,000-58.000**			It uses a cost-effectiveness threshold to set a maximum price.
The Netherlands*	✔		**20,000-80,000**			
Portugal	✔		**10,000-100.000**			
Sweden		✔				**79,400-111,700**€/QALY according to Svensson's study[413].

Note: ***** The Netherlands uses differential thresholds depending on the "burden of disease". **n.a:** not available. **ODs:** orphan drugs

Note[2]: In this table, an implicit threshold has been considered when health authorities have not defined an explicit threshold and there are publications that determine under which cost-effectiveness threshold the evaluated health interventions are approved or rejected.

TABLE 33. Elements of pricing and funding for branded medicines in the countries studied

Country	Free price	External reference pricing	Alternatives available in the country	Value-based pricing	Other types of negotiations
Germany	✔	✔	✔		
Australia			✔	✔	
Austria	✔	✔	✔	✔	
Canada		✔	✔	✔	✔
South Korea		✔	✔	✔	
Scotland				✔	✔
Spain			✔	✔	
France		✔	✔	✔	
England	✔			✔	✔
Italy				✔	✔
Japan		✔	✔	✔	✔
The Netherlands		✔		✔	
Portugal		✔		✔	
Sweden				✔	

TABLE 34. Characteristics of the external reference pricing used in the countries studied

Country	**Objective** (whether it is a binding or supporting criterion in the decision)	Number of countries	Reference countries	**Calculation method** (average, highest price, lowest price)
Germany	Support	15	Belgium, Denmark, Finland, France, Greece, Great Britain, Ireland, Italy, the Netherlands, Austria, Portugal, Sweden, Slovakia, Spain and the Czech Republic.	Not defined.
Australia	Does not use.			
Austria	Binding	27	Austria, Belgium, Bulgaria, Croatia, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Latvia, Lithuania, Luxembourg, Malta, Netherlands, Poland, Portugal, Romania, Slovakia, Slovenia, Spain, Sweden and Sweden.	Average.
Canada	Binding	7	France, Germany, Italy, Sweden, Switzerland, the United Kingdom and the United States.	Average.
South Korea	Support	7	United States, United Kingdom, Germany, France, Italy, Switzerland and Japan.	Not defined.
Scotland	Does not use.			
Spain	It does not use explicitly.			
France	Binding	4	Germany, Italy, Spain and the United Kingdom.	Lowest price.
England	Does not use.			
Italy	Does not use.			
Japan	Binding	4	United States, United Kingdom, Germany and France.	Highest price and lowest price.
The Netherlands	Binding	4	Norway, Belgium, France and the United Kingdom.	Average.
Portugal	Binding	4	Spain, France, Italy and Slovenia.	Highest price.
Sweden	Does not use.			

TABLE 35. Criteria used for pricing in the countries studied

Country	Humanistic		Clinicians				Economic			Other
	Solidarity	Equity of access	Severity of the pathology	Therapeutic value	Unmet needs	Innovation	Budgetary impact	Sustainability of the system	Cost-effectiveness	
Germany				✔			✔			Efficiency frontier.
Australia		✔	✔	✔	✔		✔		✔	Public health issues, patient affordability in the absence of public funding, ability to target therapy to patients who will benefit most.
Austria				✔						
Canada							✔		✔	
South Korea			✔	✔	✔		✔		✔	Public health issues.
Scotland				✔	✔	✔	✔		✔	
Spain			✔	✔	✔	✔	✔	✔	✔	Specific needs of certain groups.
France			✔	✔	✔	✔	✔		✔	
England							✔		✔	
Italy				✔	✔	✔	✔			Contributions to research programmes, quality of evidence.
Japan				✔		✔			✔	Paediatric medicines, first launched in Japan, RDs.
The Netherlands		✔	✔	✔	✔		✔	✔	✔	Burden of disease, justice, equality.
Portugal				✔		✔	✔		✔	
Sweden	✔	✔	✔						✔	

RDs: rare diseases.

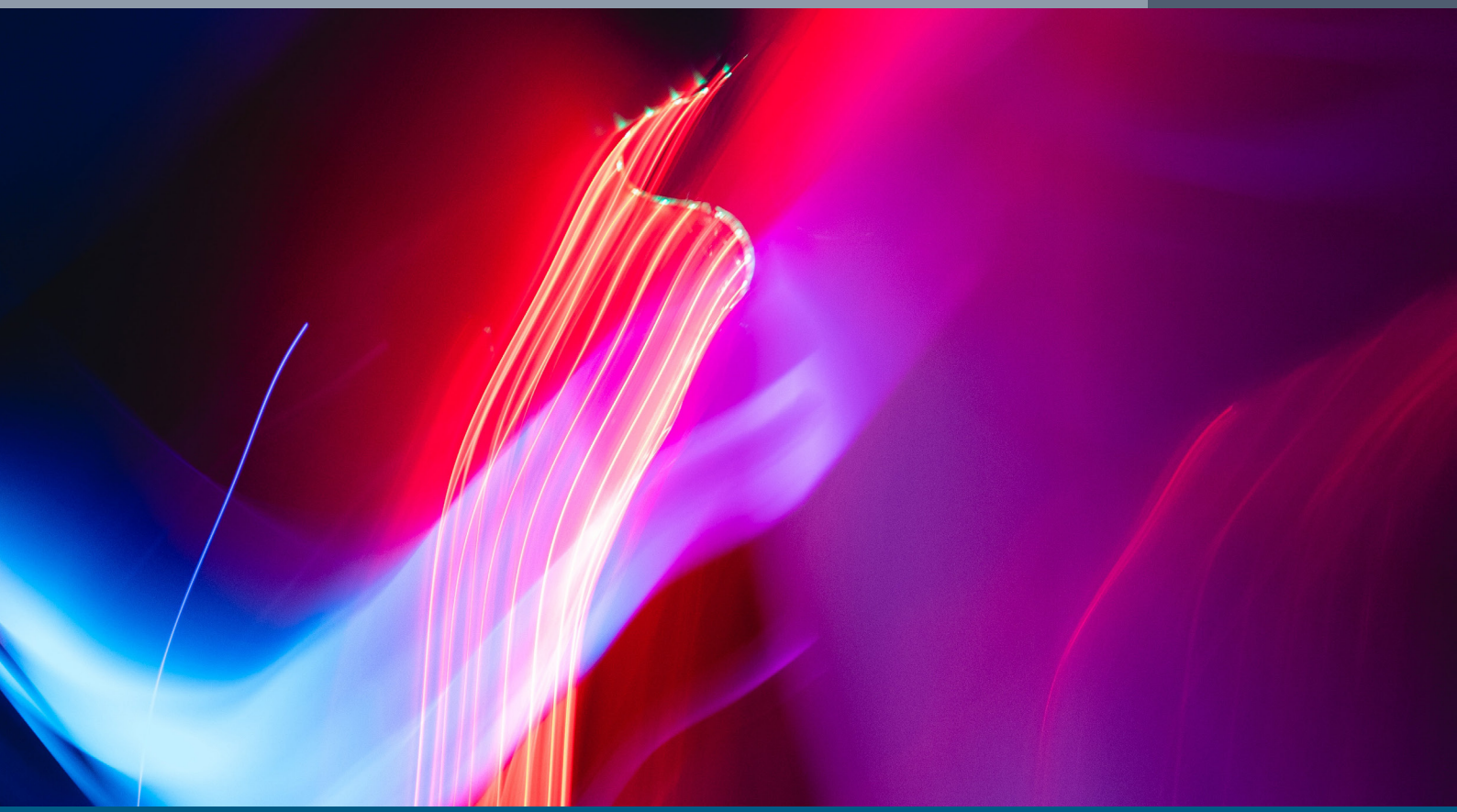
TABLE 36. Specific financial funds used in the countries studied

Country	Specific funds	Value of funds (million € per year)	Percentage share of GDP (2020)	Pathologies
Germany				
Australia				
Austria				
Canada				
South Korea				
Scotland	✔	n.a.		**3** funds for ultra-orphan diseases, hereditary blood diseases and inherited metabolic diseases.
	✔	58,9	0.07%	Orphan, ultra-orphan and end-of-life medicines.
Spain				
France				
England	✔	400 400	0.037%	Oncological. Innovative life-saving drugs.
Italy	✔	500 500	0.060%	Innovative medicines. Innovative cancer medicines.
	✔	10,5	0.001%	Orphan drugs and drugs that represent a hope for therapy, pending commercialisation, for particular, serious diseases.
Japan				
The Netherlands	✔	26,8	0.003%	Conditional funding.
Portugal				
Sweden				

Note: n.a. not available.

THE VISION OF SPAIN OF DIFFERENT AGENTS

3



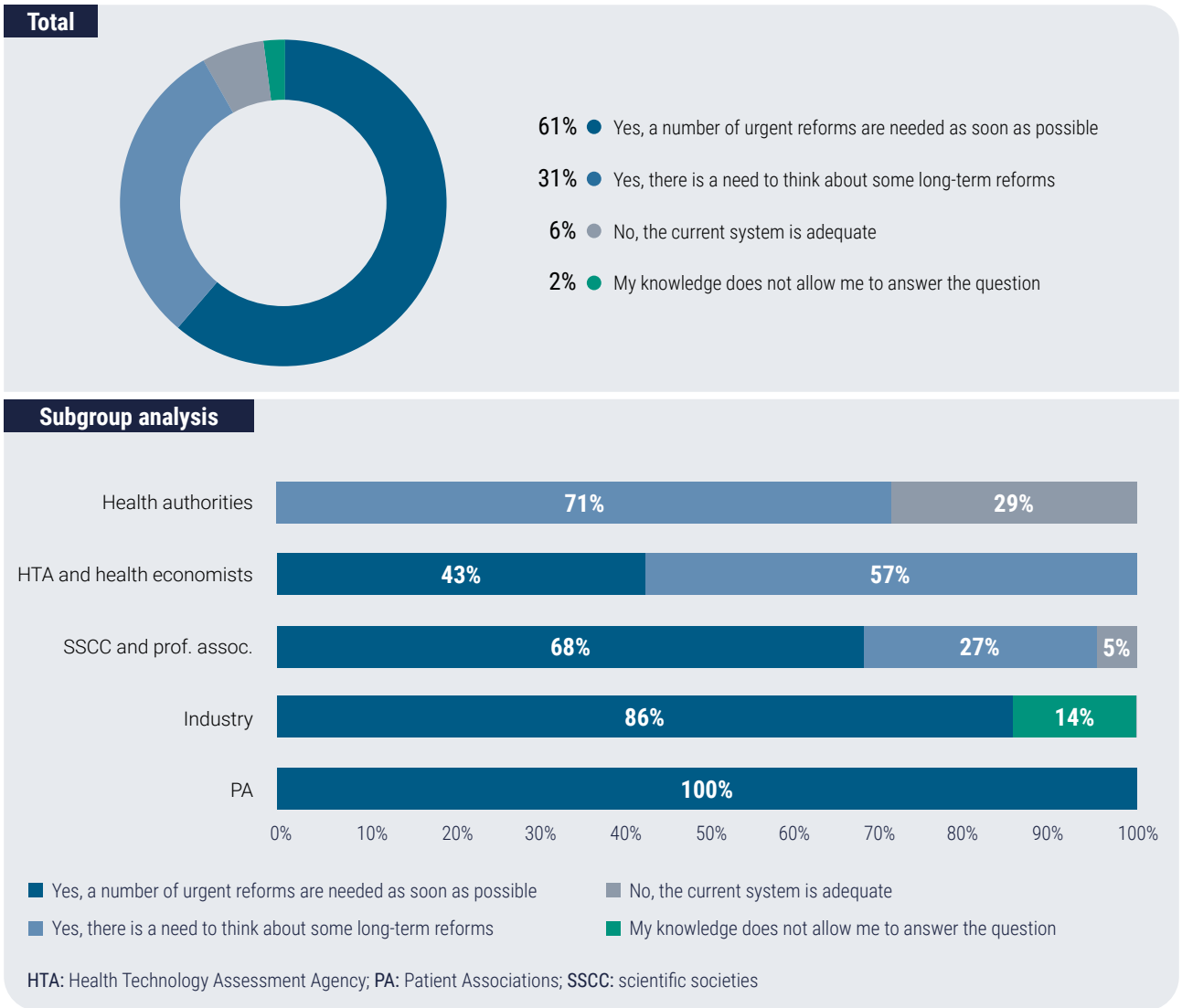
Survey results analysis

This section analyses the responses on the assessment and funding processes of medicines in Spain collected through a survey of the main actors in the system, which was answered by a total of 49 actors with five different profiles (Tabla 2).

The vast majority of stakeholders consulted (more than **90%**) consider that the assessment of innovative medicines in Spain should be reformed: **61%** believe that reforms should be urgent, while **31%** believe that some long-term reforms are needed and only **6%** thought that the current system is adequate.

Responses differ among the different groups of respondents. Among the patient associations consulted, there is unanimity that a number of reforms are urgently needed, a view similar to that of industry stakeholders (**86%**) and, to a lesser extent, representatives of scientific societies and professional associations (**68%**). In contrast, for the majority of health authorities (**71%**) and health economists and health technology assessment agencies (**57%**) consulted, some long-term reforms in medicines assessment are needed (Figure 51).

Figure 51. In general, do you consider that changes should be made to the way innovative medicines are assessed in Spain?

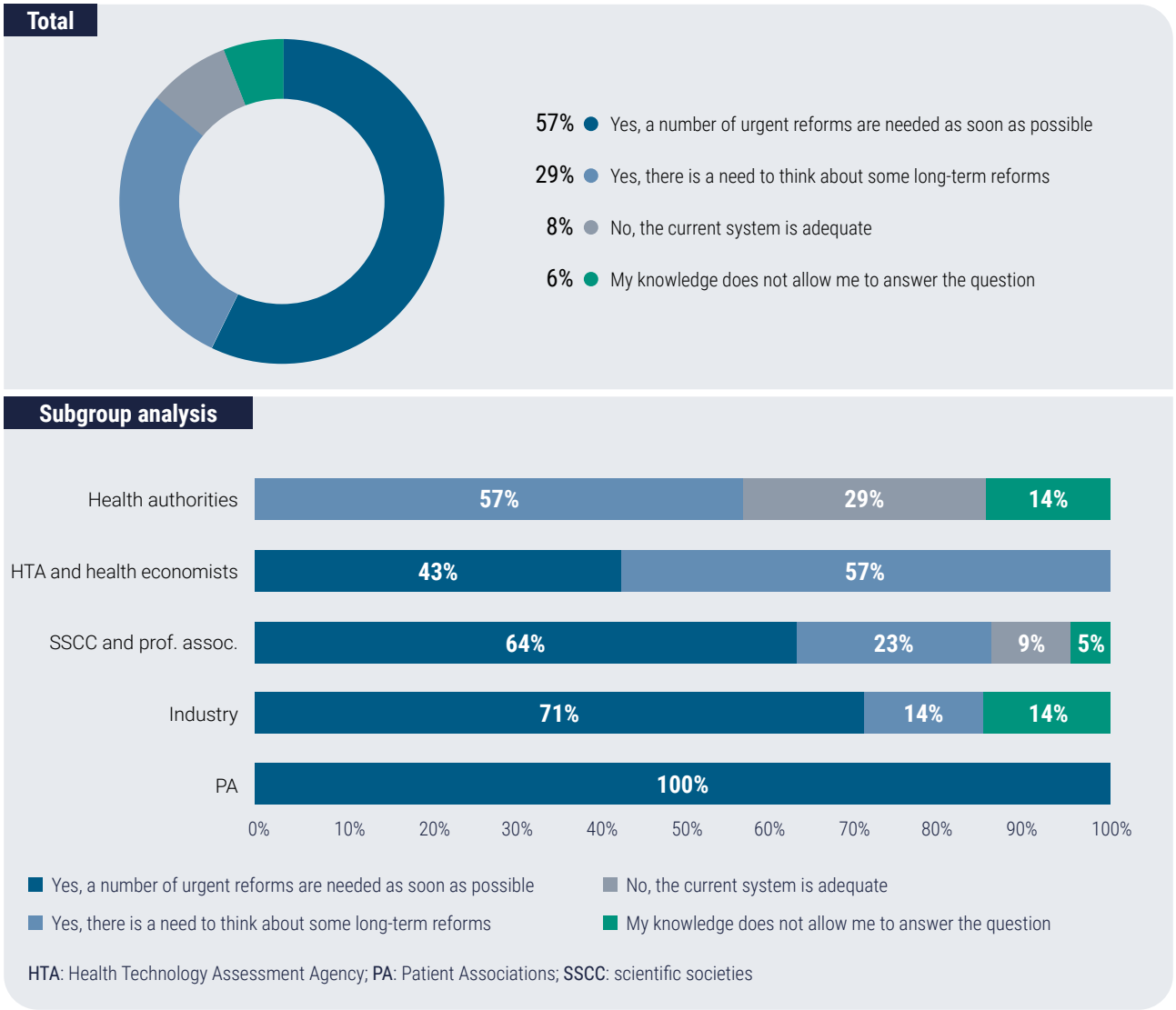


HTA: Health Technology Assessment Agency; **PA:** Patient Associations; **SSCC:** scientific societies

Similarly, the majority of respondents (**86%**) believe that reforms are needed in the way innovative medicines are priced and publicly funded in Spain. Specifically, **57%** of stakeholders believe that reforms should be carried out urgently, while **29%** say that changes are needed, but rather in the long term.

Among the different groups consulted, patient associations agree that reforms should be urgent, as do a large majority of industry representatives (**71%**) and scientific societies and professional associations (**64%**). However, more than half of the health economics and health authorities interviewed consider that some reforms in the pricing and public funding of innovative medicines in Spain should be considered, but in the long term (**Figure 52**).

Figure 52. In general, do you consider that changes should be made to the way in which the price and public funding of innovative medicines is set in Spain?



HTA: Health Technology Assessment Agency; PA: Patient Associations; SSCC: scientific societies

For the stakeholders interviewed, the most important challenges in the assessment and funding processes of innovative medicines are the uncertainty in the measurement of clinical benefit, the short timeframe and the lack of transparency in the processes. In contrast, the challenges considered to be of least relevance to this process are the lack of political leadership and the lack of explicit guidelines on economic evaluation.

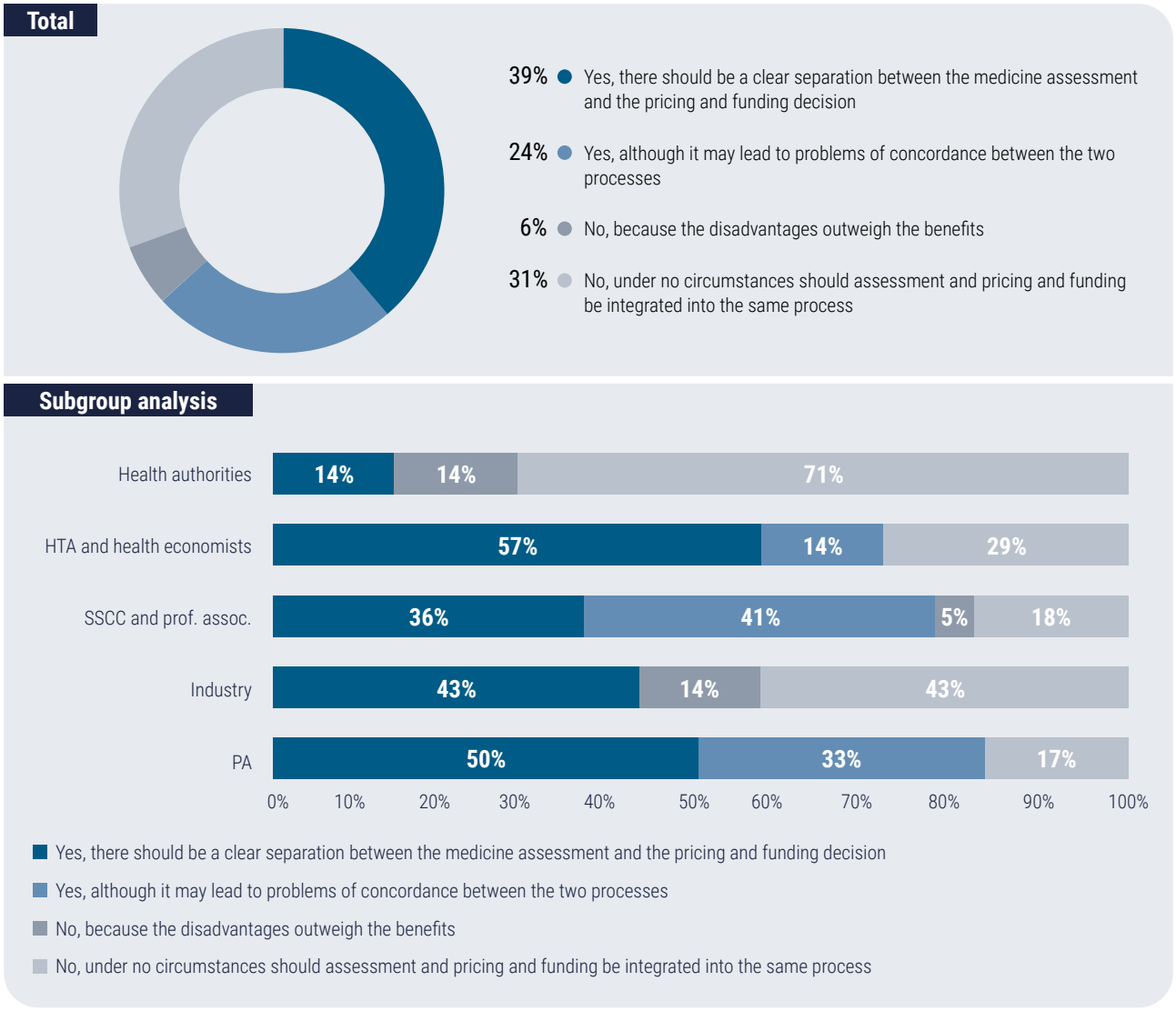
For the health authorities consulted, the two main challenges are uncertainty in the measurement of results and the lack of human resources, while economists highlight the lack of professionalisation in evaluation. For patients, the key issues are the lack of equity and speed of access, a point on which they agree with the scientific societies. The industry highlights the uncertainty in the measurement of benefit, the lack of speed and the lack of efficiency of the process (Figure 53).

Figure 53. Challenges in the assessment and funding processes of innovative medicines in the NHS (0 being the least important and 10 the most important) (average score)

Overall, **39%** of respondents believe that there should be a clear separation between the scientific-technical assessment process and the decision to fund medicines, while **24%** are in favour of such a separation, although they believe that it may lead to inconsistencies between the two processes.

In particular, health economists (**57%**) and patient associations (**50%**) are the two groups most in favour of making a clear distinction between the two processes, while the health authorities consulted are in favour of not separating them in any case into two distinct processes. Industry views on this issue are very polarised, with equal proportions of respondents in favour of separating the two processes and against separating them (Figure 54).

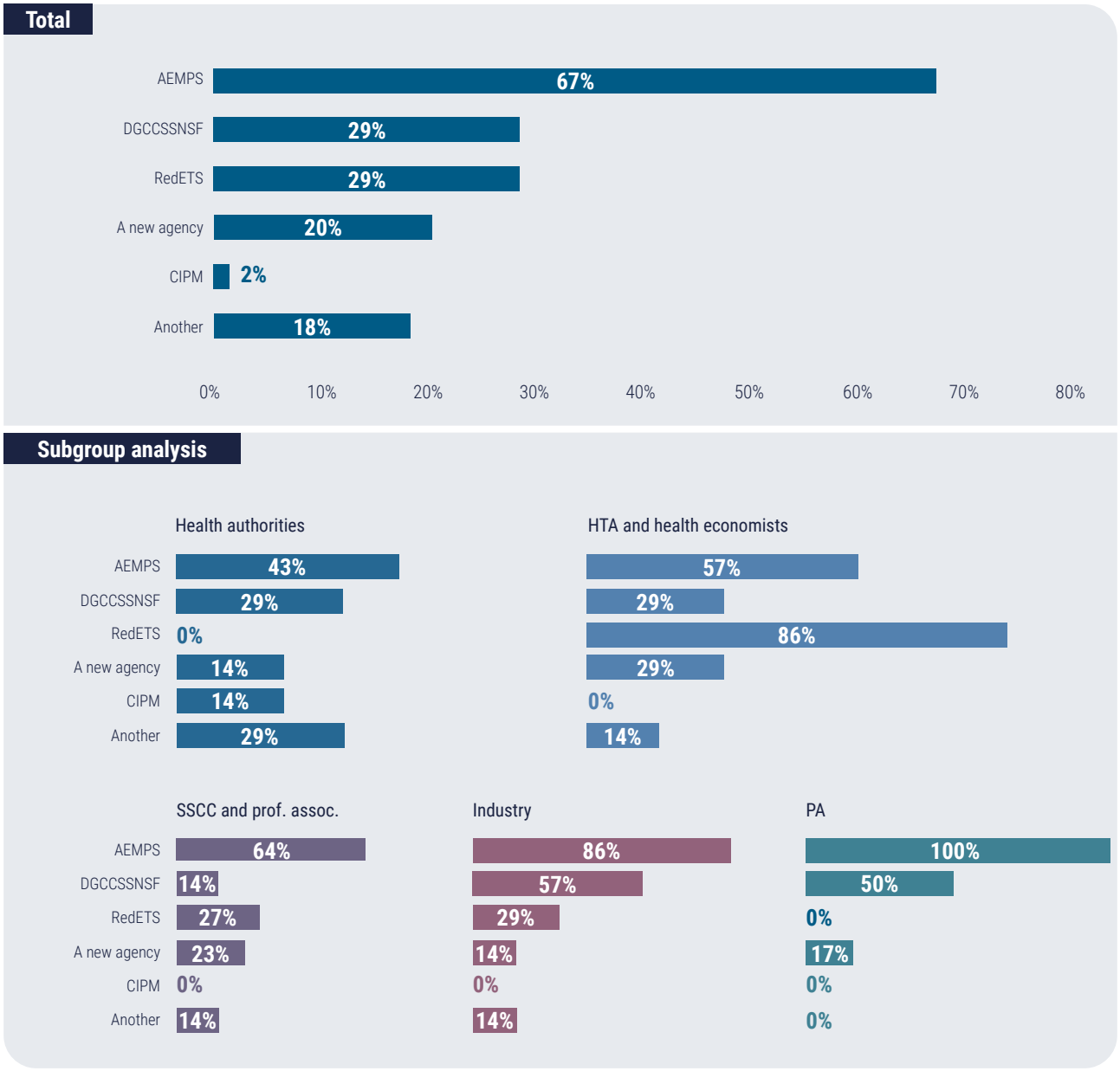
Figure 54. Do you consider that there should be a separation between scientific/technical processes (assessment) and management/policy decisions (pricing and funding)?



With regard to the agents that should lead the technical part of the assessment process, the majority of respondents (**67%**) agree that the AEMPS should be one of them (in fact, more than half of this **67%** advocate that the AEMPS should lead alone). In turn, almost a third of respondents believe that the Directorate-General of the Basic Portfolio of National Health System and Pharmacy Services (DGCCSSNSF) and the Network of Health Technology Assessment Agencies (RedETS) should be involved in this leadership. The **20%** refers to a new specific evaluation agency, either alone or together with other bodies.

Almost all subgroups agree that the AEMPS should be one of the main leaders of the assessment process. In fact, it should be the sole leader for **43%** of the health authorities consulted, **41%** of the scientific societies, **50%** of the patients and **29%** of the industry representatives consulted. In contrast, the subgroup of HTA and health economists advocates for the RedETS as the main actor in the assessment (**Figure 55**).

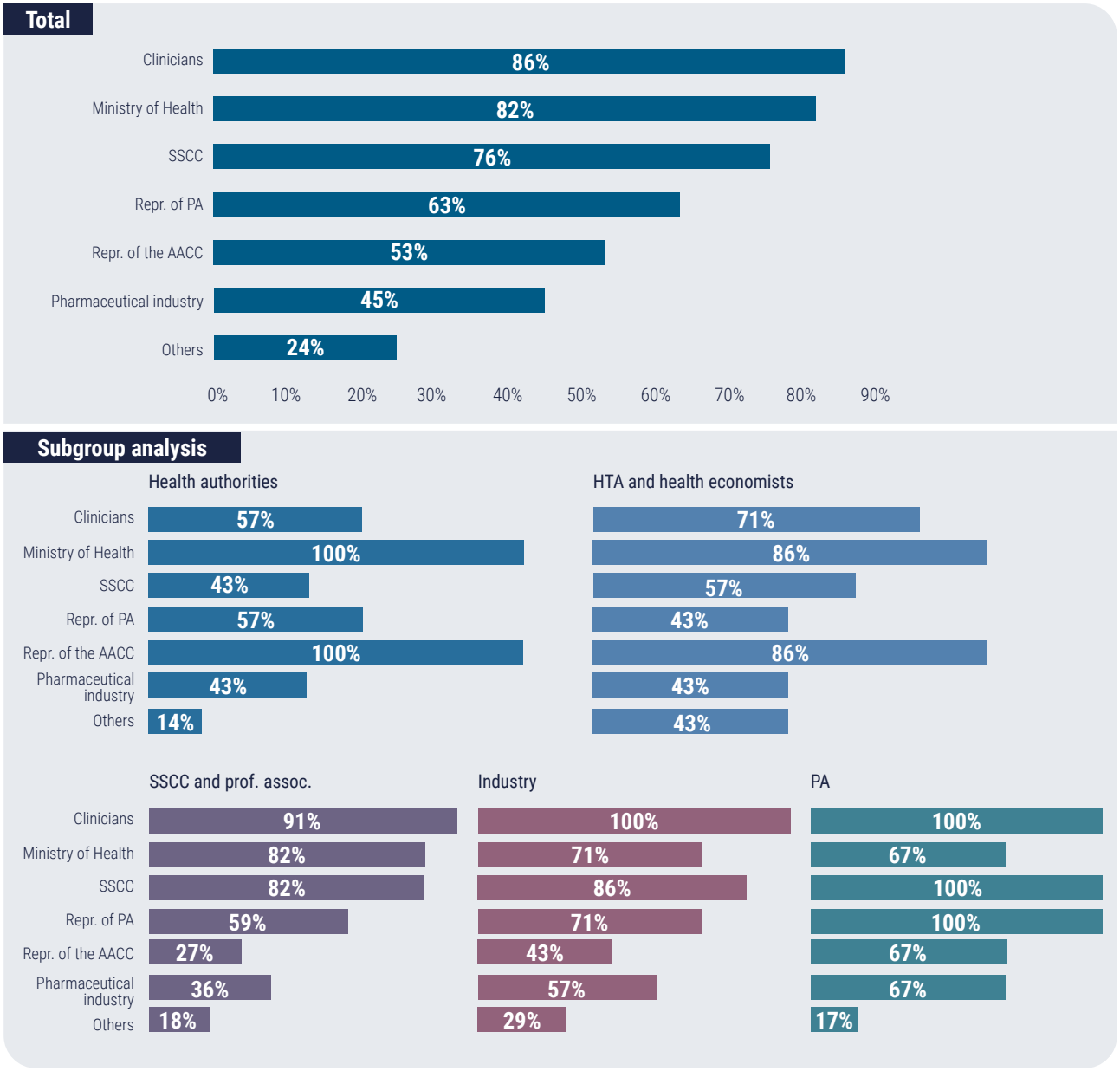
Figure 55. Who do you consider that should lead the technical part of the assessment process in Spain? (Multiple options available)



For their part, according to those consulted, the agents that should participate in the process of assessing a new medicine in Spain are clinicians, the Ministry of Health and scientific societies, and, to a lesser extent, representatives of patients' associations and the AACC. In addition, **45%** of respondents believe that representatives of the pharmaceutical industry should also be involved. Others mentioned other agents, such as professional associations, hospital pharmacists or RedETS.

For the health authorities and health economists, the Ministry and the AACC are the main actors to be involved in the process, in contrast to the scientific societies and industry, who emphasise the involvement of clinicians. Patients are the subgroup most supportive of the involvement of patients' associations (Figure 56).

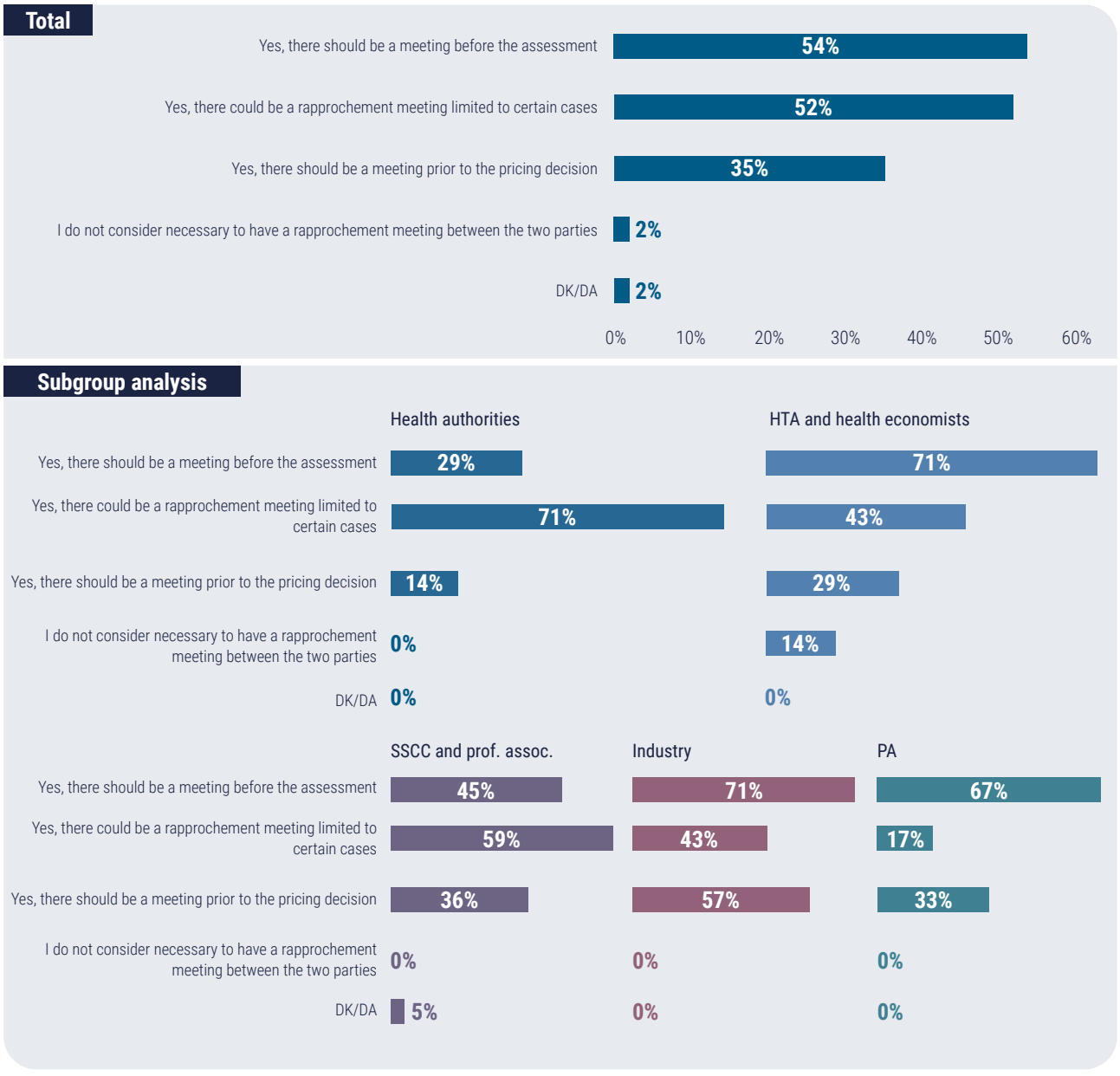
Figure 56. What type of actors do you consider that should be involved in the assessment process of a new medicine in Spain? (Multiple options available)



Virtually all respondents considered that a meeting between the pharmaceutical laboratory and the decision-makers would be an interesting way of bringing the two parties closer together, and only **2%** (1 expert, health economist) thought that a meeting between the two parties would not be necessary. **54%** of stakeholders consider that they should meet before the assessment, **52%** in certain cases and **35%** before the pricing decision.

Health economists and industry are the subgroups that most strongly advocate for a rapprochement meeting prior to the assessment, whereas for health authorities and scientific societies, the meeting should rather be limited to certain cases. The subgroup most in favour of a rapprochement meeting is industry (**57%**), followed by scientific societies (**36%**) (Figure 57).

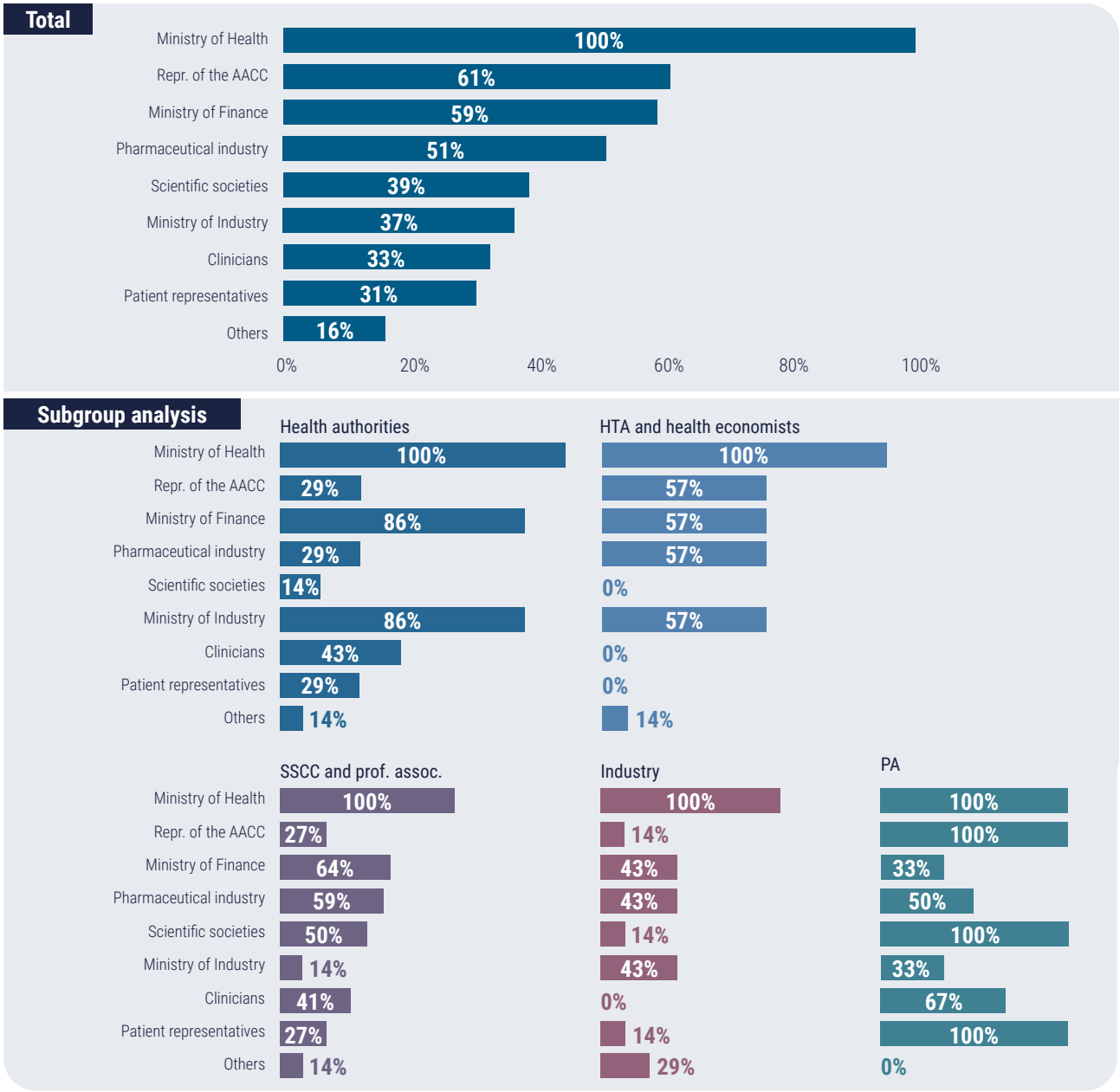
Figure 57. Do you consider interesting the possibility of a rapprochement meeting including scientific advice between the pharmaceutical laboratory and the decision-makers to bring their positions closer together?



All those interviewed agree that the Ministry of Health should be one of the agents involved in the process of obtaining the price and funding of a new medicine. A large proportion of respondents believe that representatives of the AACC, the Ministry of Finance and the pharmaceutical industry should also be involved. A total of **39%** believe that representatives of scientific societies should be involved and **31%** representatives of patients' associations. Others mentioned the participation of other agents, such as professional associations, the RedETS or the AEMPS.

Patients' associations are the subgroup that supports the involvement of a larger number of actors in the process. Health authorities particularly value the involvement of all three ministries. Economists and scientific societies are the most supportive of the pharmaceutical industry's involvement in the pricing and funding process (**Figure 58**).

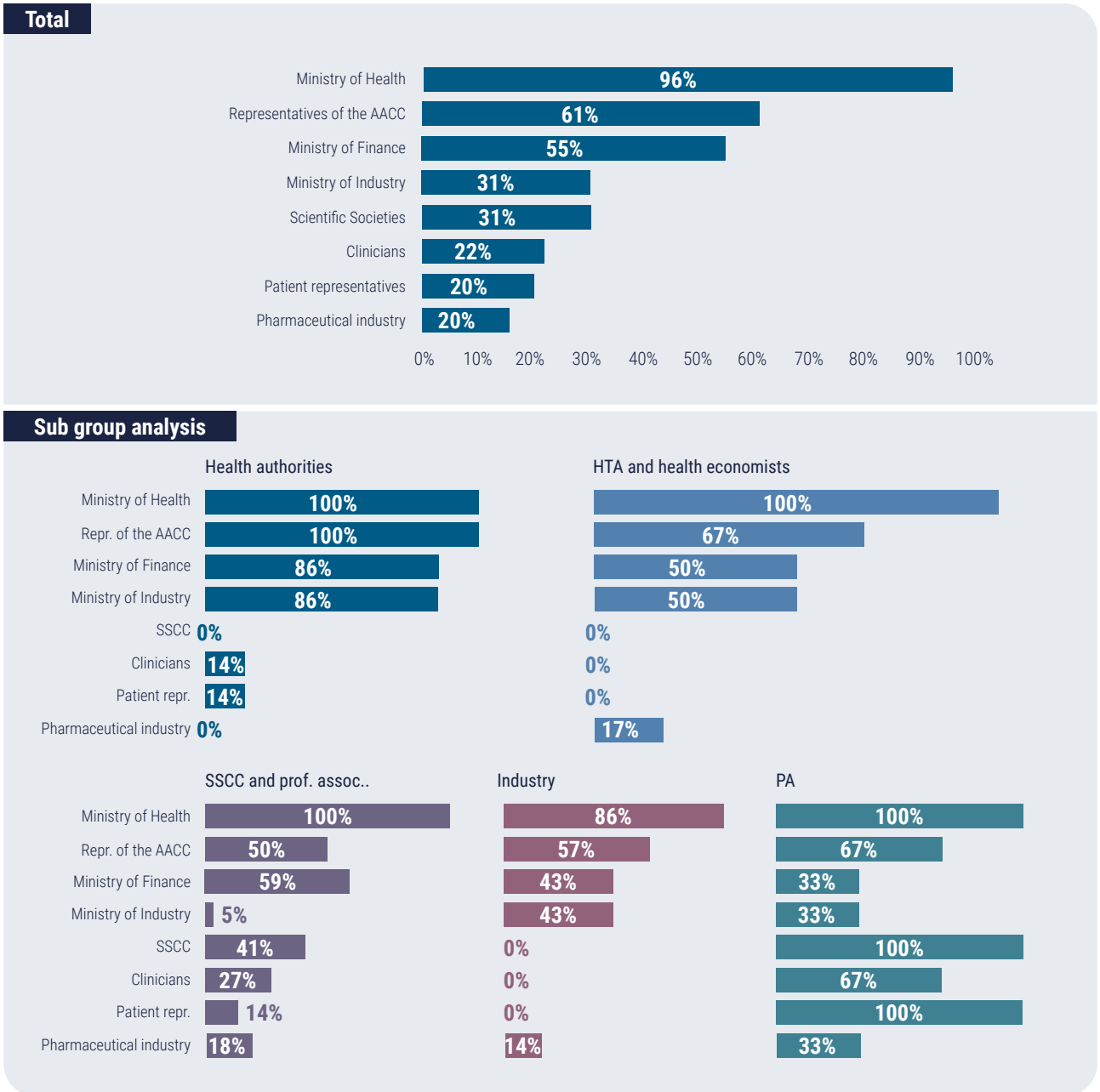
Figure 58. What type of actors do you consider that should be involved in the process of pricing and funding a new medicine in Spain? (Multiple options available)



When asked about which type of actors should have a vote or a binding say in the pricing and funding decision, the Ministry of Health is again the body most voted for by respondents, although more than half also support the binding opinion of the representatives of the AACC and the Ministry of Finance, and not so much the industry or patients.

Patient representatives are the most open to a binding participation of a wider range of actors in the system, while health economists and the pharmaceutical industry are the most restrictive, and would limit it to the three Ministries (Health, Finance and Industry), the AACC and the industry (**Figure 59**).

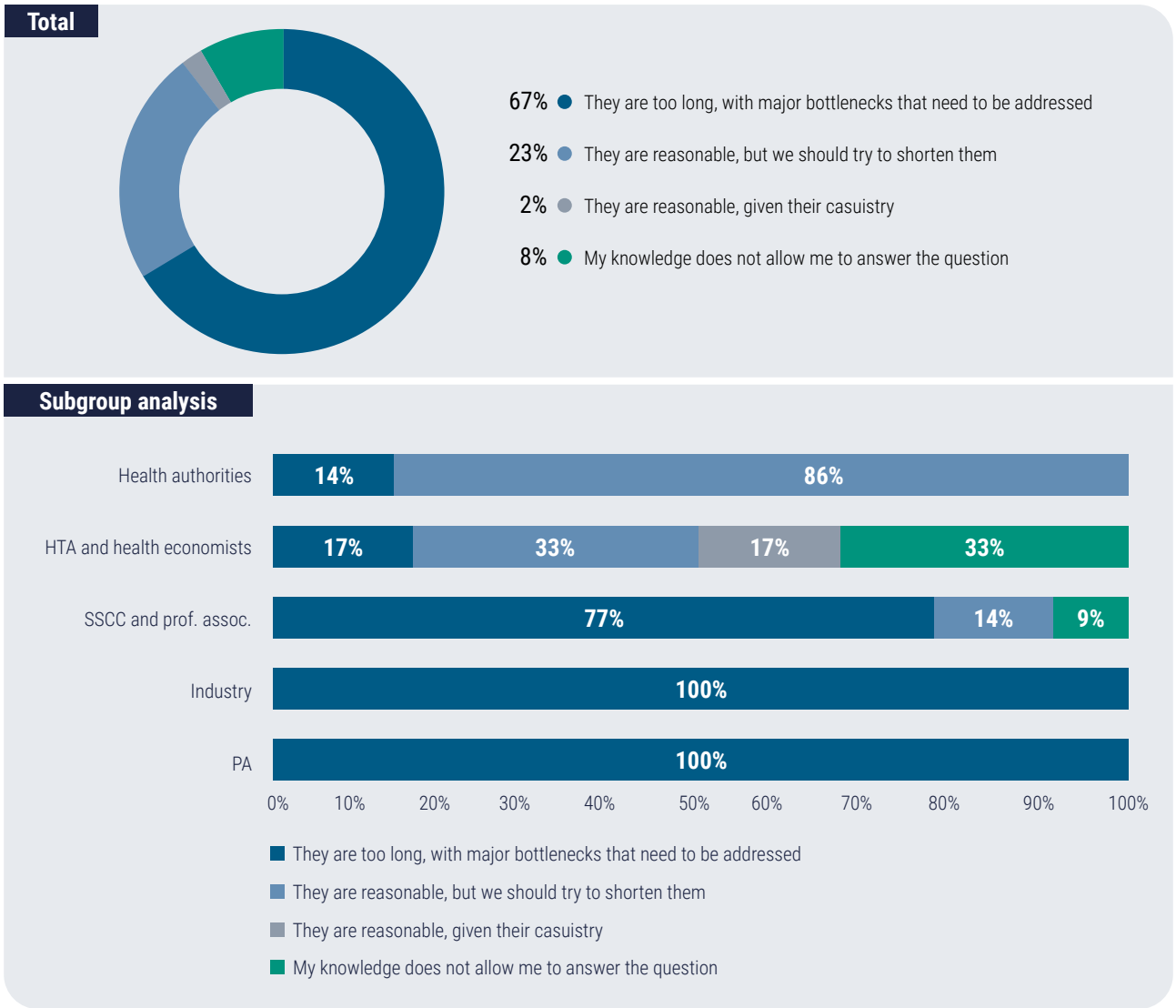
Figure 59. Of the actors selected above, which ones do you consider that should have a vote in the pricing and funding decision? (Multiple options available)



For the majority of respondents (**67%**), the current assessment times for innovative therapies in Spain are too long, with significant bottlenecks that need to be resolved, while **23%** say that the times are reasonable, but that efforts should be made to shorten them. Only **2%** think that the times are reasonable, given their casuistry.

In the different subgroups, there is clear unanimity among the representatives of industry and patient associations on the length of the assessment process, an opinion shared by a majority of scientific societies and professional associations (**77%**). For most health authorities (**86%**), the times are reasonable, although we should try to shorten them. Opinion among health economists is very divided (**Figure 60**).

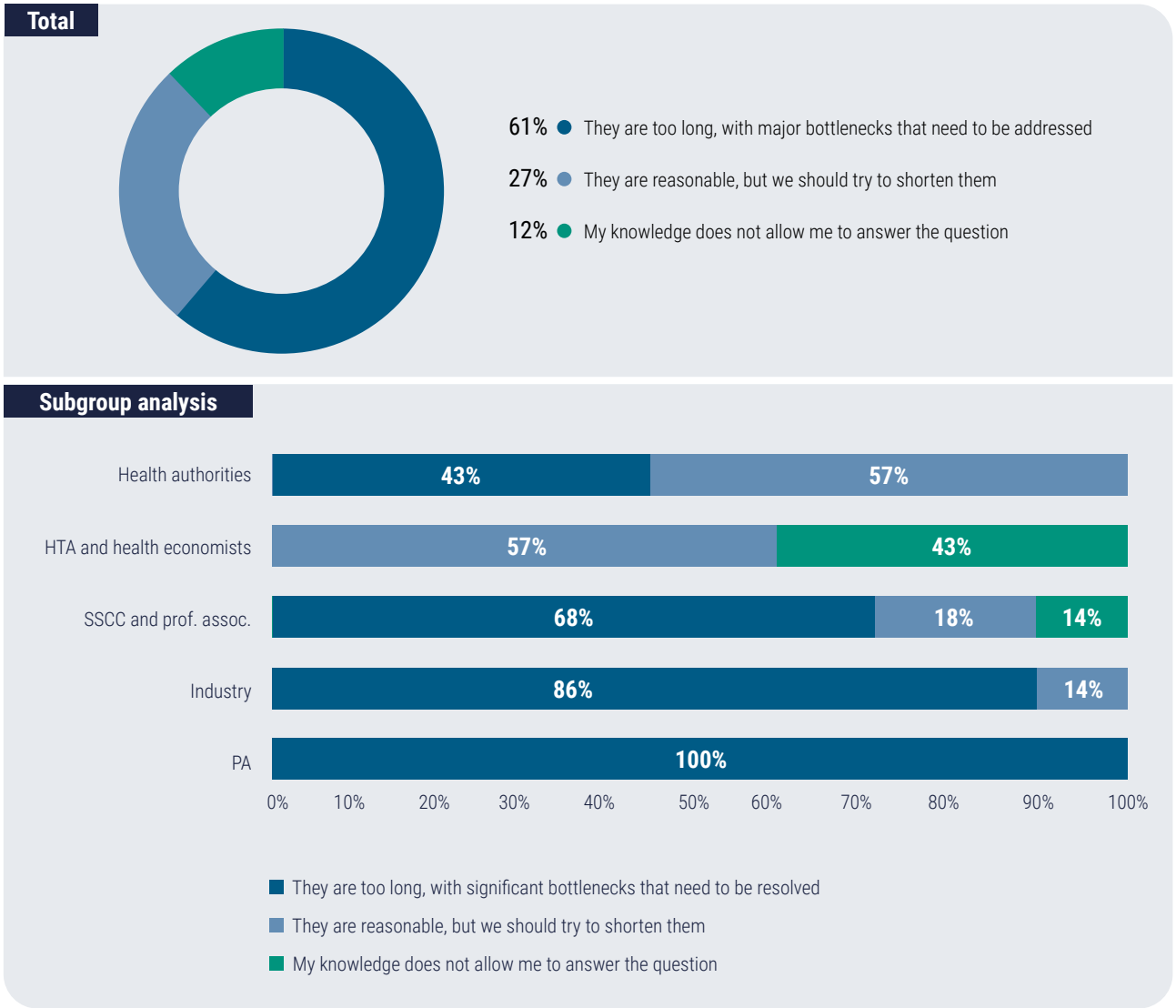
Figure 60. What is your opinion on the current timing of the assessment process for innovative therapies in Spain?



When asked about the timing of pricing and funding decisions, the percentage of agents who felt that they were too long fell slightly to **61%**, while **27%** felt that they were reasonable, but that they should try to shorten them. In this case, no expert felt that they were reasonable, given their casuistry, and the proportion claiming that their knowledge did not allow them to comment on this issue rose to **12%**.

In line with the previous question, for all the patient association representatives consulted, the times are too long, a view shared by **86%** of the industry representatives, **68%** of the scientific societies and professional associations and **43%** of the health authorities. On the other hand, for the majority of health authorities and health economists (**57%** in both cases), the times are reasonable, although we should try to shorten them (Figure 61).

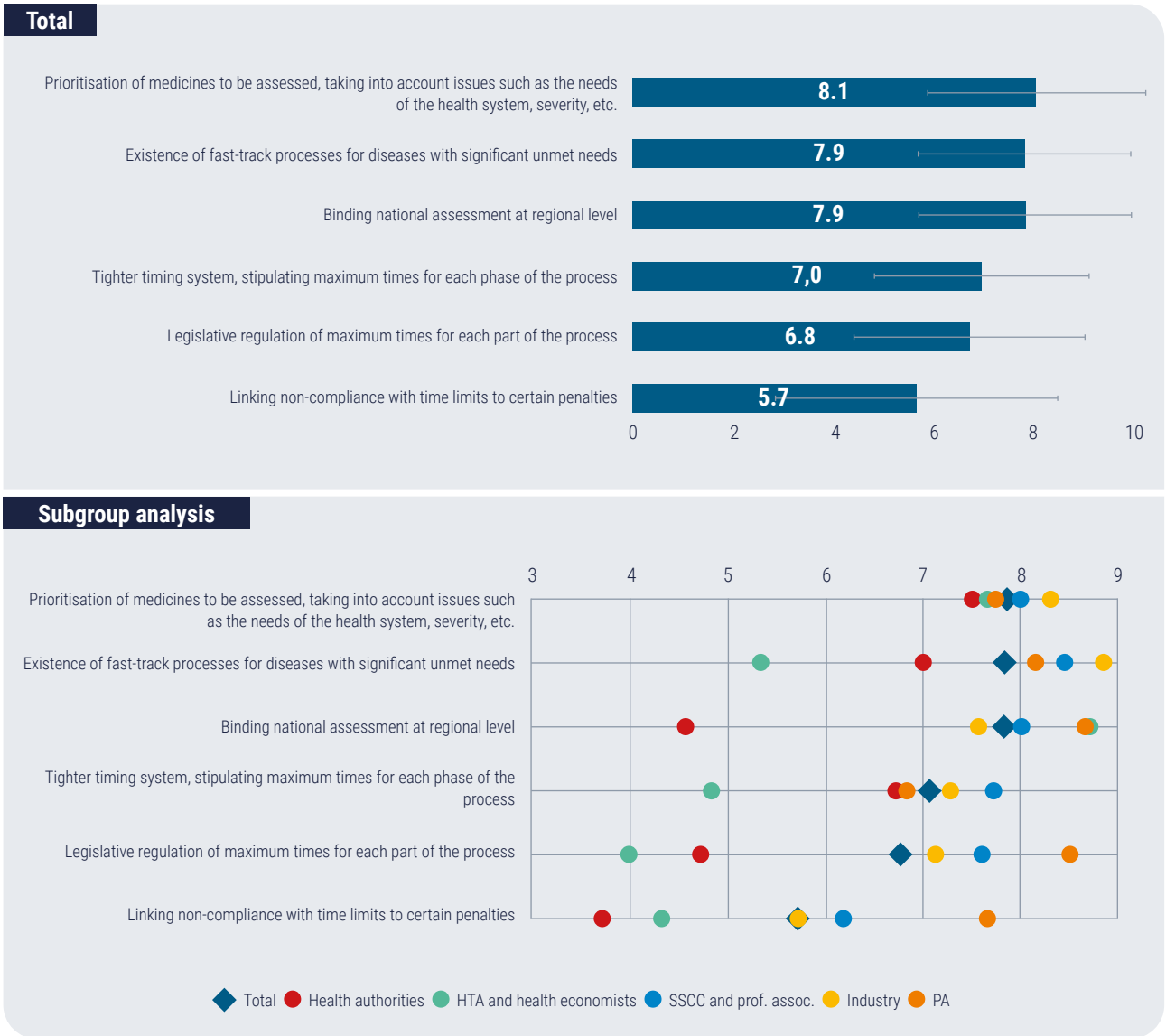
Figure 61. What is your opinion on the current timing of pricing and funding decisions for innovative therapies in Spain?



In terms of measures to speed up assessment times, respondents ranked the prioritisation of medicines to be assessment as the most relevant measure, followed by the existence of fast-track processes for diseases with significant unmet needs and binding national assessment at the regional level. On the other hand, they consider it less relevant (average of **5.7** out of **10**) to link non-compliance with timeframes to certain penalties.

For health economists and patient associations, the most relevant measure would be the binding assessment at national level, while industry and scientific societies highlight the existence of fast-track processes for diseases with significant unmet needs. There are major differences of opinion between the authorities/economists and the other subgroups. Economists and health authorities do not consider it relevant (less than **5** average points) either to regulate the maximum times for each part of the process or to link non-compliance with certain penalties. Health authorities are the subgroup that worst values the option of having a binding national assessment at regional level (Figure 62).

Figure 62. What measures do you consider that would help to speed up assessment times? (0 being not at all, and 10 being considerably) (average score)



Regarding the transparency of the assessment process, respondents prioritise the publication of a clear and detailed methodological guide, followed by the publication of all information (except for confidential information) considered during the evaluation process, as well as the final decision. On the other hand, it does not seem to be as important to publish a draft of the assessment so that it is accessible to the public for comments.

By subgroups, the scientific societies are the only subgroup that places more value on publishing the information used than on clear and detailed methodological guidance. The greatest divergence of opinion is between industry and patient representatives on the publication of a draft assessment for comment, an option that is much more highly rated by patients (**9.2**) than by industry (**4.7**) (Figure 63).

Figure 63. Points relating to the transparency of the current assessment process in the NHS (0 being the lowest possible and 10 the highest possible) (average score)

On the other hand, regarding measures aimed at promoting transparency in the pricing and funding decision, respondents prioritised the specification of the criteria considered in the decision (8.5 average points out of 10), and placed the publication of the information considered in the decision (with the exception of confidential information) and the explanation of the relative weight given to each of the criteria at practically the same level.

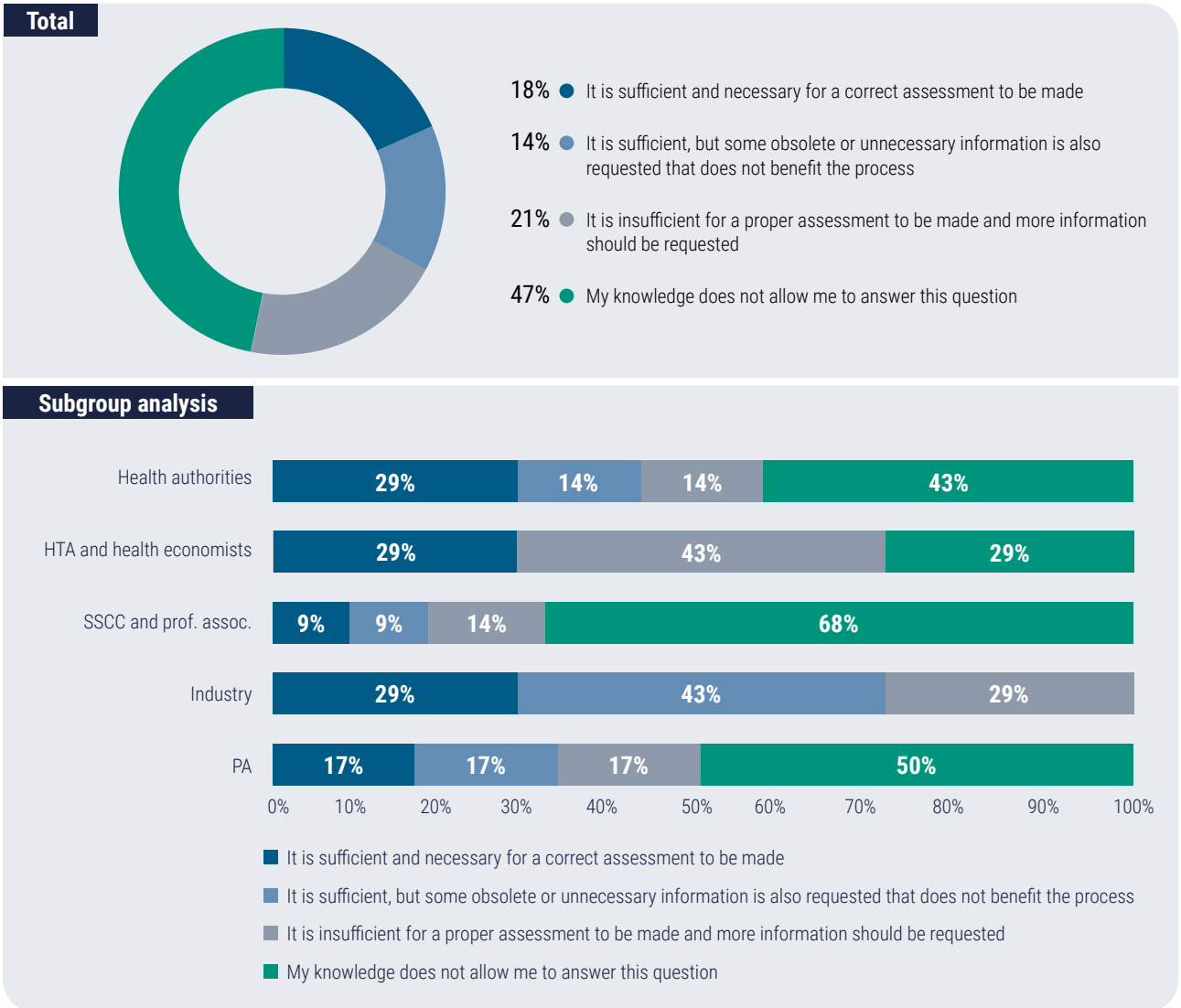
All subgroups of respondents agree on the need to specify the criteria taken into account in the pricing decision (only **6%** score this statement below **5**), although health authorities and health economists are the most sceptical about making explicit the weight of each criterion. Also notable is the low value placed by health economists on making the profile of the components of the decision committee transparent (Figure 64).

Figure 64. Points relating to the transparency of the current pricing and funding decision process in the NHS (0 being the lowest possible and 10 being the highest possible) (average score)

Regarding the information currently required from the laboratory to carry out the medicines assessment, approximately one third of the agents consulted consider that it is sufficient (**18%** believe that it is sufficient and necessary and **14%** that it is sufficient, but that there are elements required that are unnecessary), while **21%** believe that it is insufficient to be able to carry out an adequate assessment, considering it necessary to request more data from the laboratory. It is worth noting that **47%** of respondents (the highest proportion of the 50 questions in the questionnaire) considered that their knowledge does not allow them to give an opinion on this issue.

Responses vary between the different subgroups. For the majority of health economists (**43%**), the information required from the laboratory for the medicine assessment is insufficient, with **29%** for industry and **14%** for health authorities and scientific societies. Between **9%** and **29%** think that the information required is sufficient and necessary. Finally, it is worth noting the high proportion of respondents in all subgroups except industry who claim not to have sufficient knowledge to answer this question (Figure 65).

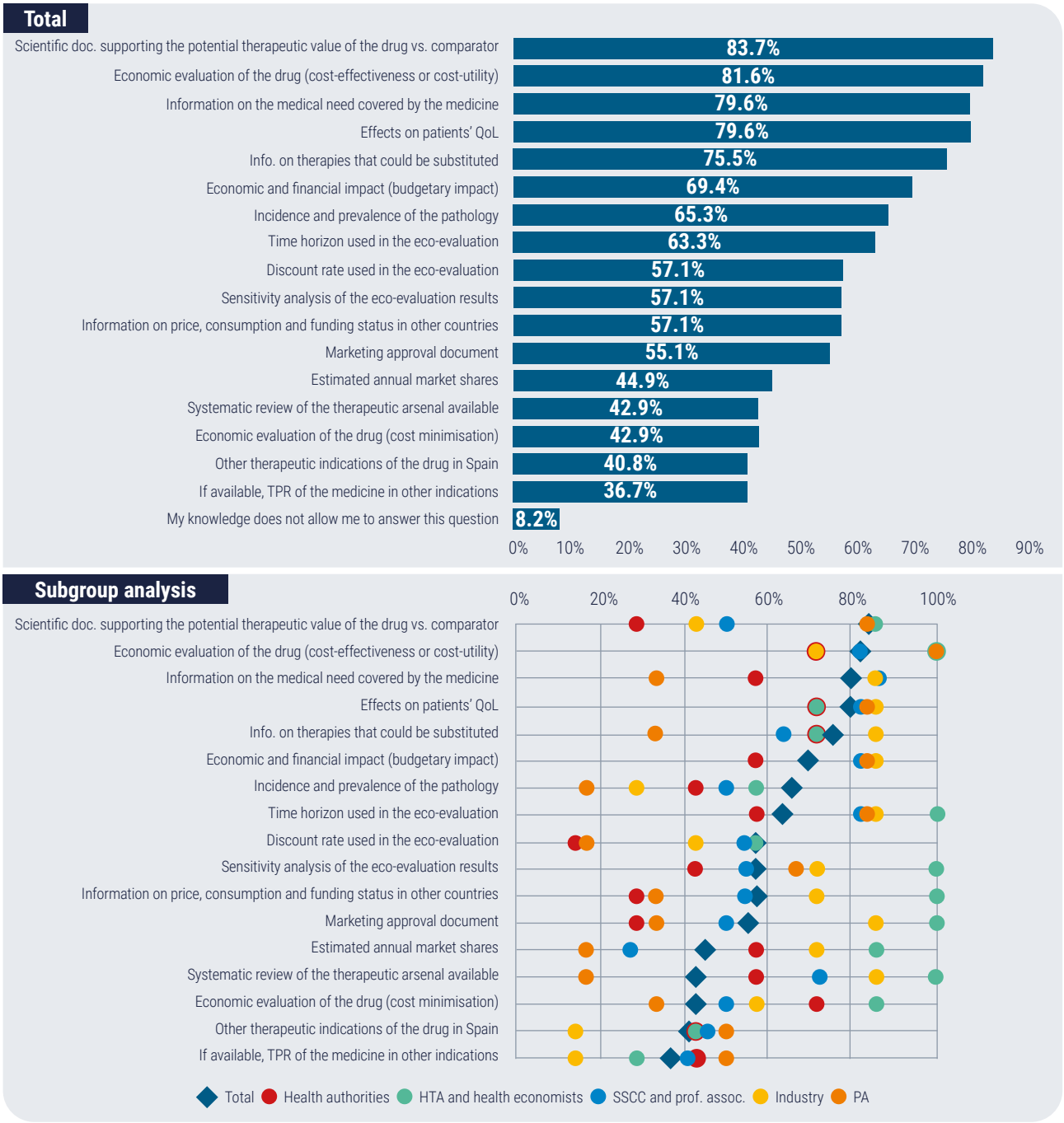
Figure 65. What is your opinion on the information currently required from the laboratory to carry out the medicine assessment?



According to those consulted, the documentation required from the sponsor laboratory that should be prioritised when assessing and setting the price and funding of a medicine is scientific information on the therapeutic value compared to the comparator, followed by the economic evaluation of the medicine, information on the medical need it meets and the effects on patients' quality of life. In contrast, it does not seem very relevant to request the TPR of the medicine in other indications or information on other indications for the medicine in Spain.

For health authorities, the most relevant documentation would be on cost minimisation, effects on quality of life and information on therapies that could be substituted (Figure 66).

Figure 66. Which of the following elements do you consider should be required from the sponsor laboratory as documentation for the assessment and pricing and funding of a medicine in Spain?

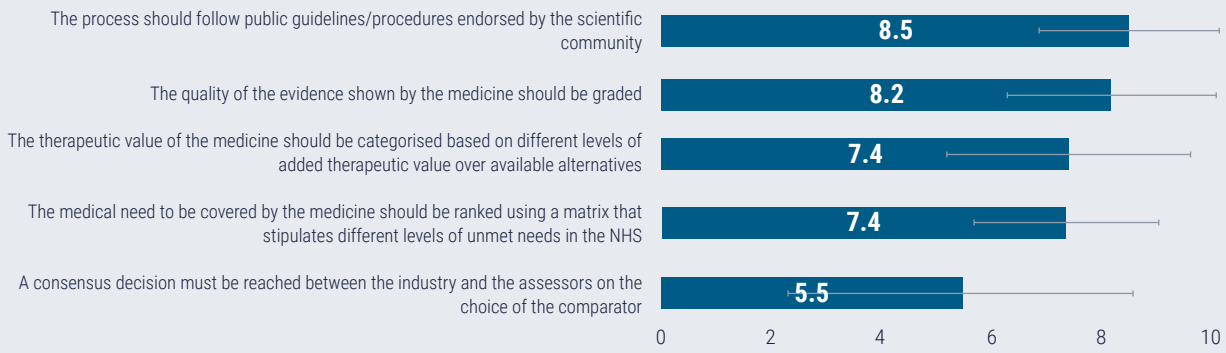


In relation to the process of clinical assessment of medicines, the agents consulted prioritise following public guidelines or procedures endorsed by the scientific community and, to a lesser extent, classifying the quality of the evidence shown by the medicine and categorising the therapeutic value of the drug at different levels over the available alternatives. On the other hand, they do not consider it very relevant to reach a consensus decision between the industry and the assessing bodies for the choice of the comparator.

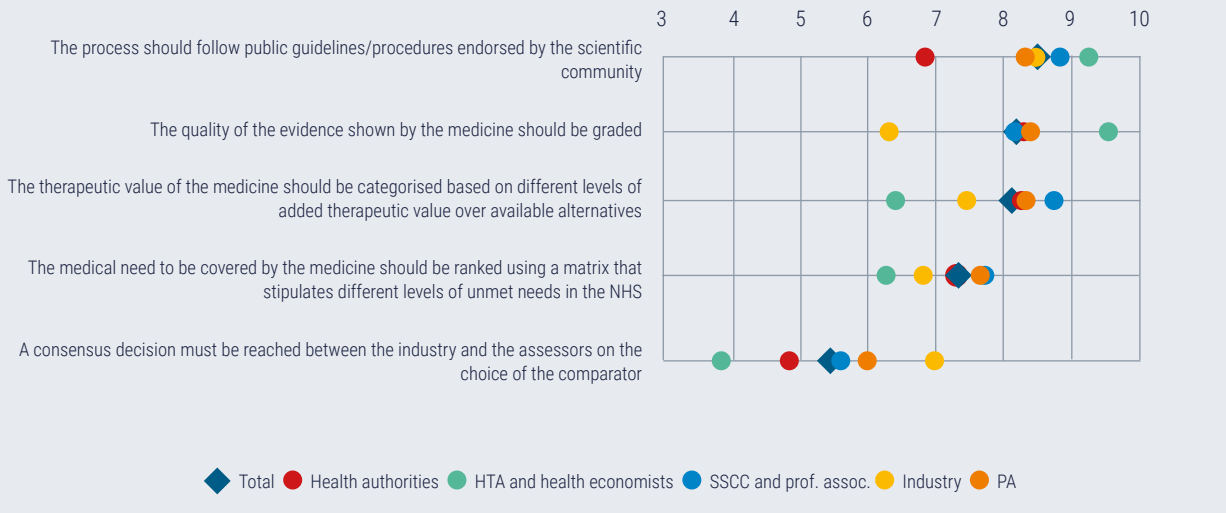
There are some significant differences between the different subgroups of respondents. On the one hand, health economists particularly value the need to classify the quality of the evidence shown by the medicine, and the alignment with procedures endorsed by the scientific community (in the latter they agree with the industry, patients and scientific societies), while they give very little weight (3.9 out of 10) to reaching decisions agreed between the industry and the assessors. For the health authorities, the most important thing is to categorise the added therapeutic value of the drug and to classify the quality of the evidence, while the industry does not attach so much importance to the latter measure, and instead values the fact of following guidelines or procedures endorsed by the scientific community (Figure 67).

Figure 67. Degree of agreement with the following points regarding the clinical assessment of medicines (0 being the minimum and 10 being the maximum) (average score)

Total



Subgroup analysis



On a number of statements related to therapeutic positioning reports (TPRs), the measure with the highest overall support among respondents is that the new TPR methodology should be homogeneous for all therapeutic alternatives, followed by conducting a TPR for each new medicine. They only relatively agree (5.4 out of 10) that the new TPRs will speed up assessment times.

By subgroups, industry representatives were the most critical of all these statements, scoring above 5 only the point regarding the need for methodological homogenisation of TPRs for all therapeutic alternatives. In contrast to the industry's opinion, the health authorities stress that the TPRs are carried out with methodological rigour, and that the new methodology helps in price and funding decisions and will speed up assessment times. The scientific societies are the subgroup most in favour of conducting a TPR for each new medicine (**Figure 68**).

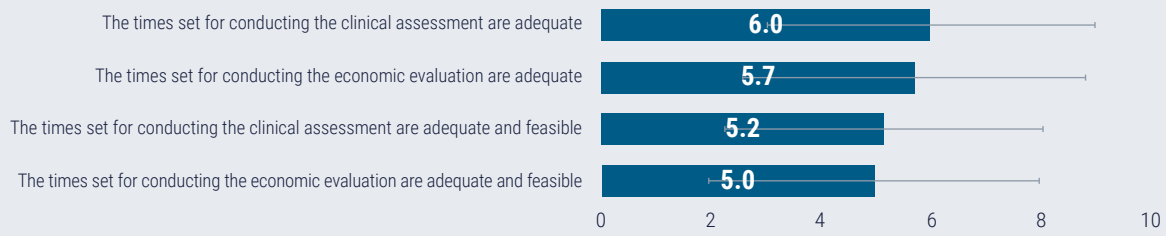
Figure 68. Degree of agreement with the following statements about the Therapeutic Positioning Reports (TPRs) (0 being the minimum and 10 the maximum) (average score)

In general, respondents partially agree that the timelines set in the TPRs for the clinical and economic evaluation of medicines (set at **20** and **10** days, respectively) are adequate and feasible, especially for the clinical part.

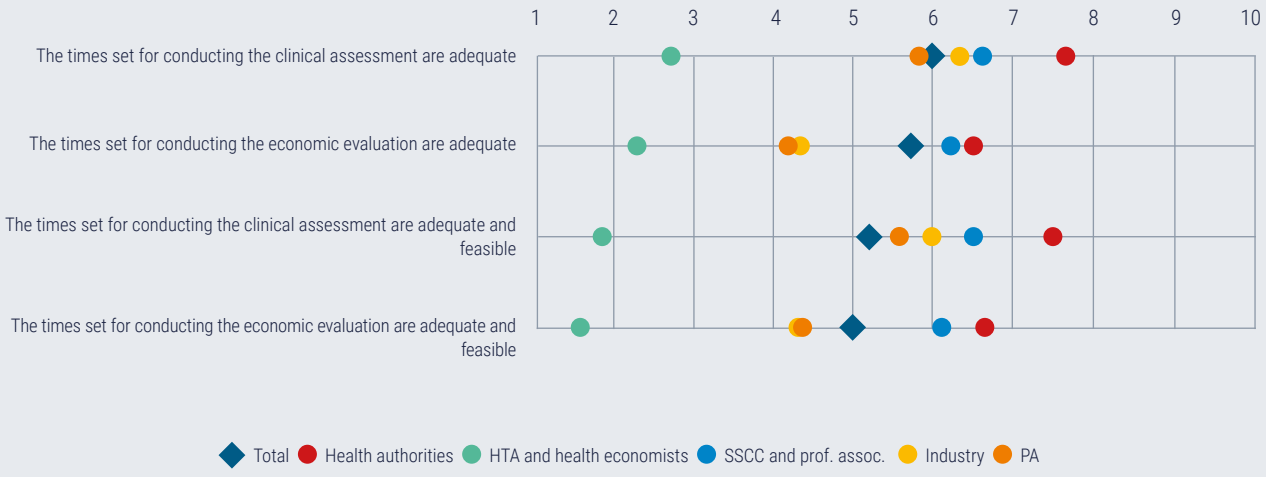
All the profiles analysed see the times set for economic evaluation as less appropriate and feasible than for clinical assessment, with industry being the subgroup with the greatest difference of opinion between the appropriateness of times for both types of evaluations. Health economists are the most critical of the timelines, while health authorities express the most favourable opinion on TPR timelines (Figure 69).

Figure 69. Degree of agreement with the following statements about the times set in the TPRs for clinical (20 days) and economic (10 days) evaluation (0 being the minimum and 10 the maximum) (average score)

Total



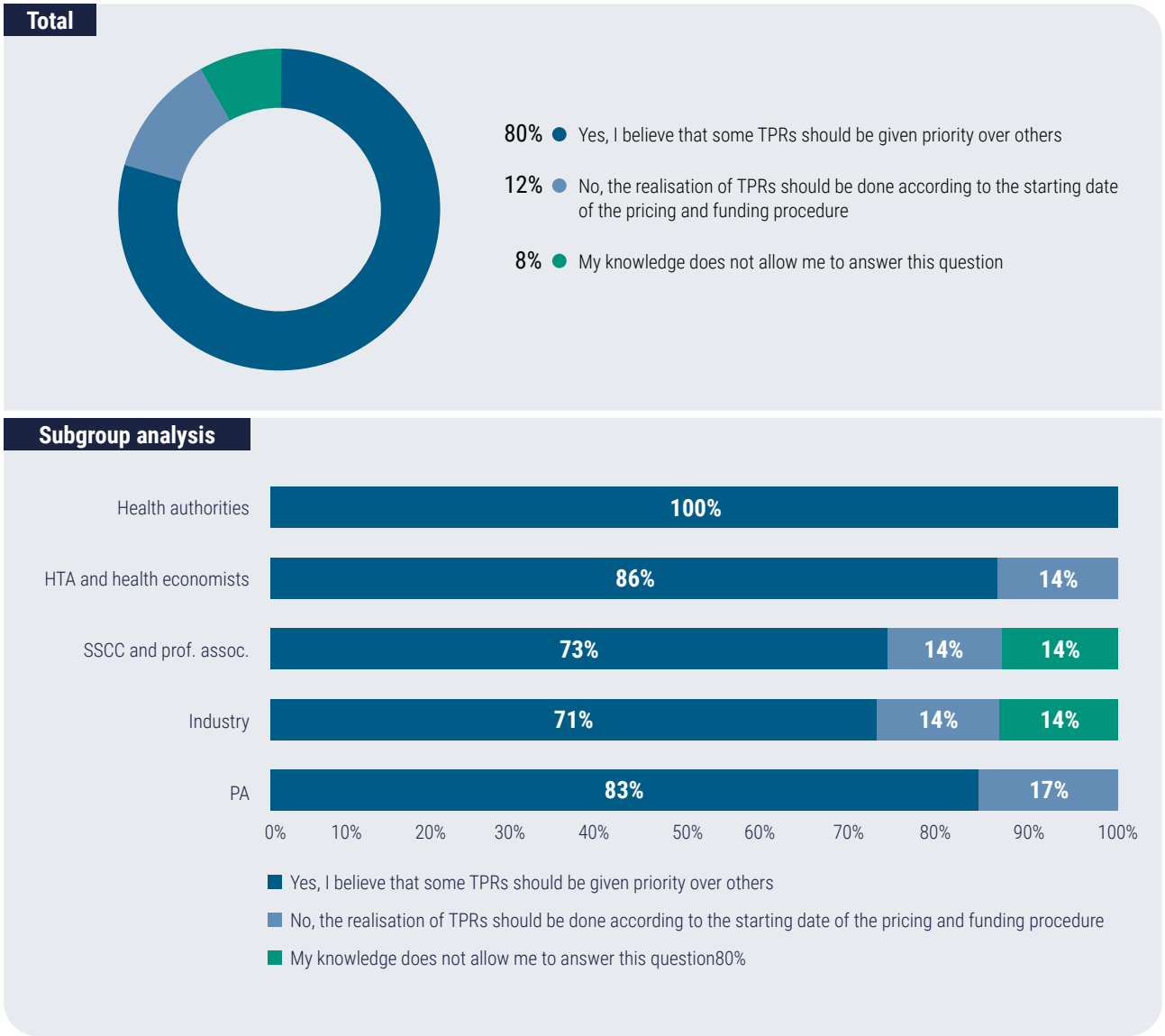
Subgroup analysis



The **80%** of those consulted consider that there should be a prioritisation in the development of some TPRs over others, while **12%** are against such prioritisation, arguing that it should be done according to the starting date of the pricing and funding procedure. About **8%** of those surveyed acknowledged that their knowledge of this issue did not allow them to answer this question.

There is a widespread opinion among the different profiles on the need for such prioritisation of TPRs, with unanimity among health authorities and support from a large proportion of health economists (**86%**), patient associations (**83%**), scientific societies (**73%**) and industry (**71%**). For **14-17%** of patients, health economists, industry and scientific societies, the implementation of the TPR should be organised according to the starting date of the pricing and funding procedure. Stakeholders with insufficient expertise to contribute to this issue belong to industry and scientific societies (**Figure 70**).

Figure 70. Do you consider that there should be a prioritisation on the development of TPRs for medicines?

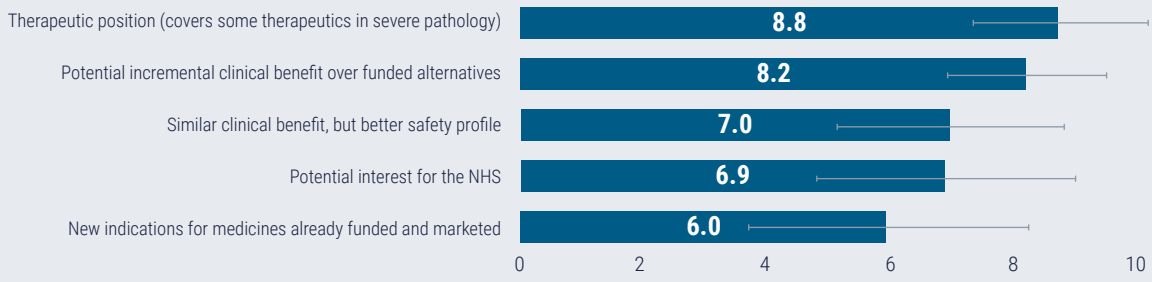


Among the agents in favour of prioritising the development of TPRs (n=39, **80%** of the total), the elements with the highest average weight in the prioritisation decision are the place in therapeutics (8.8 out of 10) and the potential incremental clinical benefit (**8.2**), while the potential interest for the NHS and new indications for medicines already funded and marketed would have less weight.

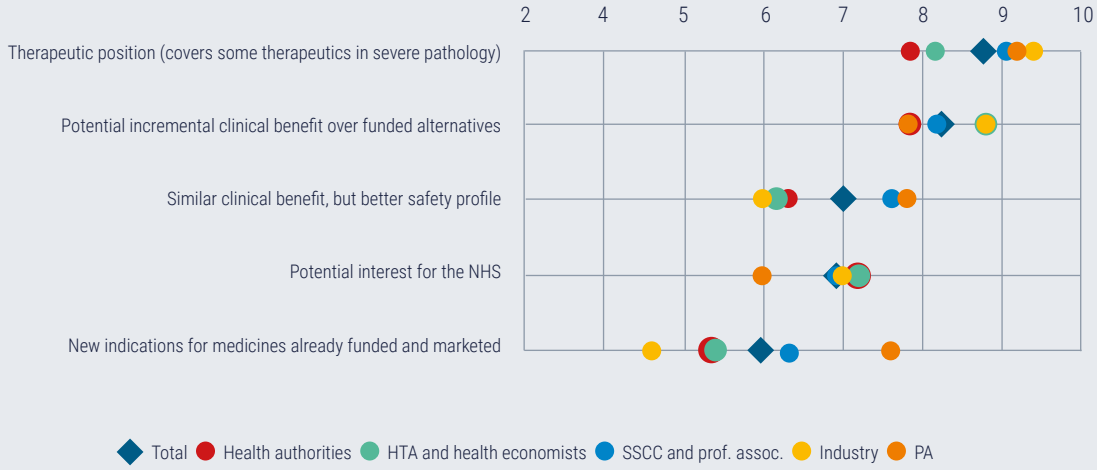
Place in therapeutics is the prioritisation criterion most valued by industry, patients and scientific societies, while health authorities rank it on a par with potential incremental clinical benefit. Health economists give the highest relative weight to the potential clinical benefit. With the exception of patient associations, the different subgroups give the lowest relative weight to new indications for medicines already funded and marketed (Figure 71).

Figure 71. Since you consider that a prioritisation should be made on the development of TPRs, please specify how much weight you consider that each of the following criteria should have in such prioritisation (average weight) (n=39)

Total



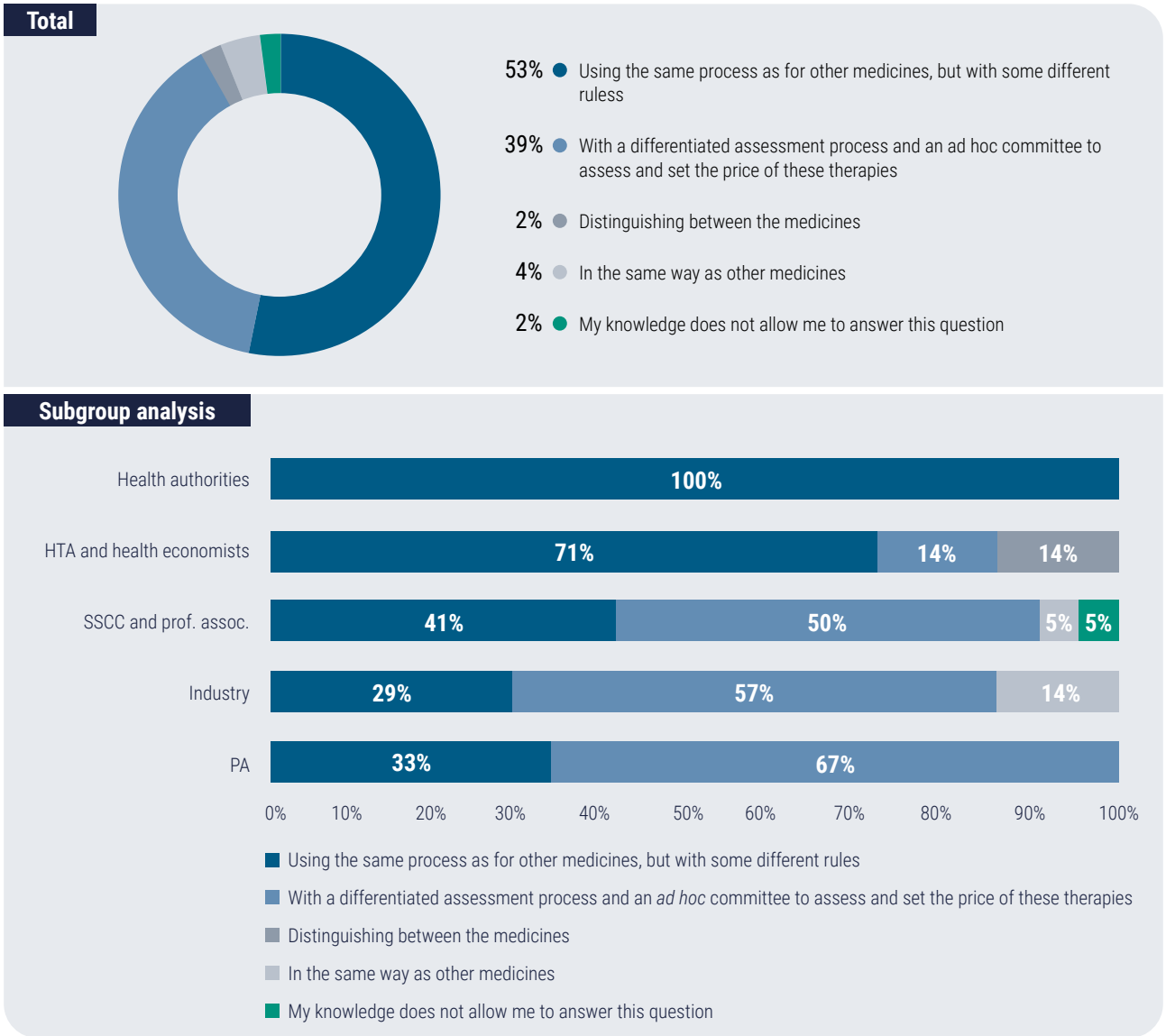
Subgroup analysis



More than half of the agents consulted believe that medicines for rare diseases in Spain should be assessed using the same process as other medicines, albeit with certain different rules, while **39%** said that a differentiated assessment process and an *ad hoc* committee should be used to assess and set the price of these therapies. The rest consider that it should be carried out in the same way as for other medicines, that distinctions should be made between orphan drugs themselves, or they do not answer the question due to lack of knowledge.

There are differences between subgroups. Among health authorities there is full consensus that it should be the same process, albeit with some distinctions. This view is shared by the majority of health economists (**71%**). In contrast, most representatives of patient associations (**67%**), industry (**57%**) and scientific societies (**50%**) value using a differentiated process with an *ad hoc* committee for these therapies (Figure 72).

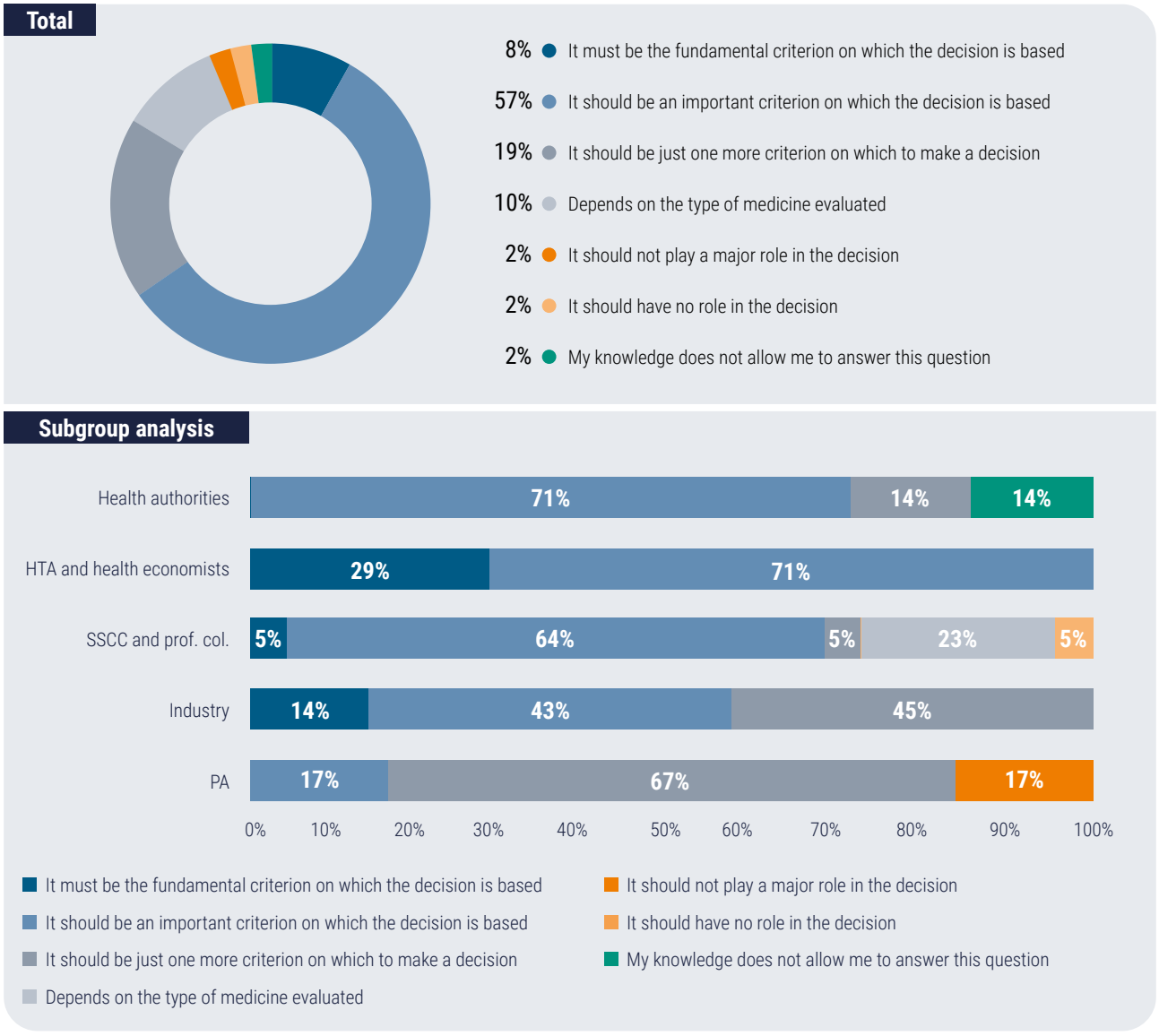
Figure 72. How do you consider that drugs for rare diseases should be assessed in Spain?



For **57%** of stakeholders, economic evaluation should be an important criterion on which to base the pricing and funding decision for a new medicine, while for **8%** it should be the main criterion, for **19%** it should be just another criterion and for **4%** it should not play a relevant role in the decision.

Opinions among subgroups are divided. Health economists are the group with the strongest emphasis on economic evaluation, with **29%** in favour of it being the key criterion and the remaining **71%** calling for it to have an important weight. For health authorities and scientific societies, the majority also advocate that economic evaluation should be an important criterion, although the rest are of the opinion that it should be just another criterion or that it depends on the type of medicine being assessed. For the majority of patient association representatives, the degree of efficiency should be just one more criterion on which to make the decision, and **17%** believe that it should not play an important role. In industry, opinions are mixed, but **86%** believe that it should be an important or additional criterion to inform decisions (Figure 73).

Figure 73. What is your opinion on the role of economic evaluation (efficiency or cost-effectiveness) in informing pricing and funding decisions for a new medicine?



Among the issues raised about the economic evaluation of innovative therapies, stakeholders prioritise that it should be methodologically rigorous and based on endorsed methodological guidelines. They also largely agree that economic evaluations should incorporate all variations in costs and health outcomes, as well as mechanisms for the appropriate management of uncertainty. Based on their responses, the statement on which they agree least is the validity of the current economic evaluation methods applied in Spain.

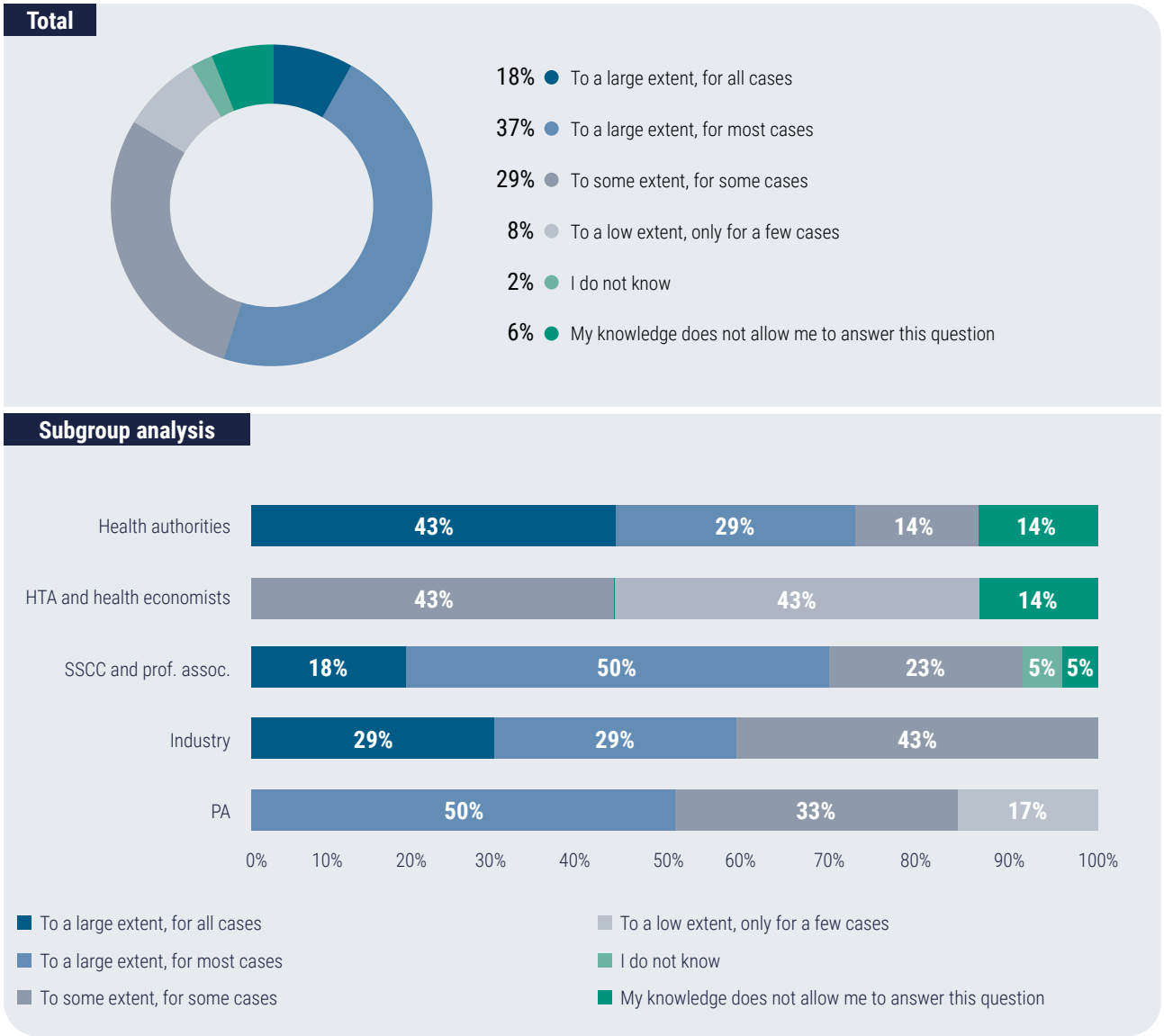
Health authorities are the subgroup most supportive of the validity of current economic evaluation methods in Spain, with an average score of 7.5 out of 10 points. It is worth noting that scientific societies are the subgroup that most value the incorporation of the dual perspective of payer and society in evaluations, followed by industry and patient associations. Industry and economists place most emphasis on the methodological rigour of evaluations and the incorporation of mechanisms to manage uncertainty (Figure 74).

Figure 74. Degree of agreement with the following points regarding the economic evaluation of innovative therapies (0 being the minimum and 10 the maximum) (average score)

55% of respondents are of the opinion that economic evaluation is currently taken into account to a large extent when deciding on the price and funding of innovative medicines in Spain (**37%** for most cases and **18%** for all cases), while **29%** consider that it is taken into account only to some extent, for some of the cases and **8%** believe that it is taken into account only for a few cases. **8%** of respondents do not know or believe that their knowledge does not allow them to answer this question.

Responses differ by subgroups of actors. Representatives of health authorities and scientific societies are the most likely to believe that economic evaluation is currently being taken into account in price setting (**68-72%**), while the group of health economists is the most sceptical, with **86%** believing that it is only taken into account to a limited extent (**Figure 75**).

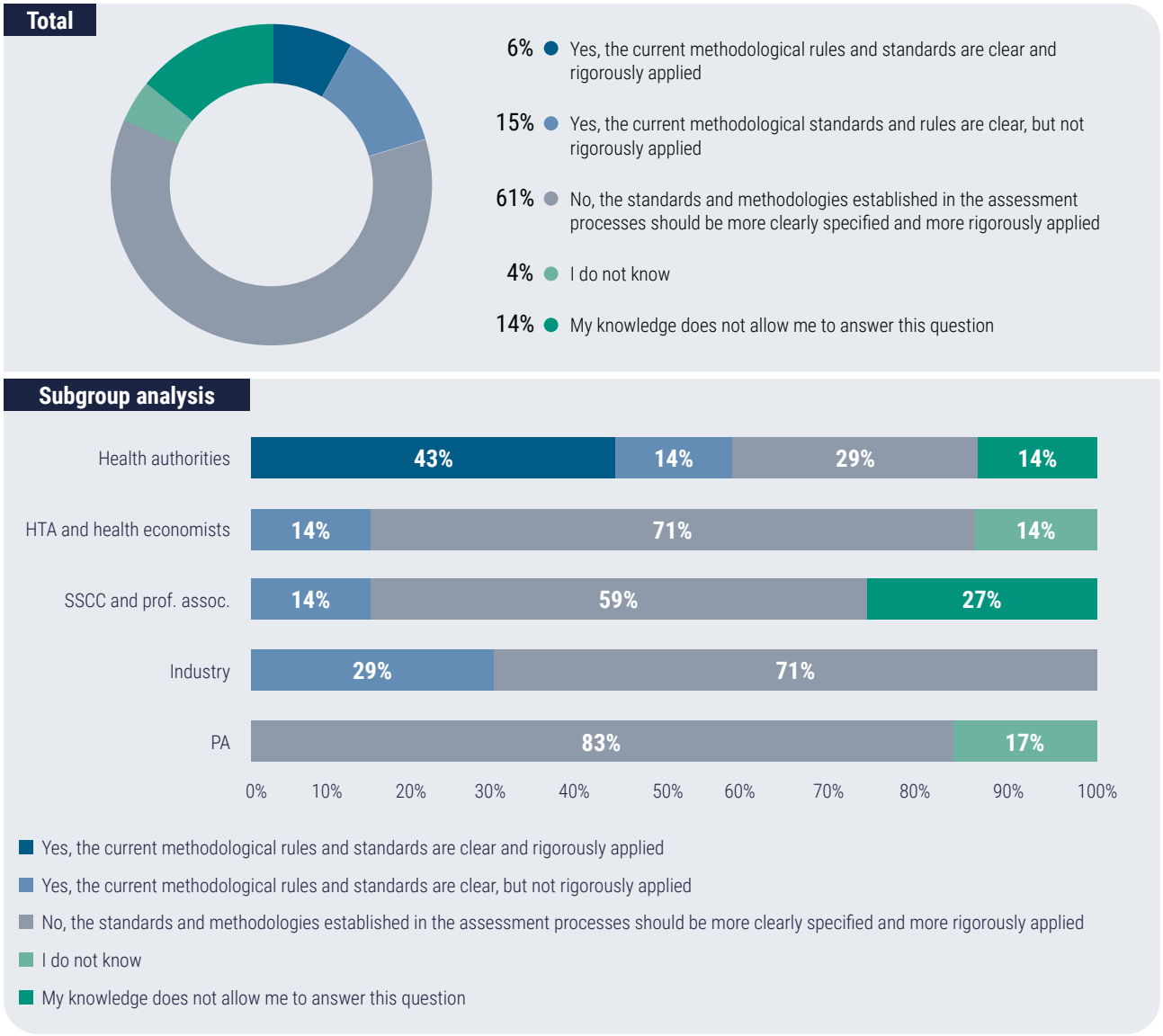
Figure 75. To what extent do you consider that the economic evaluation is currently taken into account when deciding on the price and funding of innovative medicines in Spain?



For **61%** of respondents, economic evaluation should be applied more rigorously, based on clearly established rules and methodologies in evaluation processes. On the other hand, **6%** believe that the rules are clear and rigorously applied, and **15%** believe that the current rules are clear, but not rigorously applied. The remaining **18%** do not know or do not have sufficient knowledge to answer this question.

For subgroups of actors other than health authorities, this generalised view on the need for a clearer and more rigorous application of the methodological rules of economic evaluation can be observed. On the other hand, for **43%** of the representatives of the health authorities, the current standards and rules are already rigorously applied today (**Figure 76**).

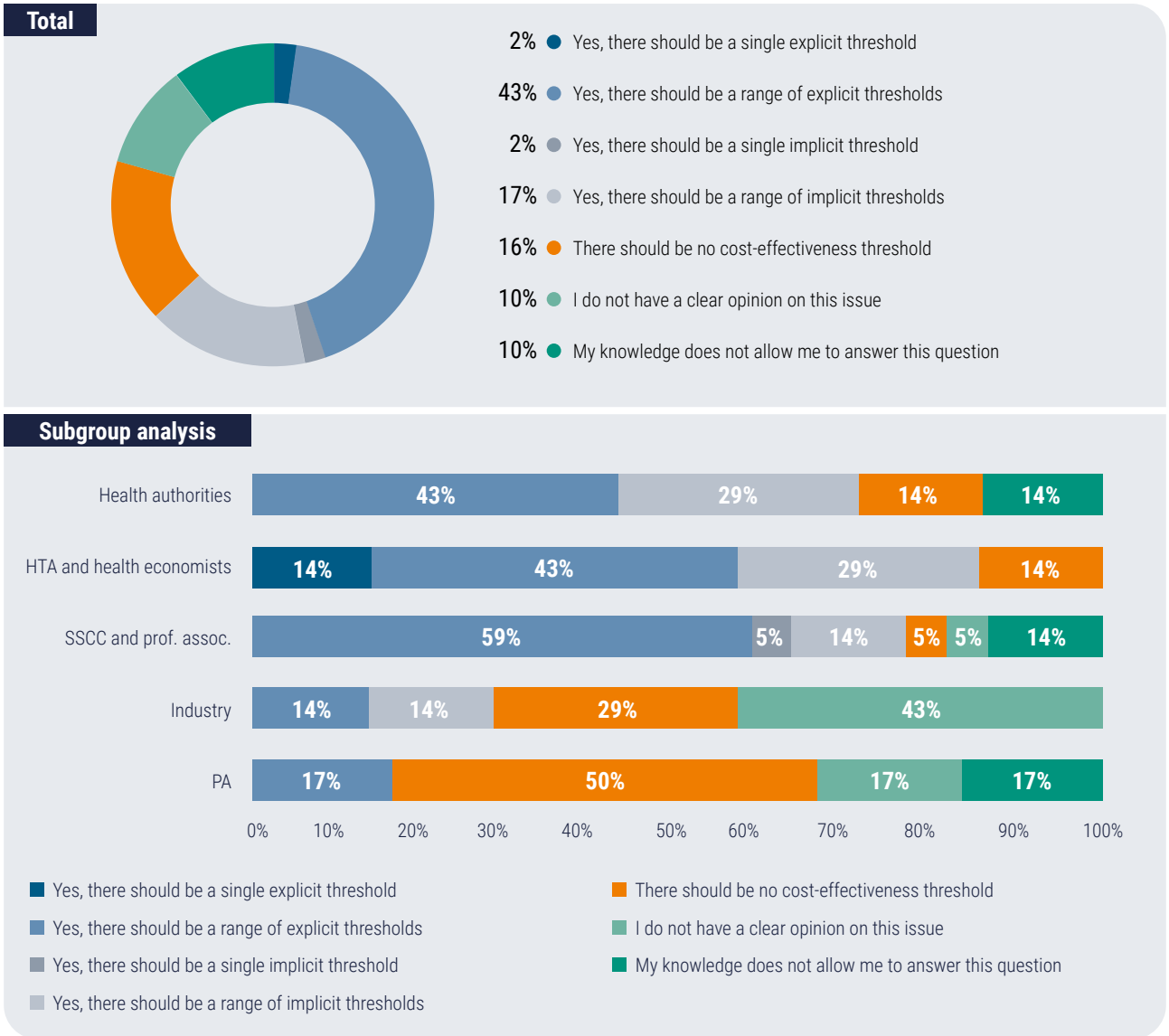
Figure 76. Do you consider that the current economic evaluation is conducted in a rigorous manner, with established methodological rules and standards for all assessed medicines?



Almost two thirds of respondents are of the opinion that a cost-effectiveness threshold should be considered in Spain, although opinions vary on the approach: **43%** believe there should be a range of explicit thresholds, **17%** believe there should be a range of implicit thresholds and **4%** believe there should be a single threshold, either explicit or implicit. On the other hand, **16%** of respondents are against a cost-effectiveness threshold, arguing that the administration should be able to decide, in accordance with current regulations, which medicine should be funded independently of cost/QALY. On the other hand, **20%** do not have a clear opinion on this issue or their knowledge does not allow them to answer the question.

Opinions on this issue differ greatly among the profiles of respondents. Health economists are the only ones who argue (**14%** of them) that there should be a single explicit willingness-to-pay threshold. The explicitness of the threshold or range of thresholds is advocated by the majority of health economists and scientific societies, while among policy makers opinions are divided. Half of the patients surveyed prefer no cost-effectiveness threshold, which is shared by **29%** of industry representatives and **14%** of health authorities and health economists (Figure 77).

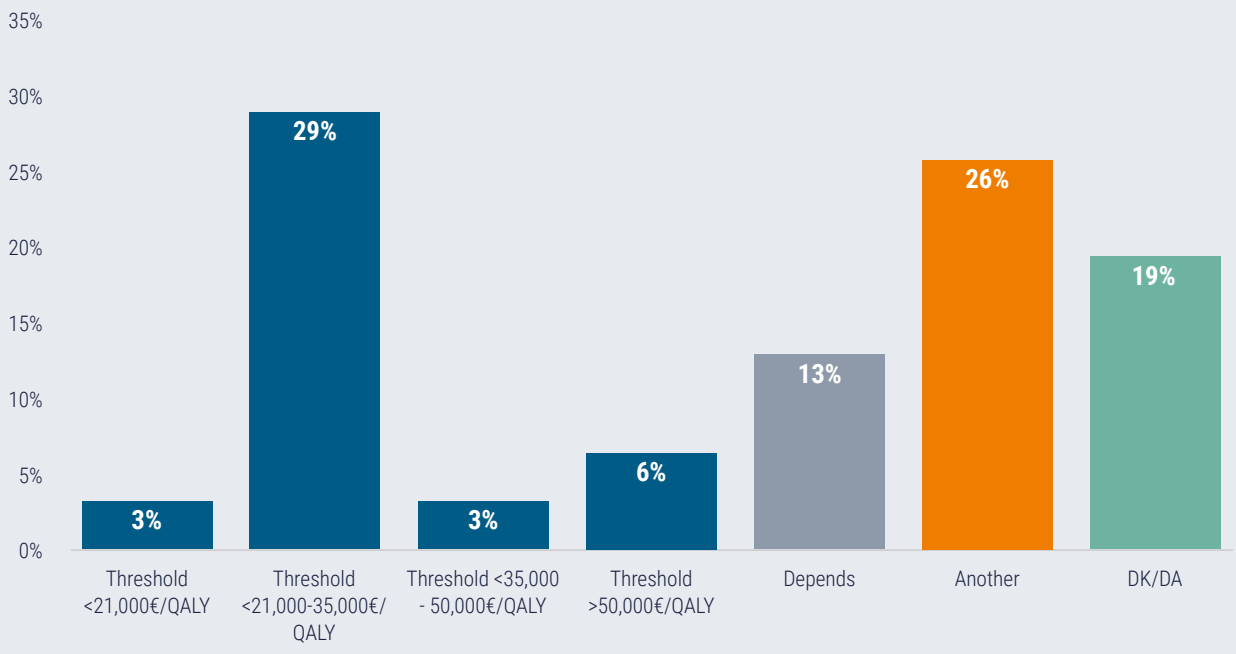
Figure 77. Do you consider that there should be a threshold of willingness to pay for a medicine in Spain (cost-effectiveness threshold or euros per quality-adjusted life year (QALY) gained)?



Among those interviewed who believe that there should be a cost-effectiveness threshold, **29%** consider that it should be between **21,000** and **35,000** euros per QALY gained, in line with the Health Technology Assessment report. Among health authorities and health economists or HTA agencies, **60%** and **50%** support this option, respectively.

On the other hand, **13%** of the agents who answered this question stated that the specific threshold would depend on the situation, with higher revisable thresholds for serious or rare diseases. On the other hand, **3%** of respondents would set the threshold below €**21,000**/QALY, **3%** between €**35,000** and €**50,000**/QALY and **6%** above €**50,000**/QALY. In addition, **26%** do not specify any specific value, but rather claims some arguments. An **19%** acknowledge that they do not know or do not have enough knowledge to answer this question (**Figure 78**).

Figure 78. Since you consider that there should be a threshold(s) of willingness to pay for a drug in Spain, where do you consider that this threshold/threshold should be in terms of euros per QALY gained? (n=31)

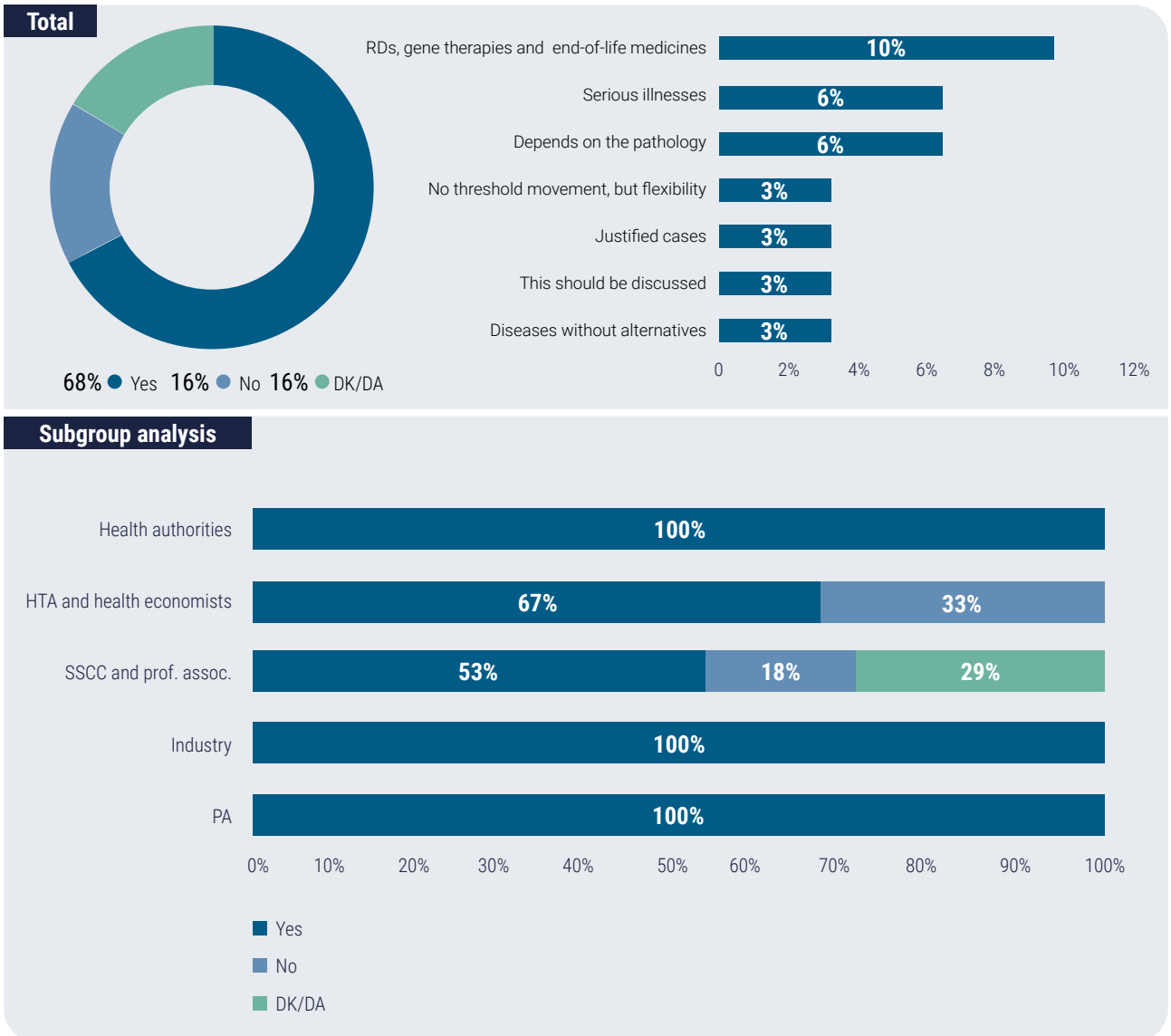


Other: encompasses answers such as: the threshold to be reached by consensus in the relevant committees; it should be the result of a technical analysis; it would apply scales from other European states; it should be appropriate to national income levels.

In addition, stakeholders were asked whether they believe there should be differential cost-effectiveness thresholds in some cases. Two thirds of respondents are of the opinion that there should indeed be differential thresholds for certain cases (either explicit or implicit thresholds), compared to **16%** who believe that there should not be such differentiations. In any case, only **34%** of those in favour of a differential threshold detail in which cases such thresholds should be used. Most agree that they should be taken into account for rare diseases, gene therapies and/or end-of-life medicines followed by serious diseases, or only for some pathologies.

There are few differences between the different subgroups analysed. All of them agree that there should be differential thresholds, with health authorities, industry and patients all agreeing in favour of such a measure. On the other hand, one third of the economists and **18%** of the members of the scientific societies are against the application of differential thresholds for some diseases or types of drugs (Figure 79).

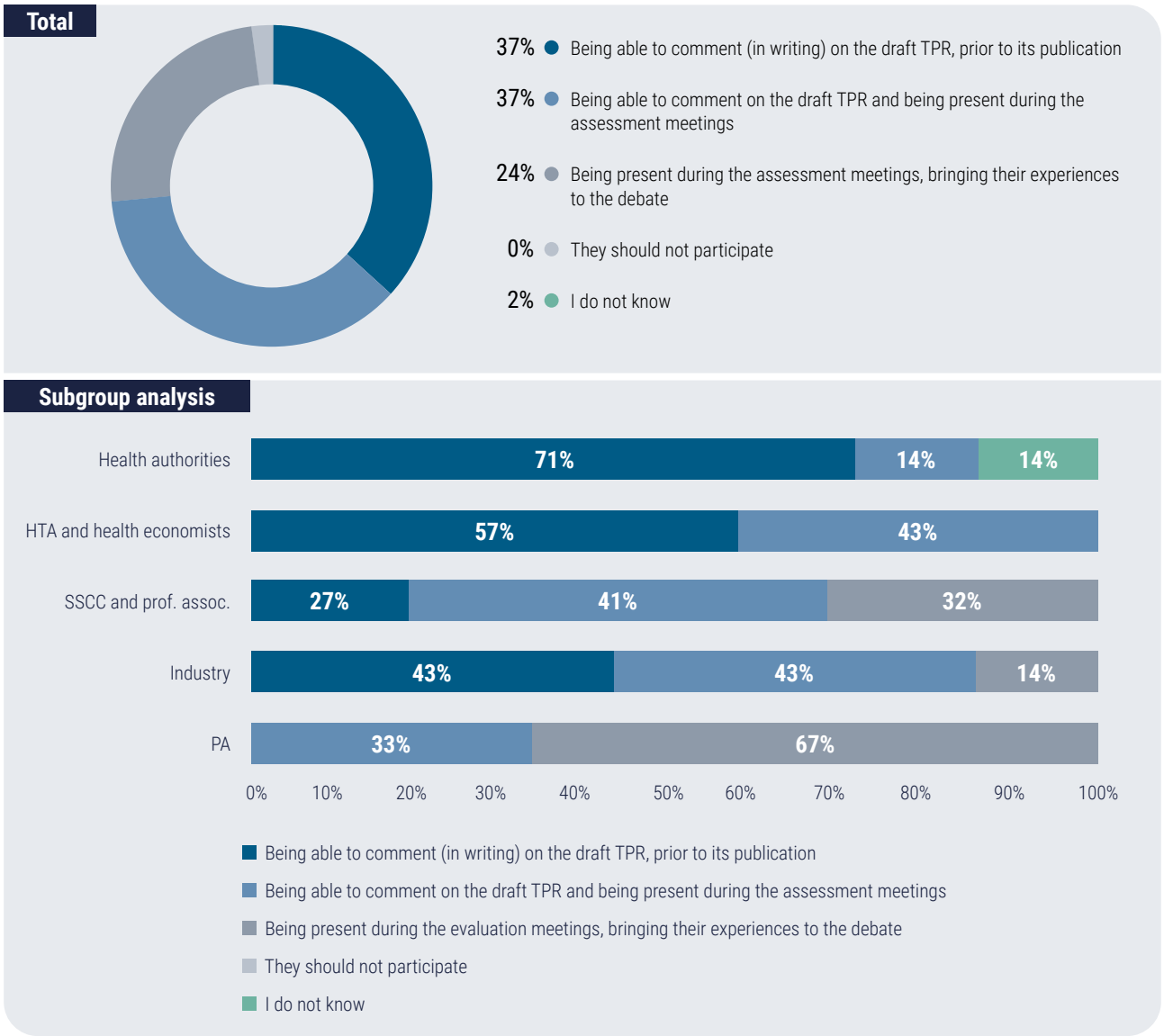
Figure 79. Do you consider that there should be differentiated thresholds in some cases? In which cases? (n=31)



Regarding the participation of scientific societies in the medicines assessment process, **37%** of respondents think that it would be useful at the stage of providing written comments on the draft TPR prior to its publication. A further **37%** believe that it would be useful to comment on the draft TPR, but also to be present during the assessment meetings. On the other hand, **24%** of the respondents consider that their role should be to be present during the assessment meetings, bringing their experiences to the discussion. It is worth noting that none of the stakeholders consider that SSCC should not be involved in the process at all.

By subgroups, most health authorities and health economists are in favour of SSCC being able to comment on the draft TPR before it is published, while most patients' associations advocate that they should be present during the meetings, providing their comments. Among the scientific societies themselves there is a diversity of opinions, although a majority support greater involvement of the SSCC by being present during the assessment meetings to contribute their experiences to the debate (Figure 80).

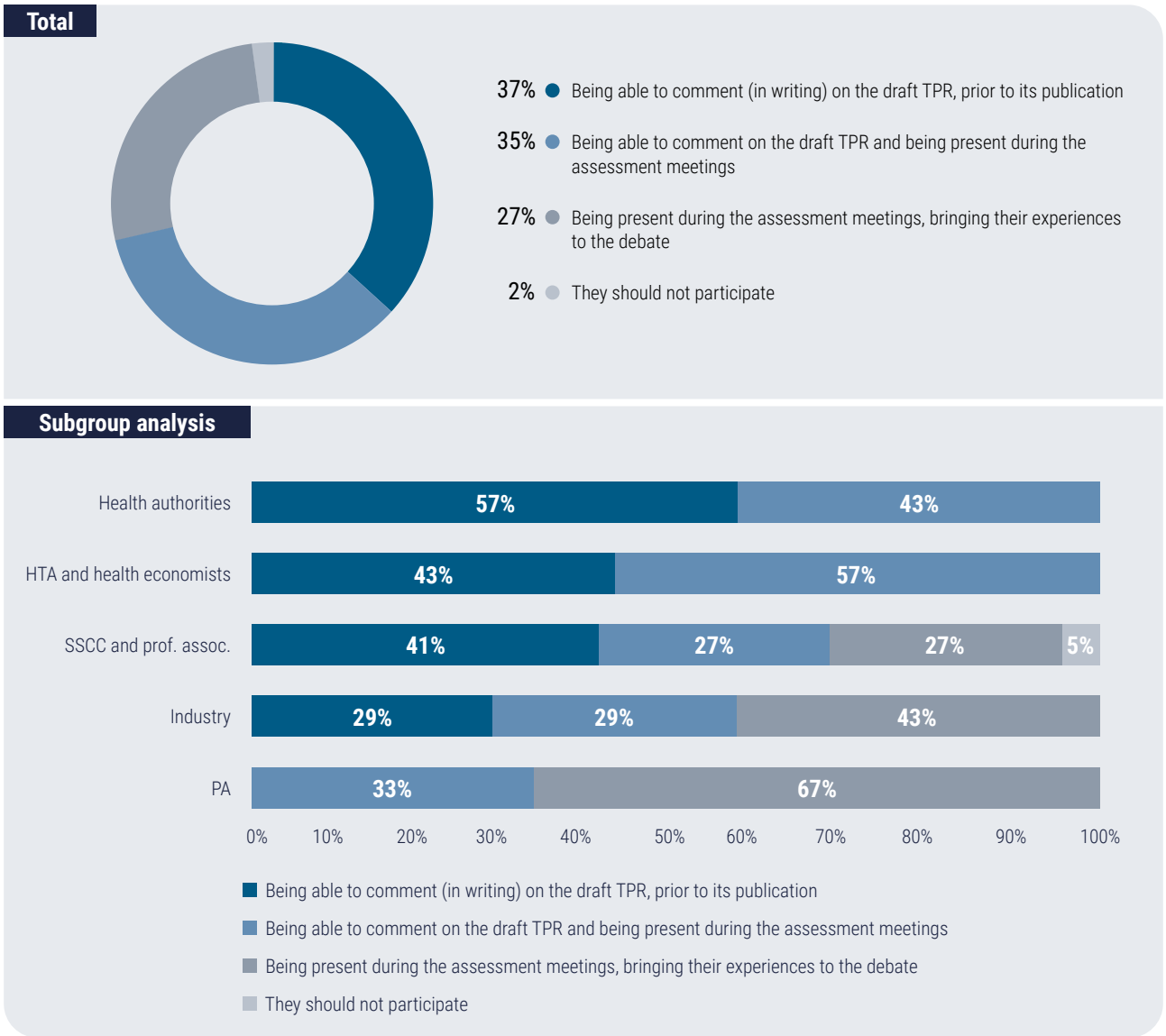
Figure 80. How do you consider that scientific societies should be involved in the medicines assessment process? (Multiple options available)



Similarly, almost all stakeholders consulted consider that patients should be involved in some way in the medicines assessment process. Only **2%** said that they should not be involved in the process. On the other hand, **37%** believe that they should be able to comment on the draft TPR prior to its publication; **35%** believe that, in addition to commenting, they should also be able to be present during the assessment meetings; and **27%** believe that they should be able to be present at the assessment meetings, contributing with their experiences to the discussion.

There are substantial differences between subgroups. Most of the health authorities consulted advocate that patients should be able to comment prior to the publication of the TPR, while most economists support that they should also be able to be present at the assessment meetings. On the other hand, industry and patient associations are more supportive of patients being able to be present at the assessment meetings, bringing their experiences to the debate. Among the scientific societies, opinions are very divided, with 5% considering that patients should not be involved in the assessment (Figure 81).

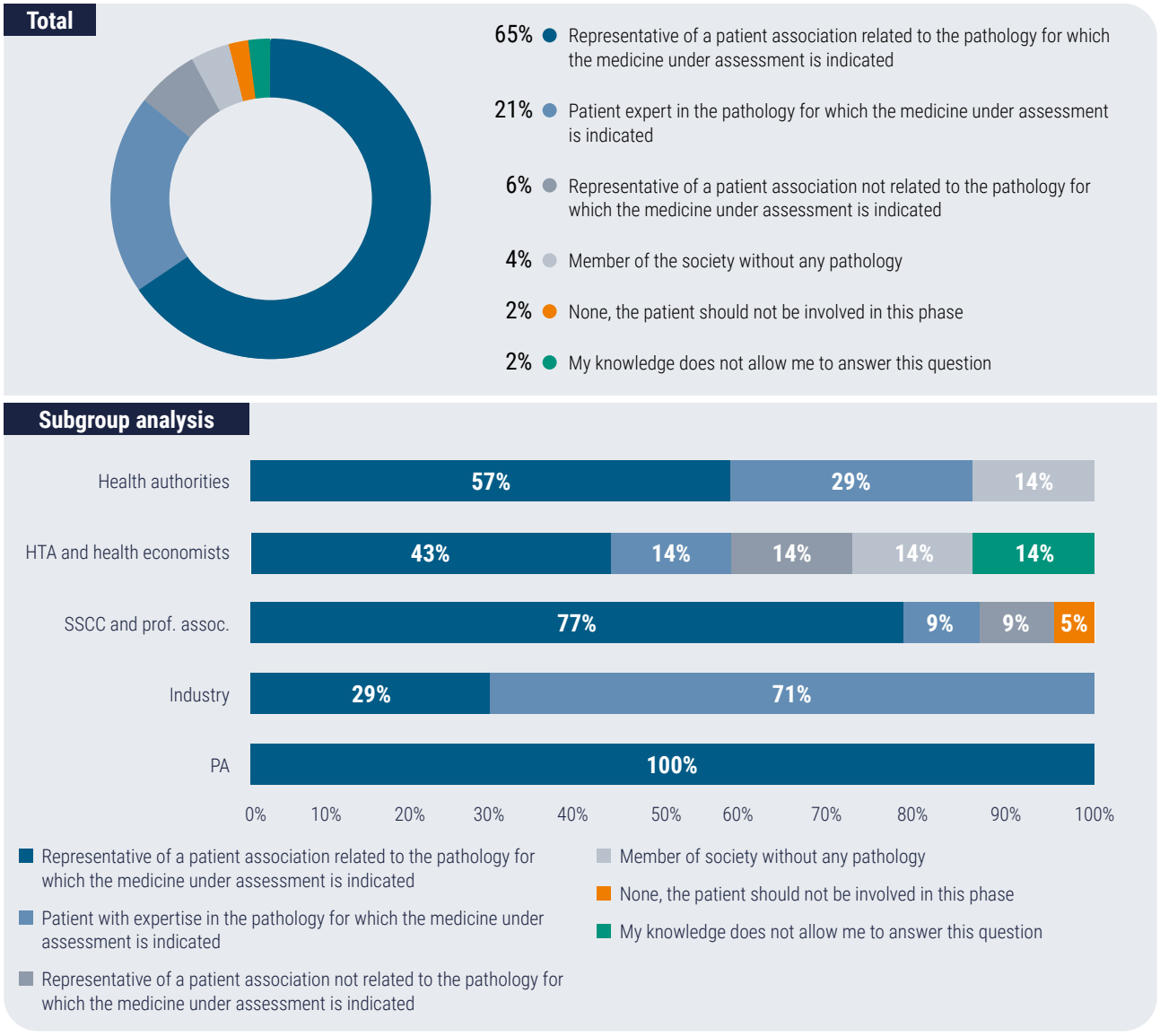
Figure 81. How do you consider that the patient should be involved in the assessment process? (Multiple options available)



For the majority of respondents (**65%**), the profile of patients participating in the medicines assessment process should be that of representatives of patients' associations related to the pathology for which the medicine under assessment is indicated. For **21%**, the most appropriate profile would be a patient who is an expert in the pathology for which the drug is indicated. **10%** believe that it would be preferable to include representatives of patient associations unrelated to the indication of the drug under assessment or a member of society with no pathology. Only **2%** believe that the patient should not be involved at this stage.

All the patient associations consulted agree on the desirability of including representatives of patient associations related to the pathology being assessed in the assessment process, a point on which most of the scientific societies (**77%**), health authorities (**57%**) and health economists (**43%**) agree. The industry is the only subgroup that does not agree, preferring the profile of a patient who is an expert in the pathology for which the drug under assessment is indicated (Figure 82).

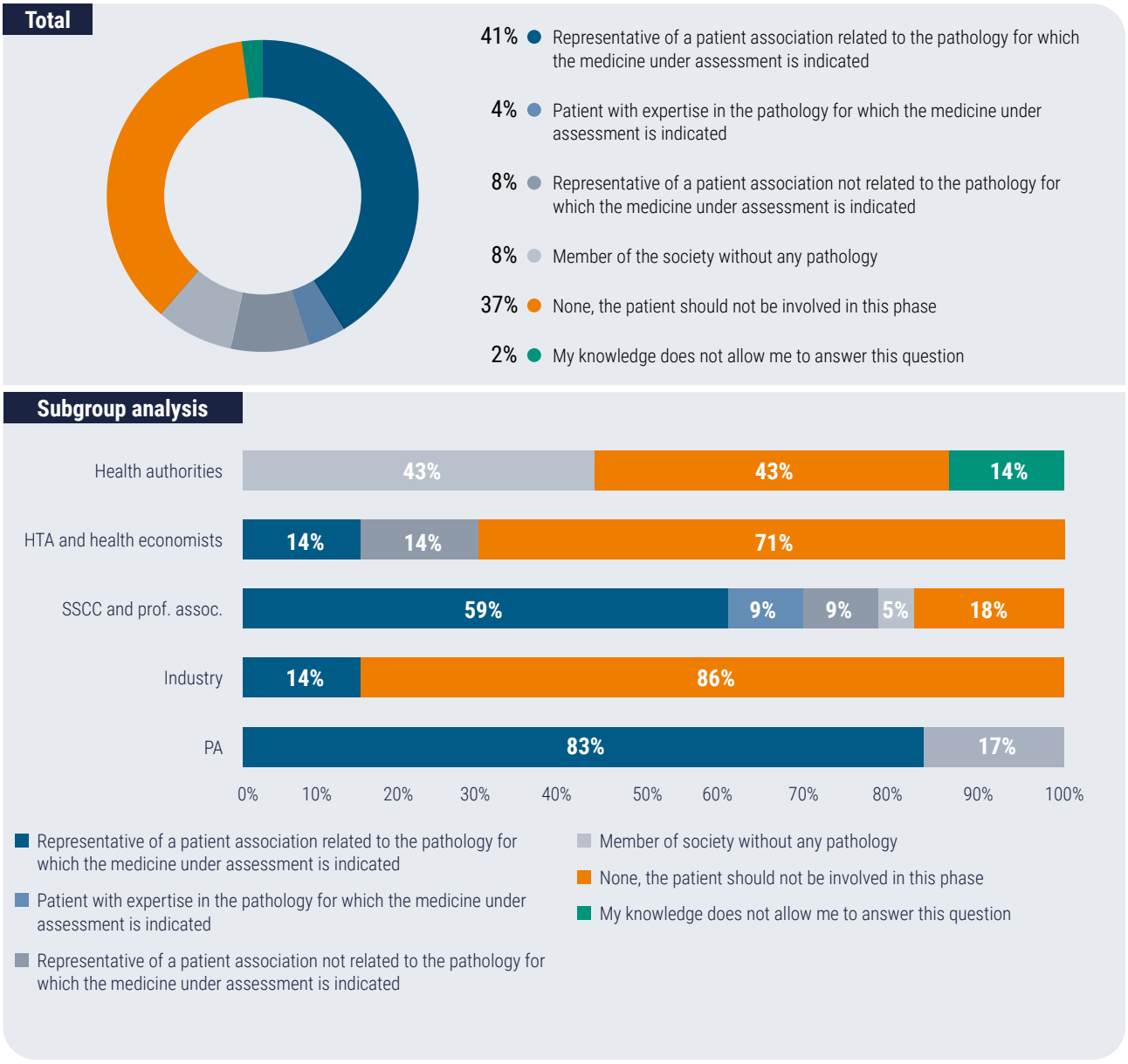
Figure 82. On patient participation in the assessment process, what do you consider the patient profile should be like?



On the other hand, opinions on the profile of the patient involved in the pricing and public funding decision are very different. In this case, **41%** think that it should be a representative of a patient association related to the pathology, while **37%** say that the patient should not be involved in this phase of the process.

There are major differences between the subgroups surveyed. Most health authorities, industry representatives and health economists advocate that the patient should not be involved in the pricing and funding process. In contrast, patient associations and scientific societies are of the opinion that a representative of a patient association related to the pathology of the evaluated medicine should be involved (Figure 83).

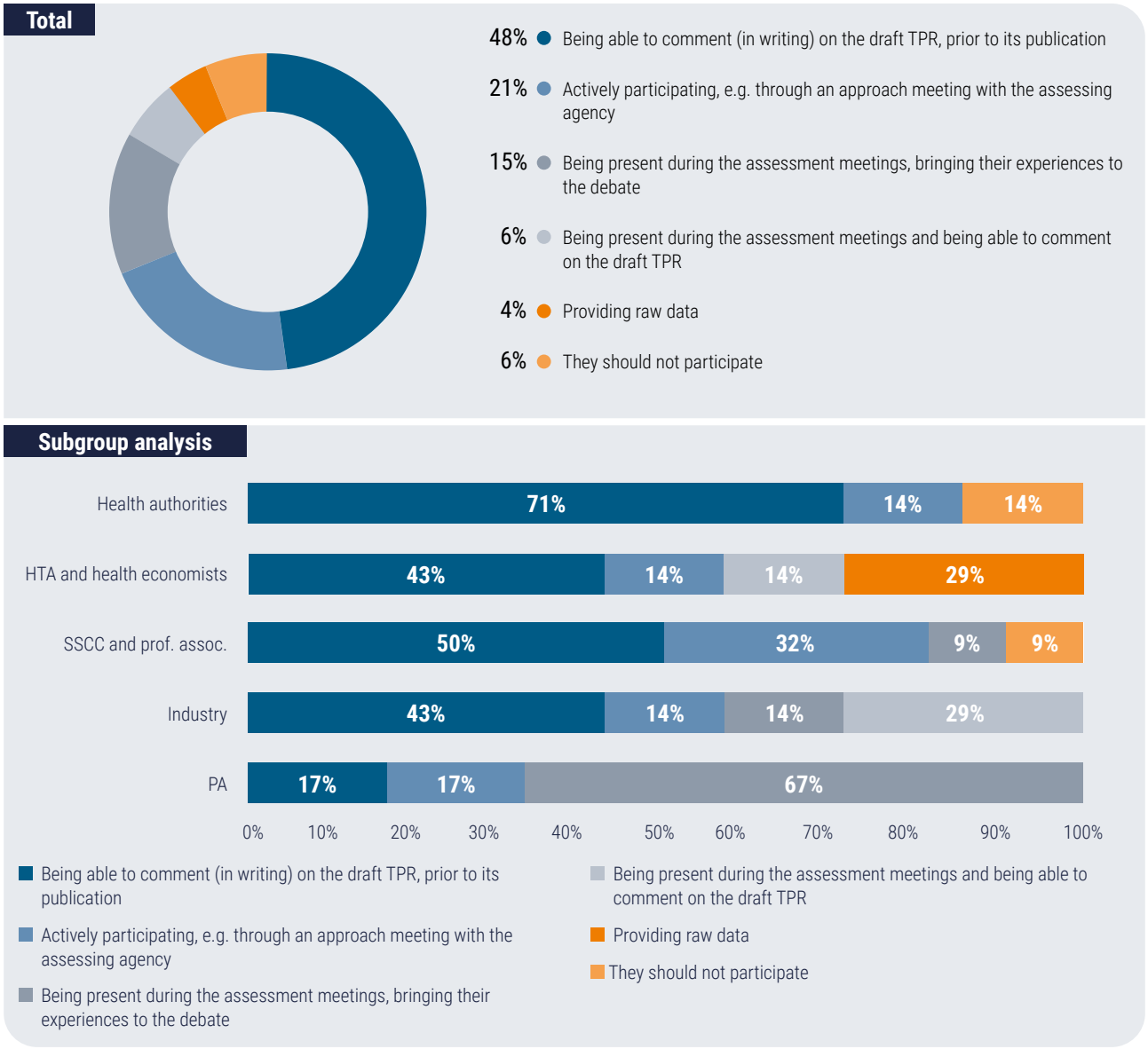
Figure 83. How do you consider that the profile of the patient involved in the pricing and public funding decision should be?



Regarding the role of the sponsor in the drug assessment process, almost half of the respondents believe that the sponsor should be able to make written comments on the draft TPR prior to its publication; **21%** believe it should be able to participate through a rapprochement meeting with the assessing agency; and **15%** believe it should be able to be present during the assessment meetings, contributing its experiences to the discussion. The **6%** believe that the sponsor should not be involved in this part of the process.

Most health authorities are of the opinion that the role of the sponsor should be limited to commenting on the draft TPR, with **50%** of the scientific societies and **43%** of health economists and industry agreeing. For their part, patients' associations advocate that the sponsor should be able to contribute with their experiences to the debate during the assessment sessions (Figure 84).

Figure 84. What role do you consider the sponsor laboratory should play in the medicine assessment process?



According to those consulted, the main challenge in terms of drug pricing and funding in Spain is the lack of explicit and transparent criteria in decision-making, followed by the absence of information systems to monitor results and the difficulty in implementing innovative financial agreements.

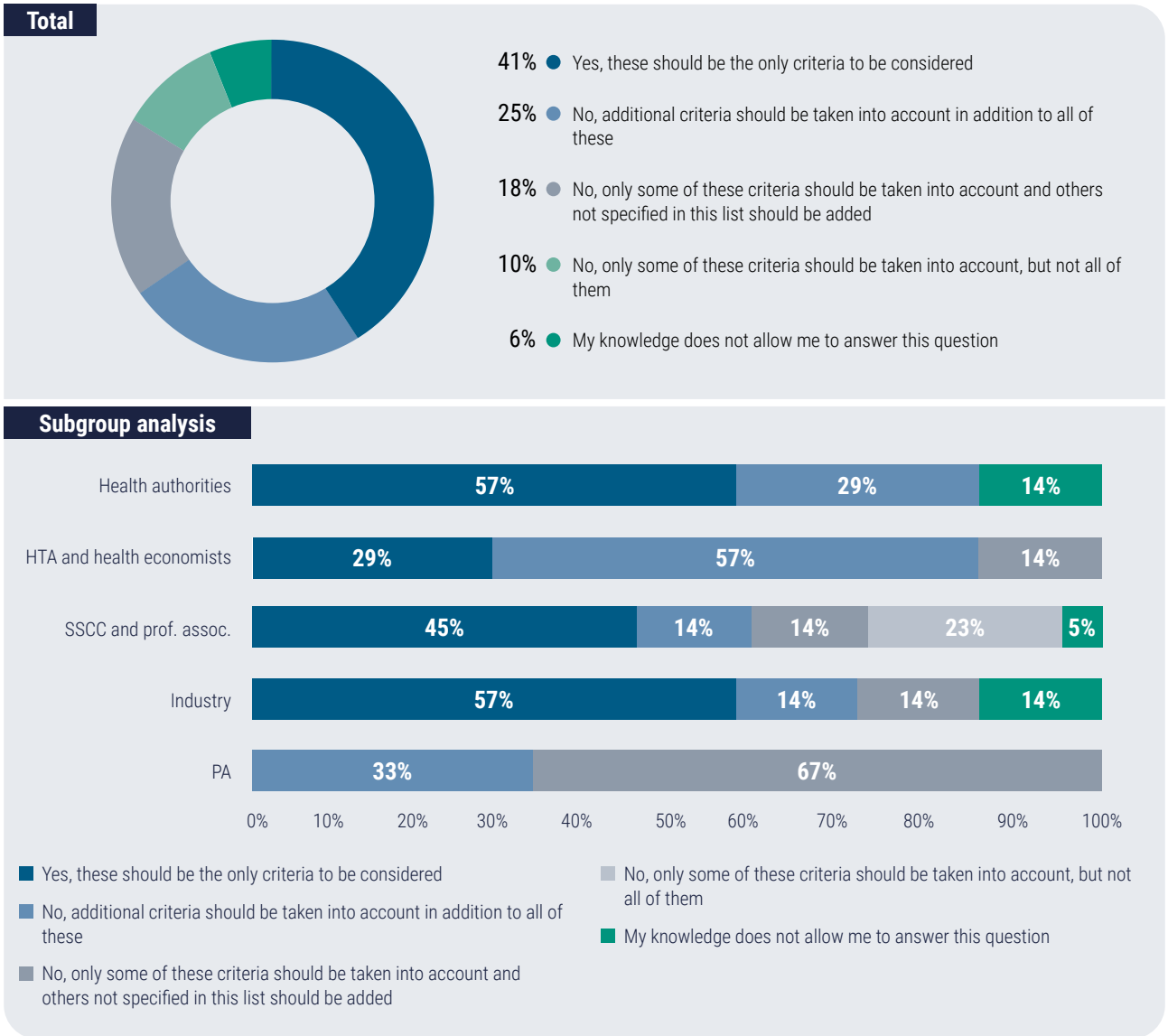
There are some differences between subgroups. Thus, the main challenge for health economists and industry is the lack of explicit and transparent decision-making criteria, a view not shared by health authorities (with an average score of 4.8 out of 10). For the health administration, the biggest challenge is the uncertainty in terms of outcomes and number of patient candidates. They are also the subgroup that attaches least importance to the fact that the discussion may be excessively focused on the price and not the value of the medicine. For patients' associations, the main challenge is the lack of information systems to monitor outcomes (Figure 85).

Figure 85. Challenges in medicine pricing and funding (0 is the lowest and 10 is the highest relevance) (average relevance)

Article 92 of Royal Legislative Decree 1/2015 establishes six criteria for public funding of medicines. Among the respondents, **41%** are of the opinion that these should be the only criteria to be considered, while **25%** believe that additional criteria should also be taken into account. In the opinion of **18%**, only some of these criteria should be taken into account and others not specified in the list should be added. Finally, **10%** said that only some of these criteria should be taken into account, but not all of them.

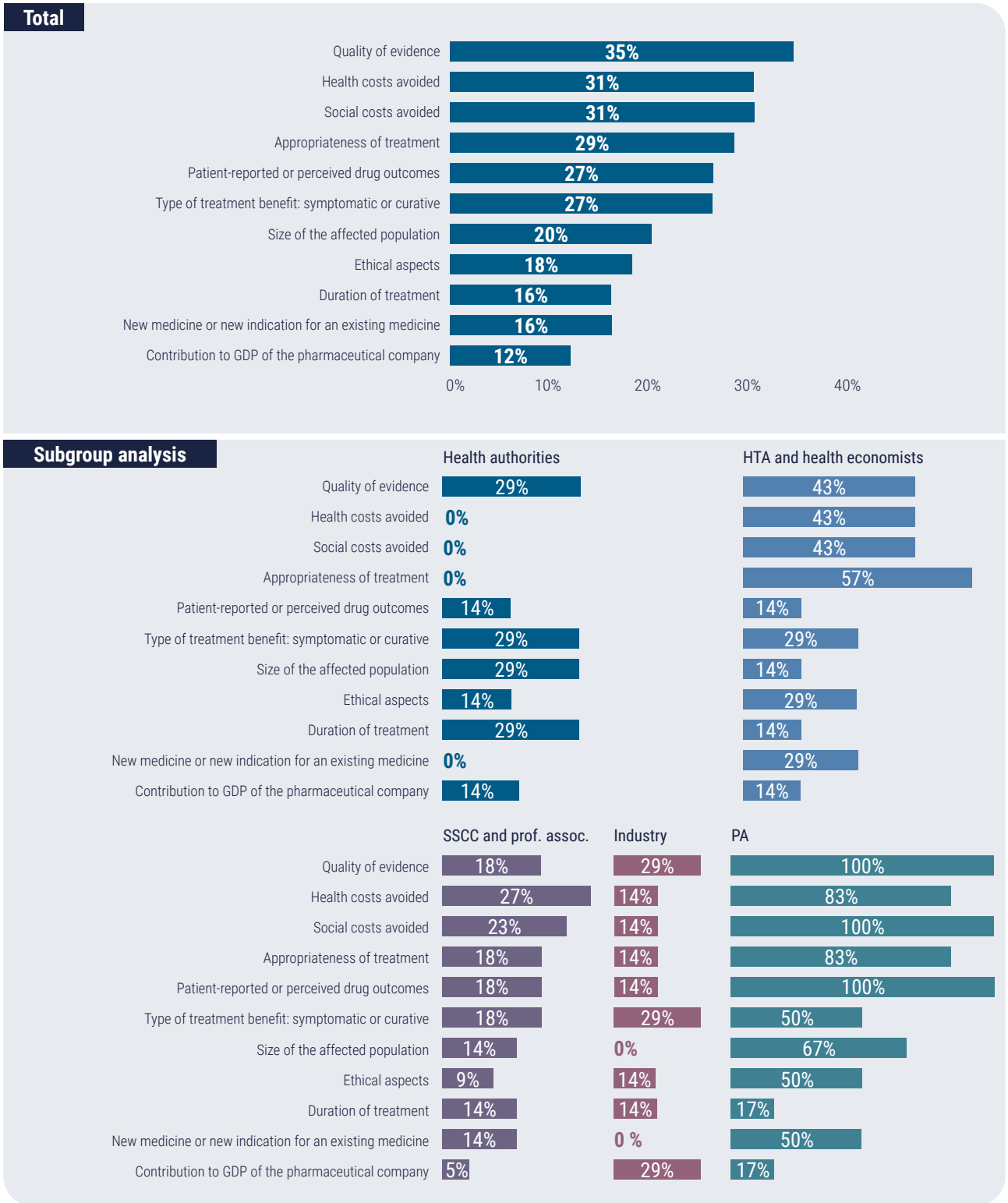
Among health authorities and industry representatives **57%** agree that these six criteria should be the only ones to be considered, in contrast to health economists, who mostly opt for additional criteria to be taken into account as well. Patients' representatives are the most divided in this respect, with **67%** believing that only some of the criteria set out in the law should be taken into account, while additional criteria should be added. Opinions among the scientific societies are divided, although most of them opt for sticking to the standard criteria (Figure 86).

Figure 86. Do you agree that the pricing decision should be based only on the criteria set out in Article 92 of Royal Legislative Decree 1/2015?



Quality of evidence, health costs avoided and social costs avoided are the three additional criteria most commonly mentioned by stakeholders to be taken into account in the funding decision, followed by appropriateness, PROs and type of treatment benefit. Of the suggested list, the criterion with the least support was the contribution to the GDP of the pharmaceutical company promoting the evaluated product (Figure 87).

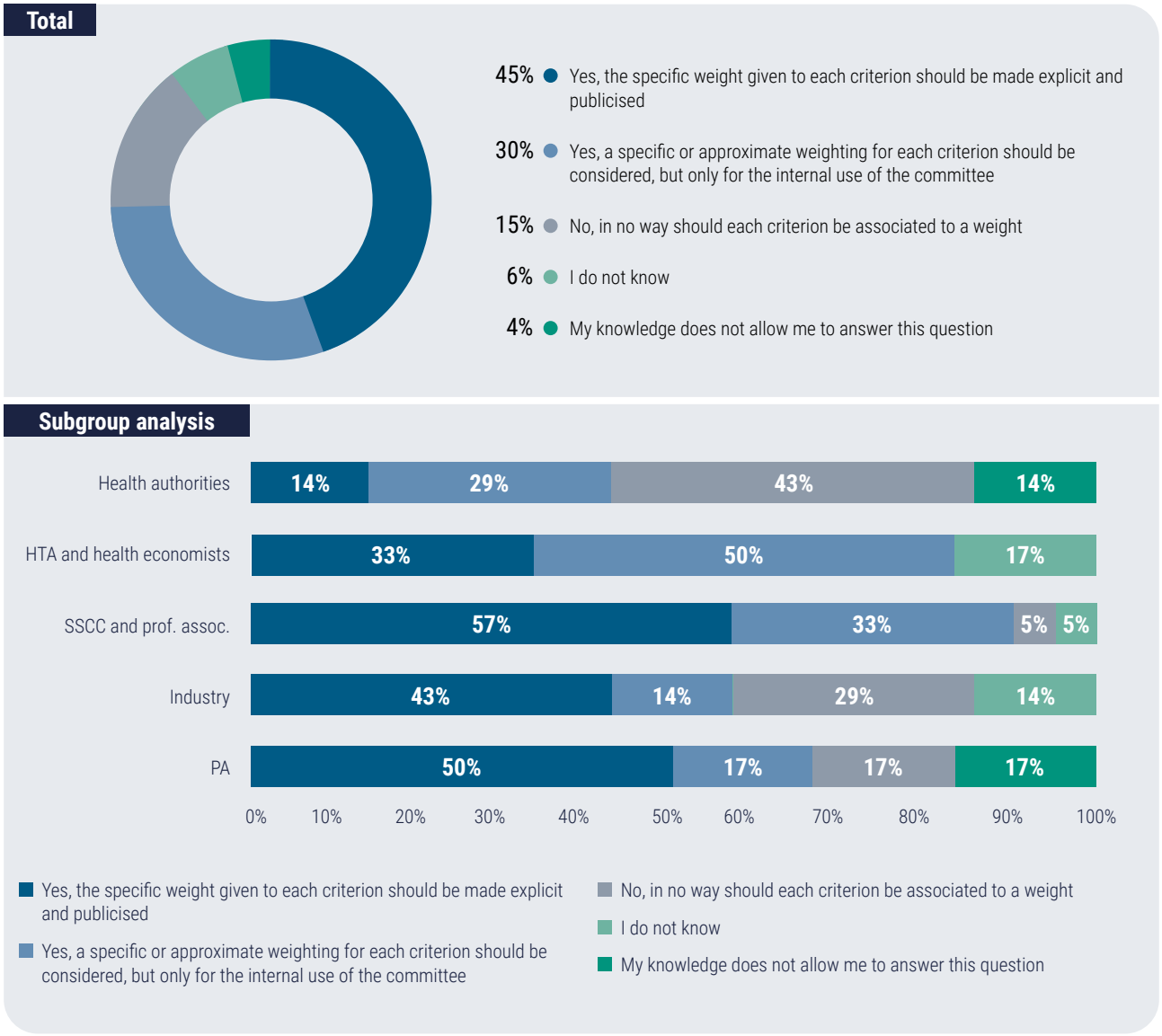
Figure 87. Should additional criteria be taken into account in the funding decision? (Multiple options available) (n=22)



Regarding the relative weighting of each criterion set out in Royal Legislative Decree 1/2015, **45%** of those consulted believe that it should be made explicit, while **30%** believe that this weighting (concrete or approximate) should be implicit, only for the internal use of the decision-making committee. On the other hand, **15%** believe that under no circumstances should each criterion be associated with a specific weighting. Finally, **10%** do not know or believe that their knowledge does not allow them to answer this question.

Opinions differ widely among the different subgroups consulted. Most representatives of scientific societies, industry and patients support the use of specific weights for the criteria in the law. On the other hand, for half of the health economists, the weighting should be for internal committee use only. At the other extreme are the health authorities, most of whom (**43%**) do not believe that each criterion should be associated with a specific weighting (**Figure 88**).

Figure 88. Do you consider that a specific weighting should be defined for each of the criteria specified in the Royal Legislative Decree mentioned above?



The criteria with the highest average weight to be considered in the pricing and funding of the medicine are the therapeutic value, social and incremental clinical benefit (considering cost-effectiveness) and ethical aspects, followed by the health costs avoided and the severity of the disease. On the other hand, the contribution to the GDP of the sponsor laboratory, the degree of innovation of the medicine or the budgetary impact on the NHS do not seem very relevant. It is therefore noteworthy, that the six criteria set out in the law are not the ones that receive the greatest average weight.

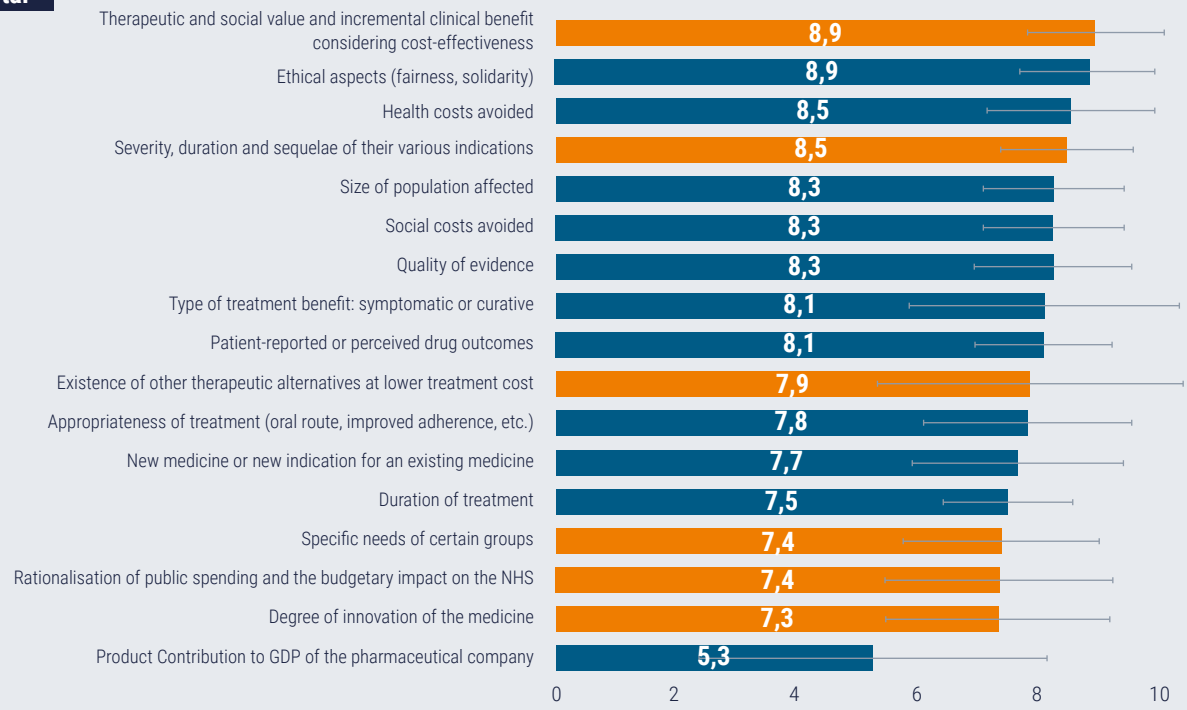
The results differ substantially between subgroups. For health authorities, the criterion with the highest average weight is the existence of therapeutic alternatives at lower treatment cost (9 out of 10), followed by the therapeutic value, social and incremental clinical benefit, ethical aspects, the size of the affected population, the type of treatment benefit and the quality of evidence. In contrast, the decision should not be affected by health care costs avoided, social costs avoided, appropriateness of the treatment, contribution to the sponsor's GDP, or whether it is a new drug or a new indication for an existing drug.

For health economists, the most important criterion is also the therapeutic value, social and incremental clinical benefit of the drug (10 out of 10), followed by ethical aspects, quality of evidence and the existence of lower-cost alternatives, while, on the other hand, they believe that the degree of innovation of the drug is the criterion that should weigh least in the decision (5,6).

The industry has a diametrically opposed opinion to that of the health authorities on the weight of certain criteria, such as health costs avoided (10 for the industry, 0 for the authorities), size of the affected population (0 vs 9), social costs avoided (8 vs 0), appropriateness of treatment (8 vs 0) or contribution to the GDP of the pharmaceutical industry (7 vs 0). For patients' associations, the most important criterion should be the ethical aspects, followed by the duration of treatment. Finally, scientific societies particularly value the therapeutic value/clinical benefit, ethical aspects and the size of the affected population (**Figure 89**).

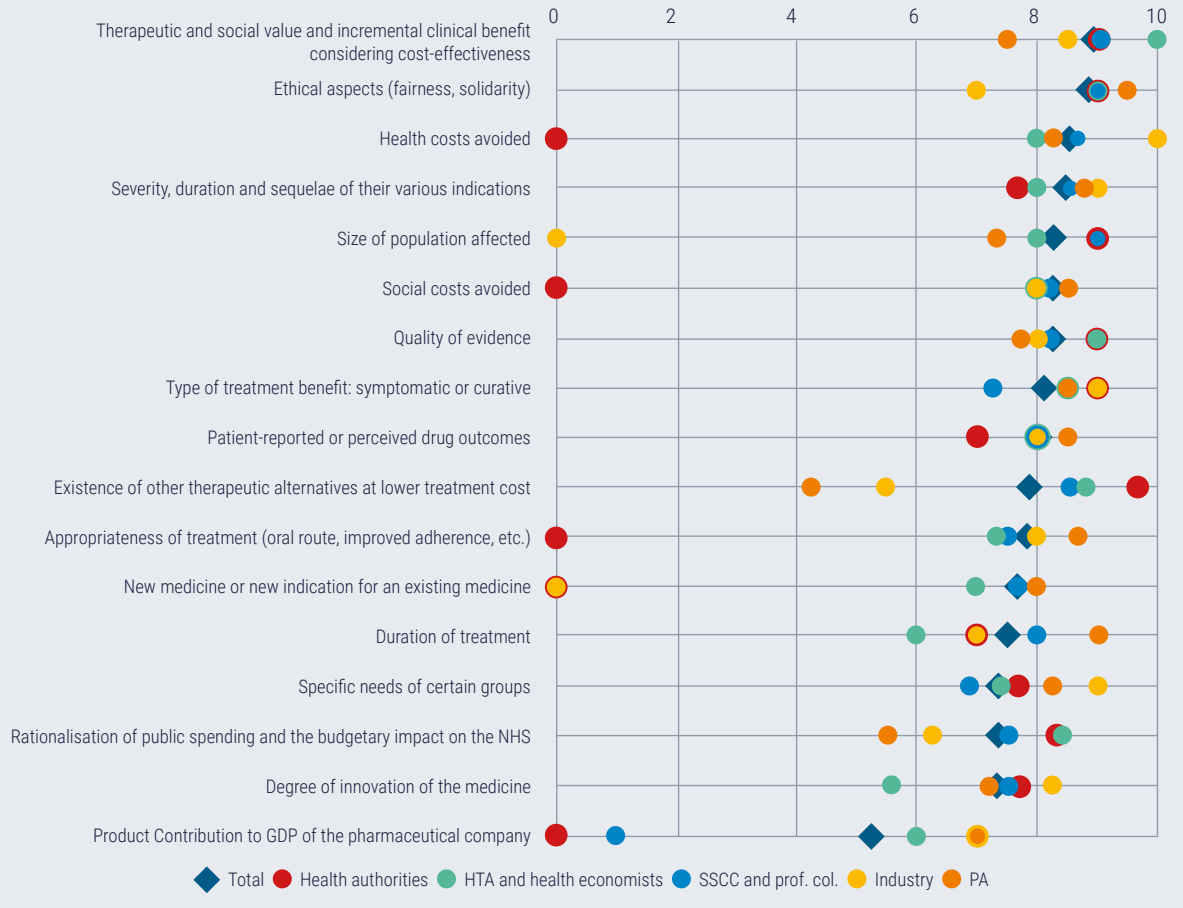
Figure 89. Weight of criteria you expect to be considered in pricing and funding (0 being the minimum weight and 10 the maximum weight) (average weight)

Total



Note: the criteria shaded in orange are those set out in article 92 of Royal Legislative Decree 1/2015

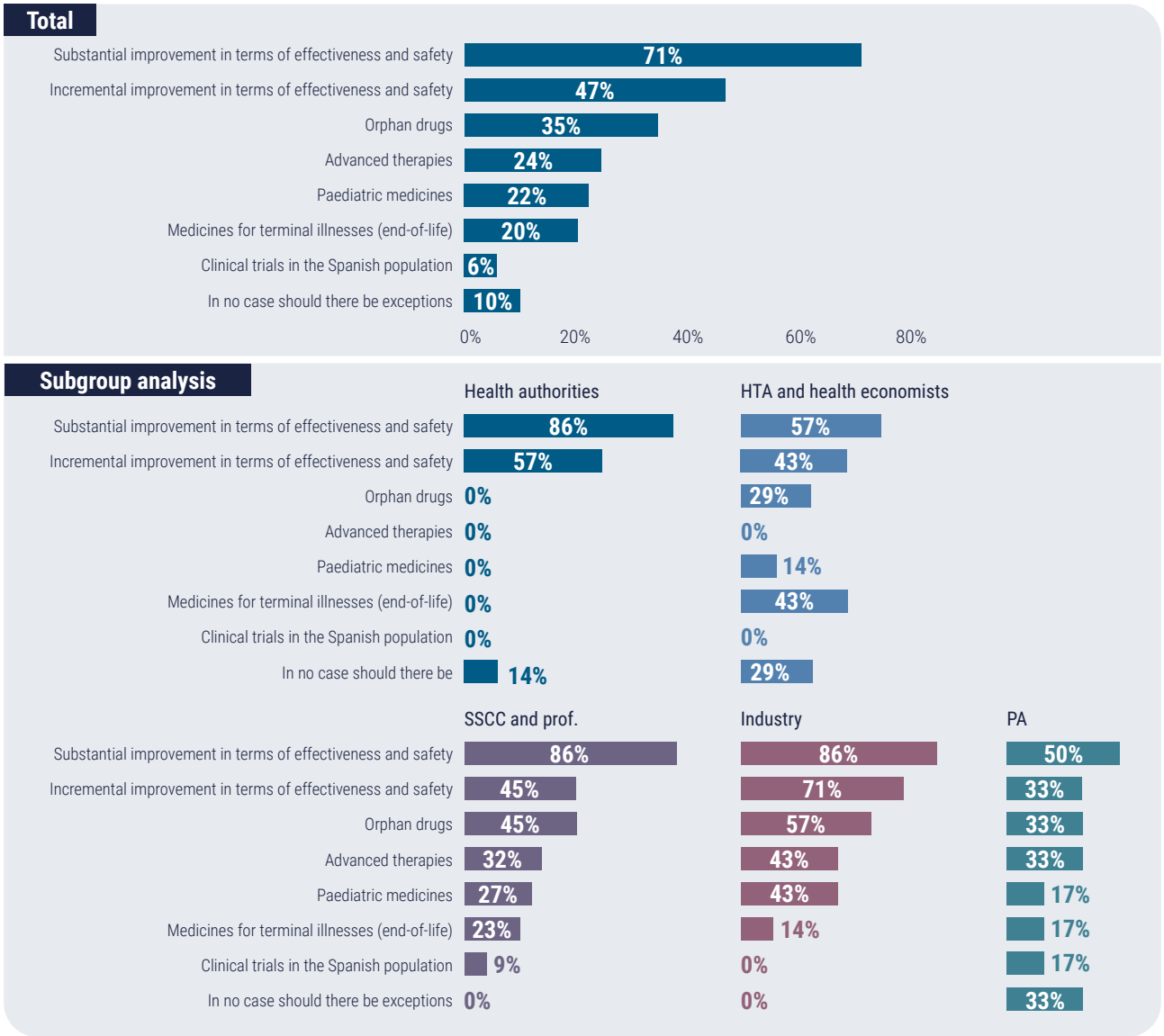
Subgroup analysis



Regarding the premium pricing of medicines over alternatives, **71%** of respondents believe that it could be allowed for a substantial improvement in terms of effectiveness and safety. For **47%**, this relative price premium could be allowed for incremental improvements. For their part, **35%** said it could be for orphan drugs, **24%** for advanced therapies, **22%** for paediatric cases and **20%** for terminal illnesses. Finally, **10%** of respondents believe that in no case should a price premium over available alternatives be allowed.

By subgroups, the majority (**86%**) of health authorities, scientific societies and industry favour a price premium for substantial improvements in effectiveness/safety. Economists are most supportive of a price premium for end-of-life medicines; industry for orphan drugs, advanced therapies and paediatric use (**Figure 90**).

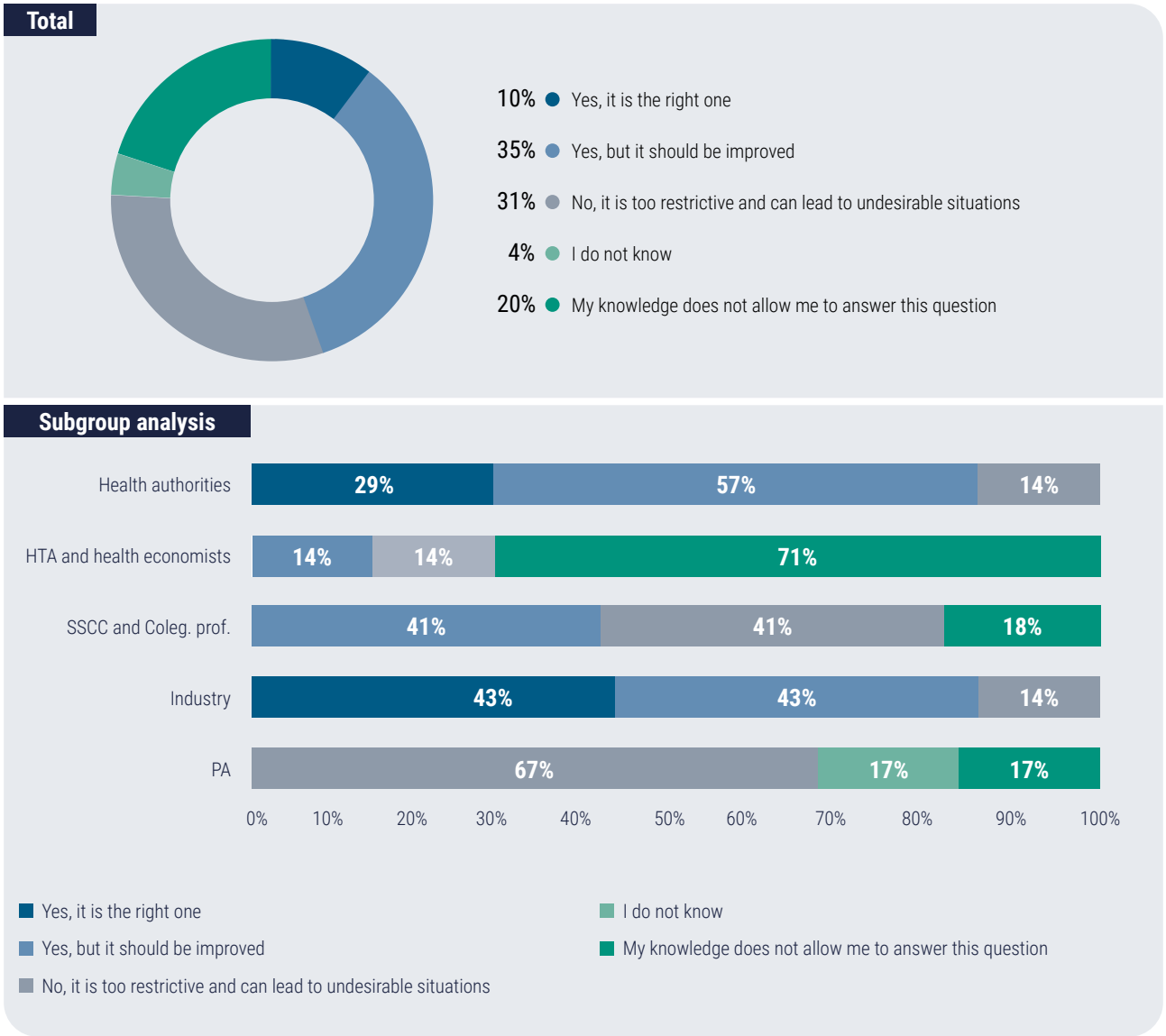
Figure 90. In which cases do you consider that the innovative medicine could be allowed to have a higher price than the available alternatives? (Multiple options available)



There are marked differences of opinion among stakeholders regarding the current system of access to medicines pending marketing or not funded in Spain. While **45%** believe that the current system meets its objectives (**10%** believe that it is adequate and **35%** that it meets its objective but needs to be improved), **31%** consider that it is too restrictive and leads to undesirable situations. It is worth noting that almost a quarter of respondents do not have a clear opinion on this issue or say they do not have sufficient knowledge to be able to judge this.

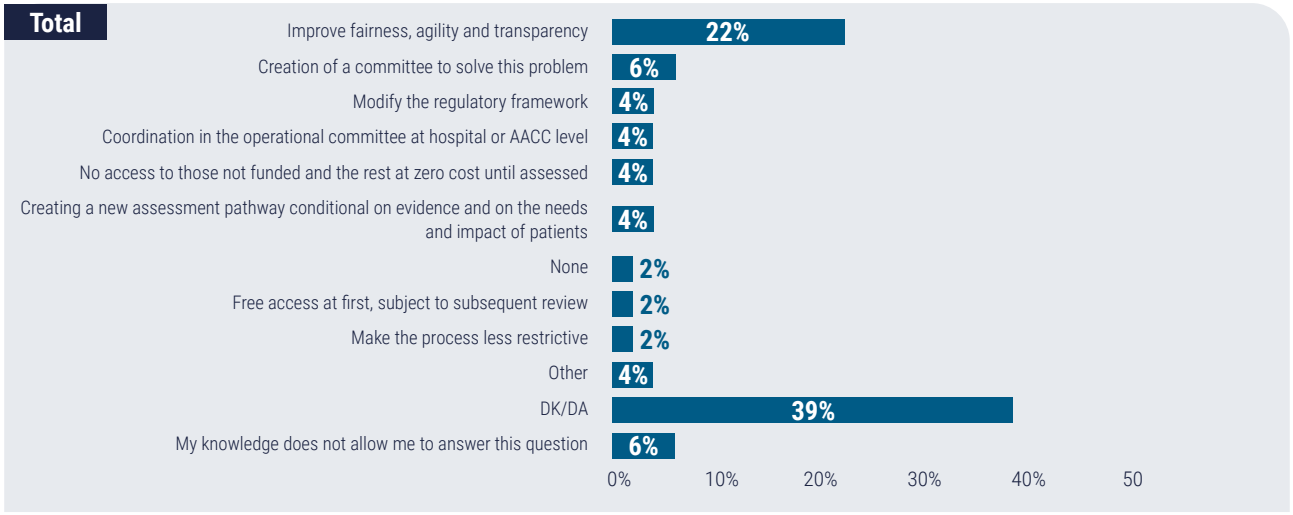
The vast majority of representatives of health authorities (**86%**) and industry (**86%**) are of the opinion that the current system meets its objectives, although the former are somewhat more critical of the improvement needed. In contrast, two thirds of the patient associations consulted say that the current system of access to this type of drugs is too restrictive. The opinions of the scientific societies are very divided. Finally, a high proportion of economists acknowledge that they do not know enough about it (Figure 91).

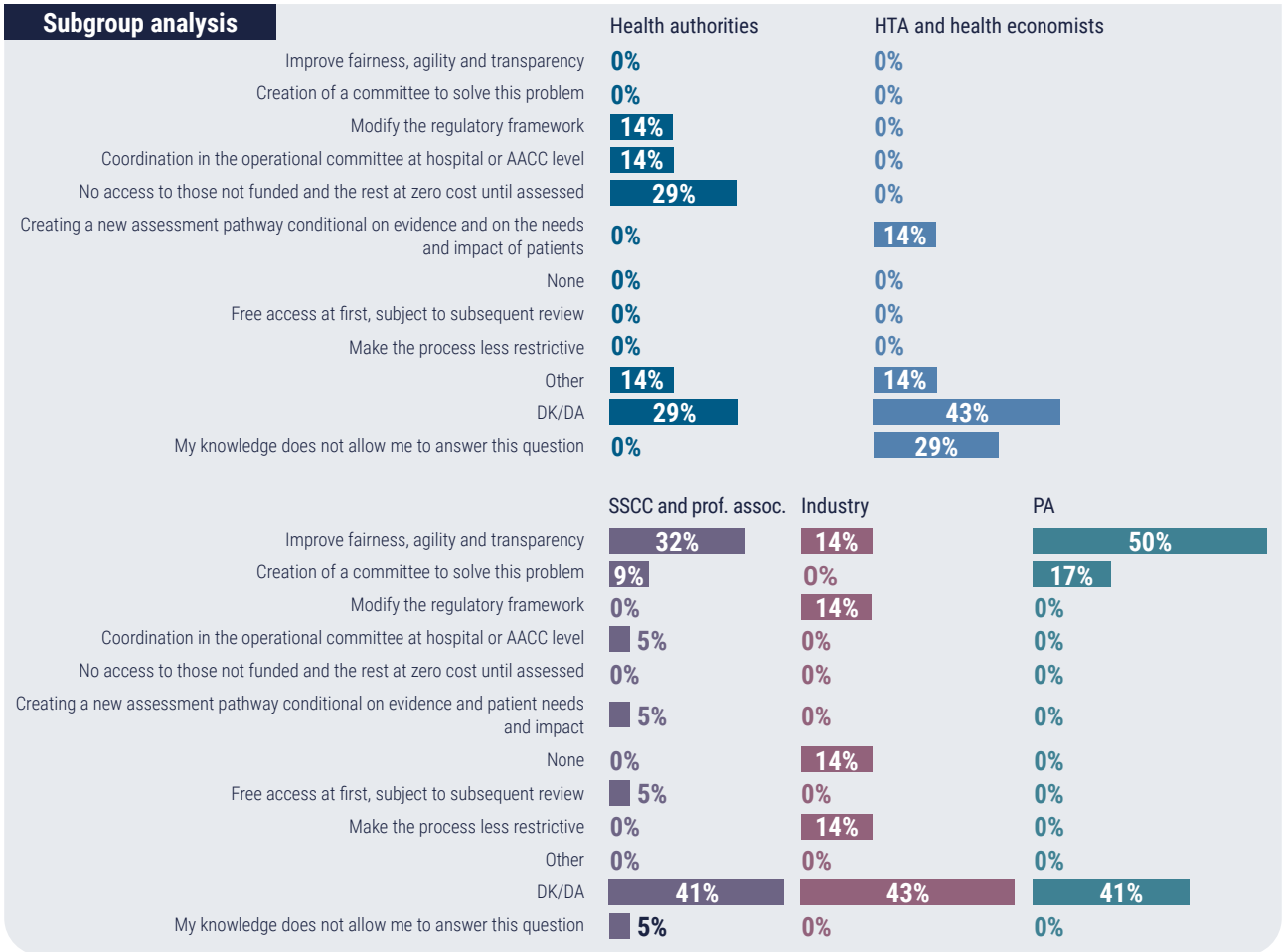
Figure 91. Do you consider that the current system of access to unmarketed or unfunded medicines in Spain meets its objective?



Following on from the previous question, respondents were asked what actions they would take to improve the current system of access to pending or unfunded medicines. In this open-ended question, most of the proposed actions are related to improving fairness, agility and transparency, followed by the creation of an *ad hoc* committee, modification of the regulatory framework, hospital or regional coordination, creation of a new non-conditional assessment pathway or restricting access to non-funded medicines. A total of **45%** claimed not to know or not to have sufficient knowledge to respond (**Figure 92**).

Figure 92. What actions would you take to improve the current system of access to medicines pending marketing or unfunded medicines mentioned in the previous question?

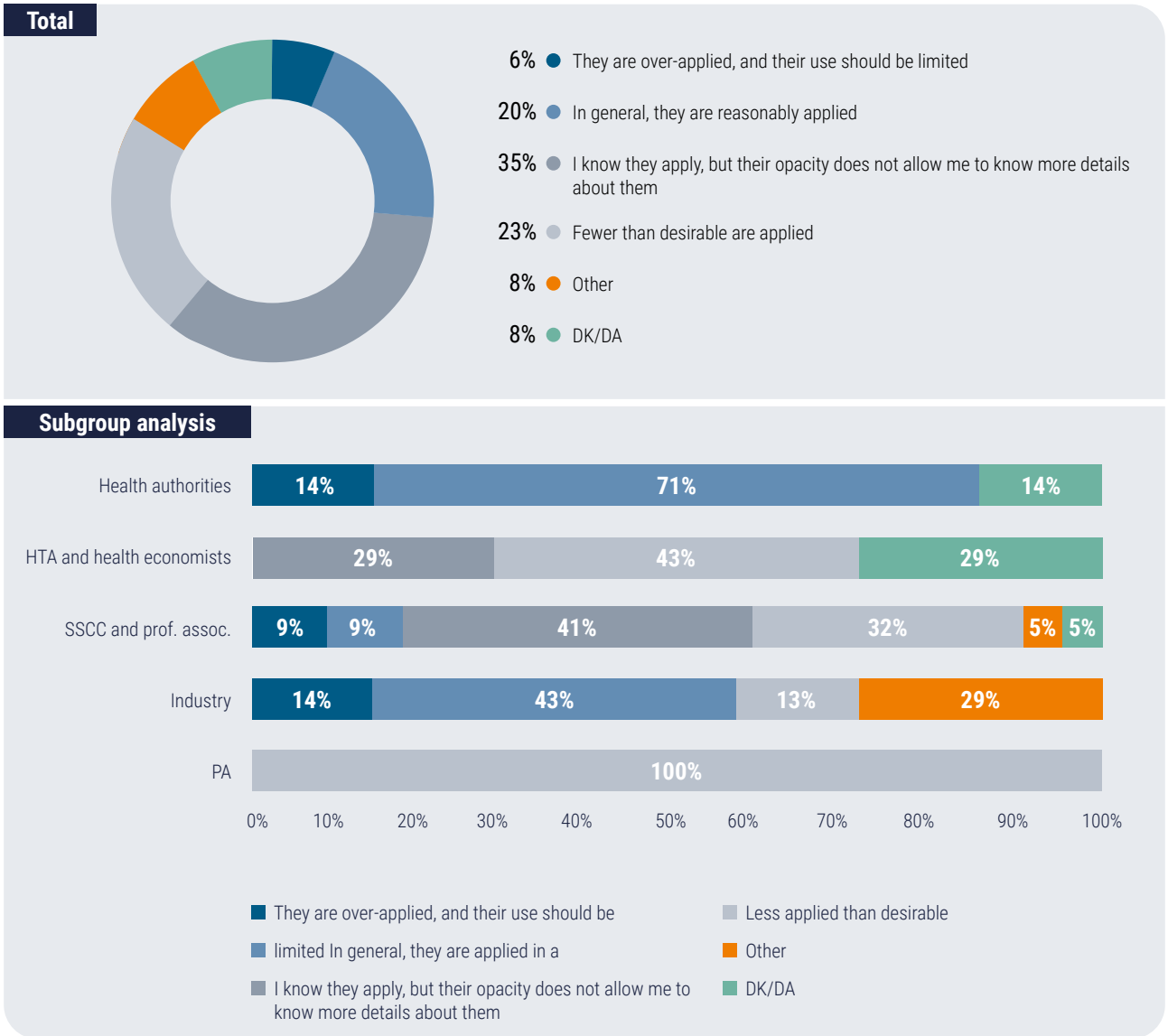




Regarding the financial agreements for medicines in Spain, there is no general consensus. Almost a quarter of respondents think that in general, they are reasonably applied. On the other hand, **6%** believe that they are applied excessively and that their use should be limited, while **23%** believe that they are applied less than desirable. In turn, one third highlighted that the biggest problem is the opacity of these agreements, which does not allow them to have an informed opinion on their use.

Health authorities and industry agree that such agreements are generally reasonably enforced, while most representatives of scientific societies believe that they are less enforced than desirable. Health economists and patient associations highlight the opacity of these agreements (Figure 93).

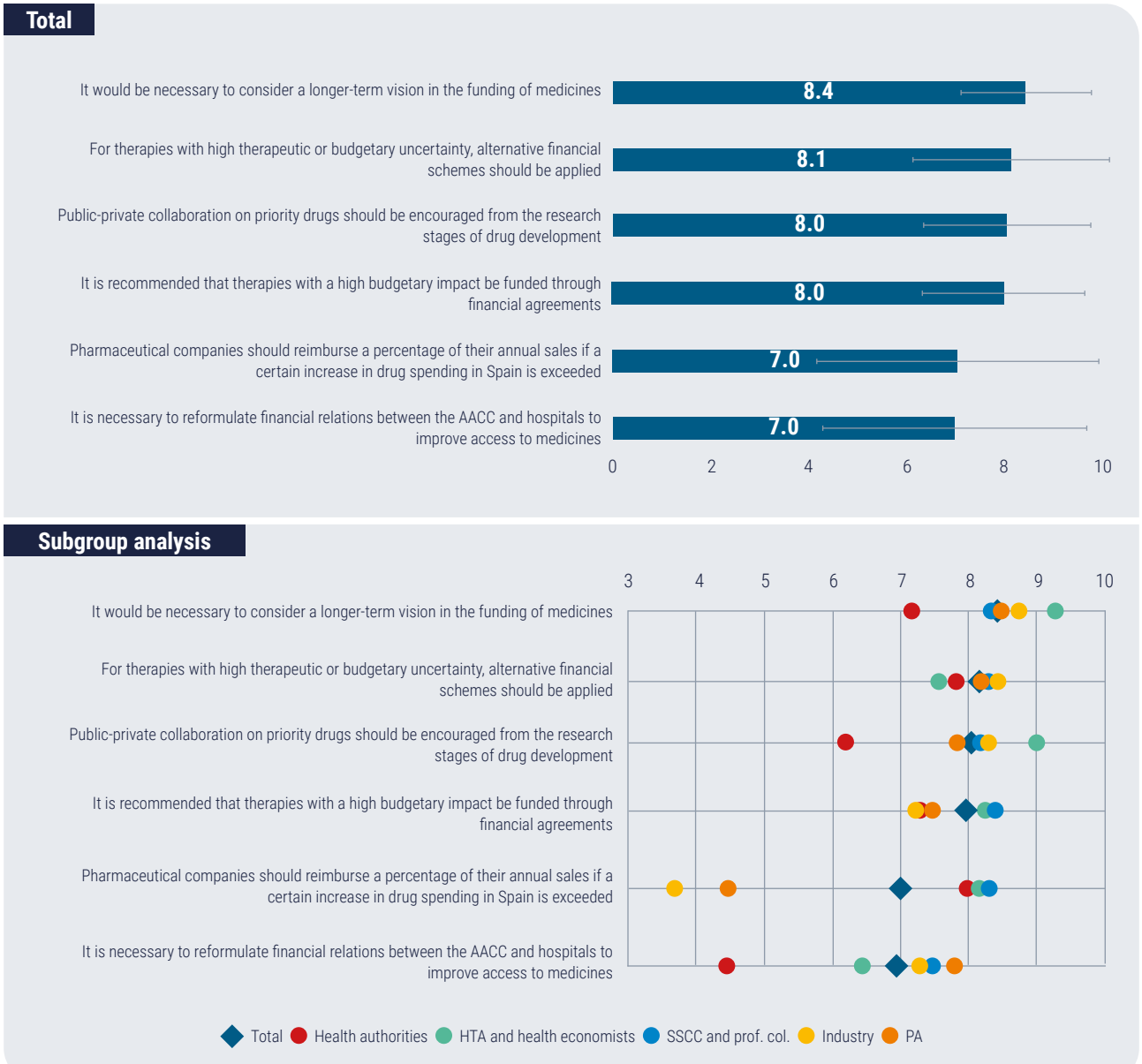
Figure 93. What is your opinion on the current financial agreements for medicines in Spain?



With regard to pricing and financial agreements for innovative medicines, stakeholders particularly agree that a longer-term view on funding should be considered, and that financial schemes should be implemented for therapies with high therapeutic or budgetary uncertainty.

All subgroups agree that a longer-term view on funding should be considered, with health economists being the strongest advocates. They also agree to apply alternative financial schemes for therapies with high uncertainty and for those with high budgetary impact. In contrast, opinions diverge as to whether pharmaceutical companies should reimburse a percentage of their annual sales if they exceed a certain increase in expenditure (industry and patients disagree), or whether the financial relations between AACC and hospitals should be reformulated to improve access (**Figure 94**).

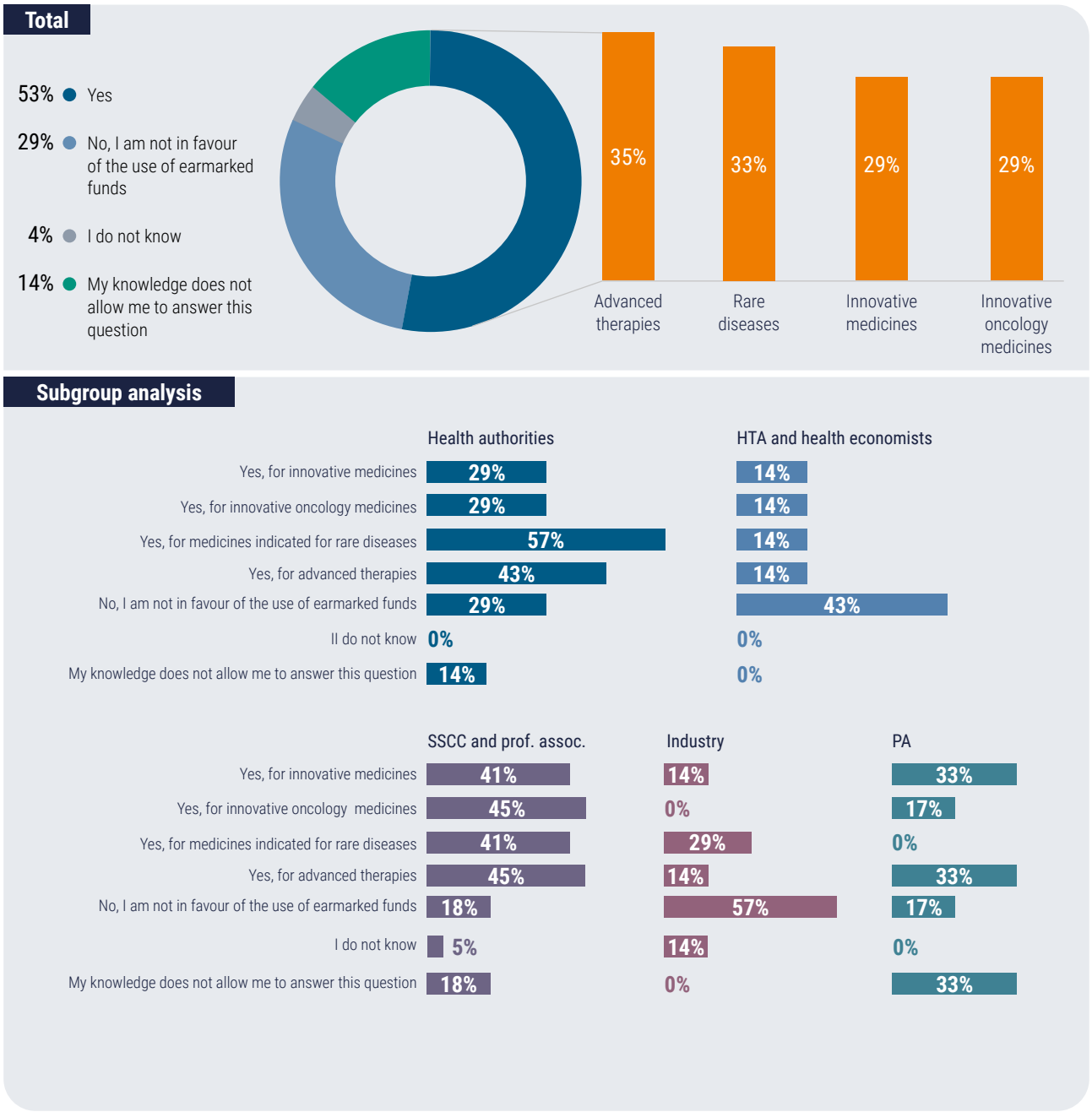
Figure 94. Opinion on price and financial agreements for innovative medicines in Spain (0 being the lowest possible level of agreement and 10 being the highest) (average score)



Slightly more than half of the stakeholders are in favour of creating some kind of earmarked budget fund to finance certain innovative therapies. Thirty-five percent would see this as appropriate for funding advanced therapies, **33%** for rare diseases and **29%** for innovative medicines or innovative oncology drugs. **29%** of respondents are not in favour of such earmarked funds.

By subgroups, between **50%** and **59%** of representatives of health authorities, health economists, scientific societies and patients' associations are in favour of creating earmarked budget funds to finance certain innovative therapies. In contrast, the majority of industry is of the opinion that such funds should not be created (**Figure 95**).

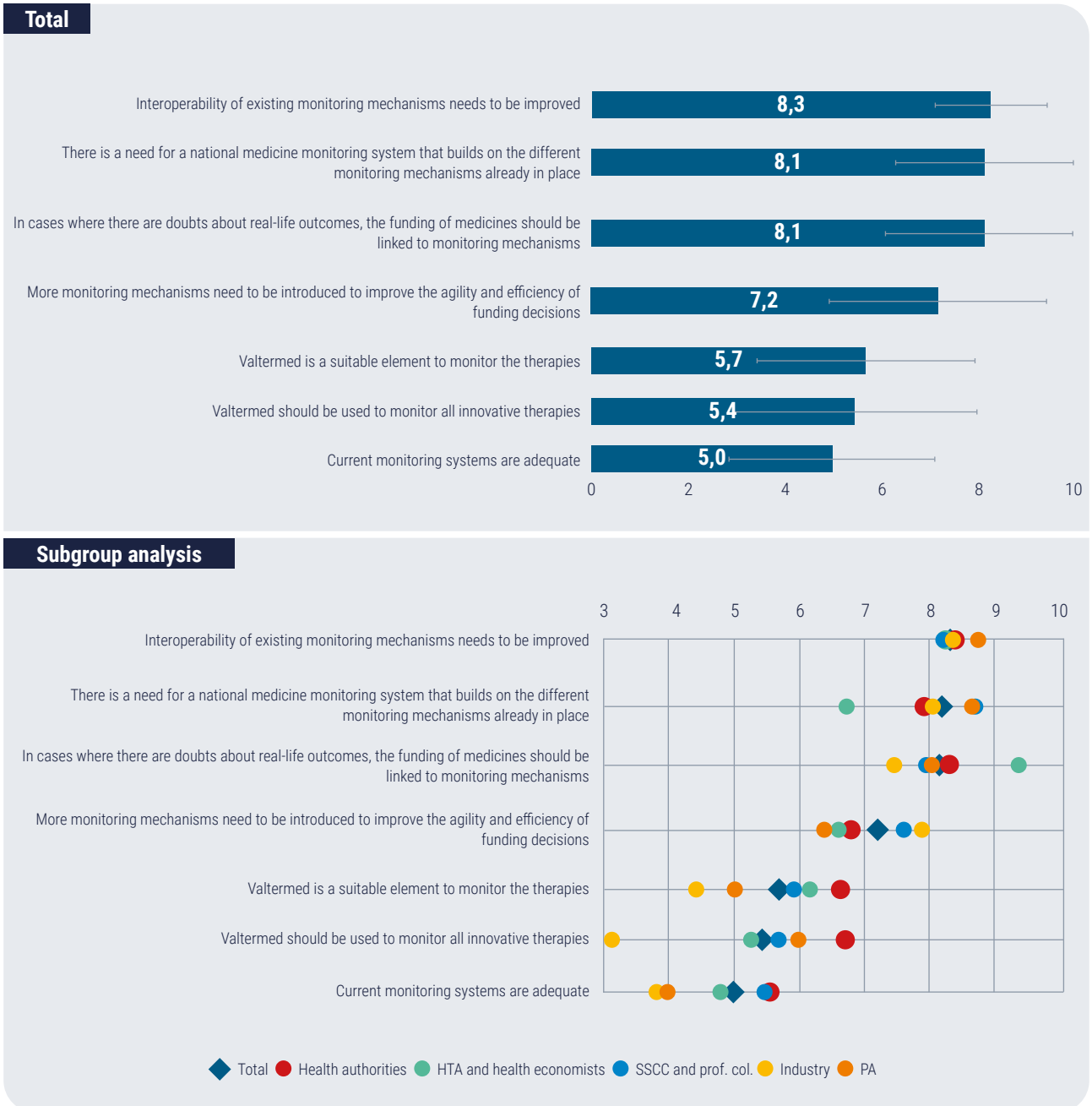
Figure 95. Do you consider that earmarked budget funds should be created for the funding of certain therapies? (Multiple options available)



Regarding monitoring mechanisms for medicines in Spain, respondents agree that there is a need to improve the interoperability of existing mechanisms, that there is a need for a system at national level that builds on the different monitoring mechanisms already in place, and that in cases where there are doubts about real-life outcomes, funding should be linked to monitoring mechanisms. Stakeholders only partially agree that the current monitoring systems are adequate.

The biggest differences between health authorities and industry relate to the adequacy of Valtermed for monitoring therapies, and whether Valtermed should be used for all innovative therapies. Notably, economists, industry and patients are least in agreement on the statement "current monitoring systems are adequate" (Figure 96).

Figure 96. Degree of agreement with the following points regarding the monitoring of medicines in Spain (0 being the lowest and 10 the highest) (average score)

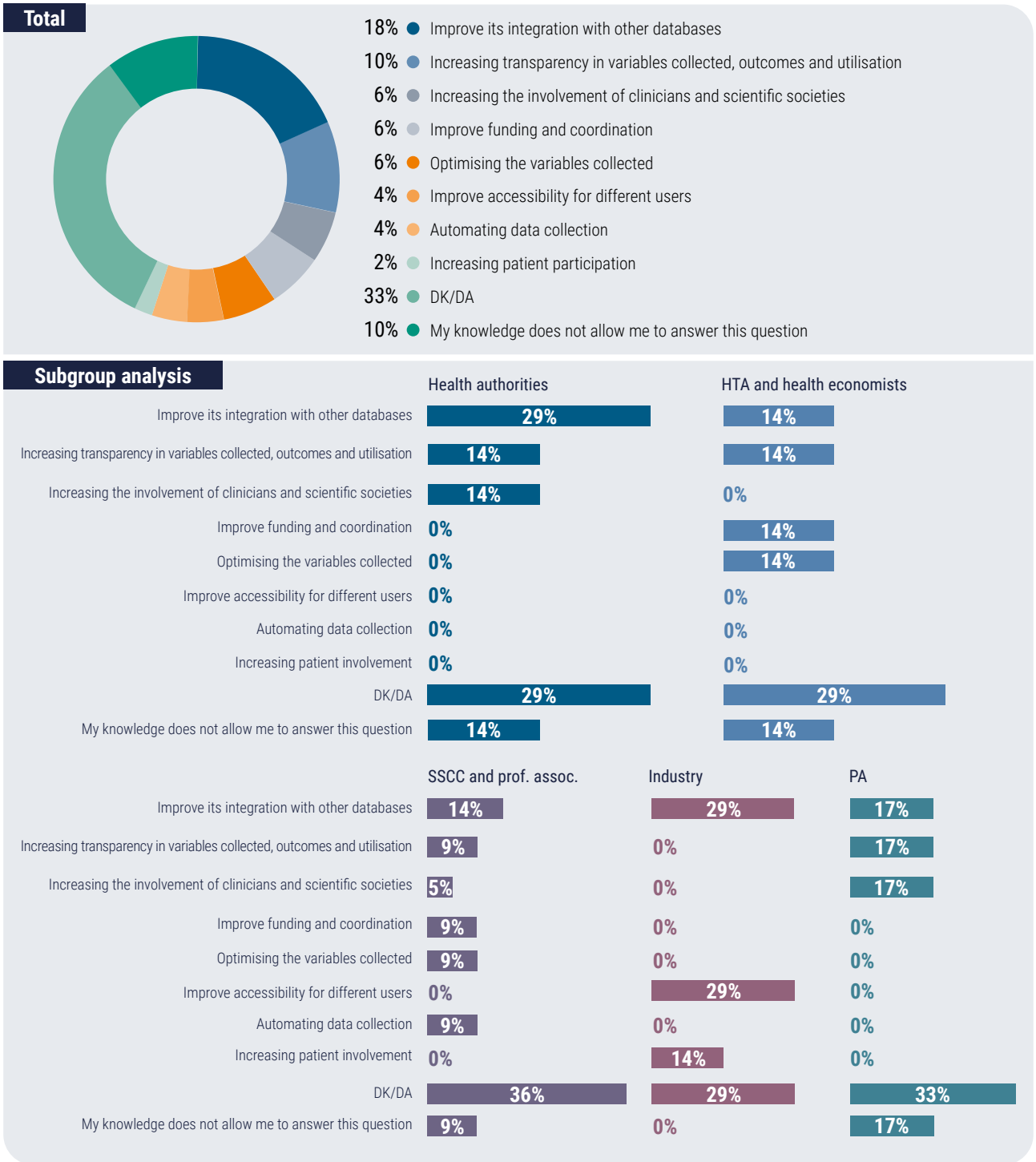


INDEX

According to those consulted, Valtermed could be optimised by improving its integration with other databases; increasing transparency in the variables collected, their results and their use; increasing the participation of clinicians and scientific societies; improving funding and coordination; optimising the variables collected; and improving user accessibility.

All subgroups agree on the desirability of improving their integration with other databases. Authorities emphasise transparency and participation, while economists emphasise collected variables, and industry emphasises accessibility (**Figure 97**).

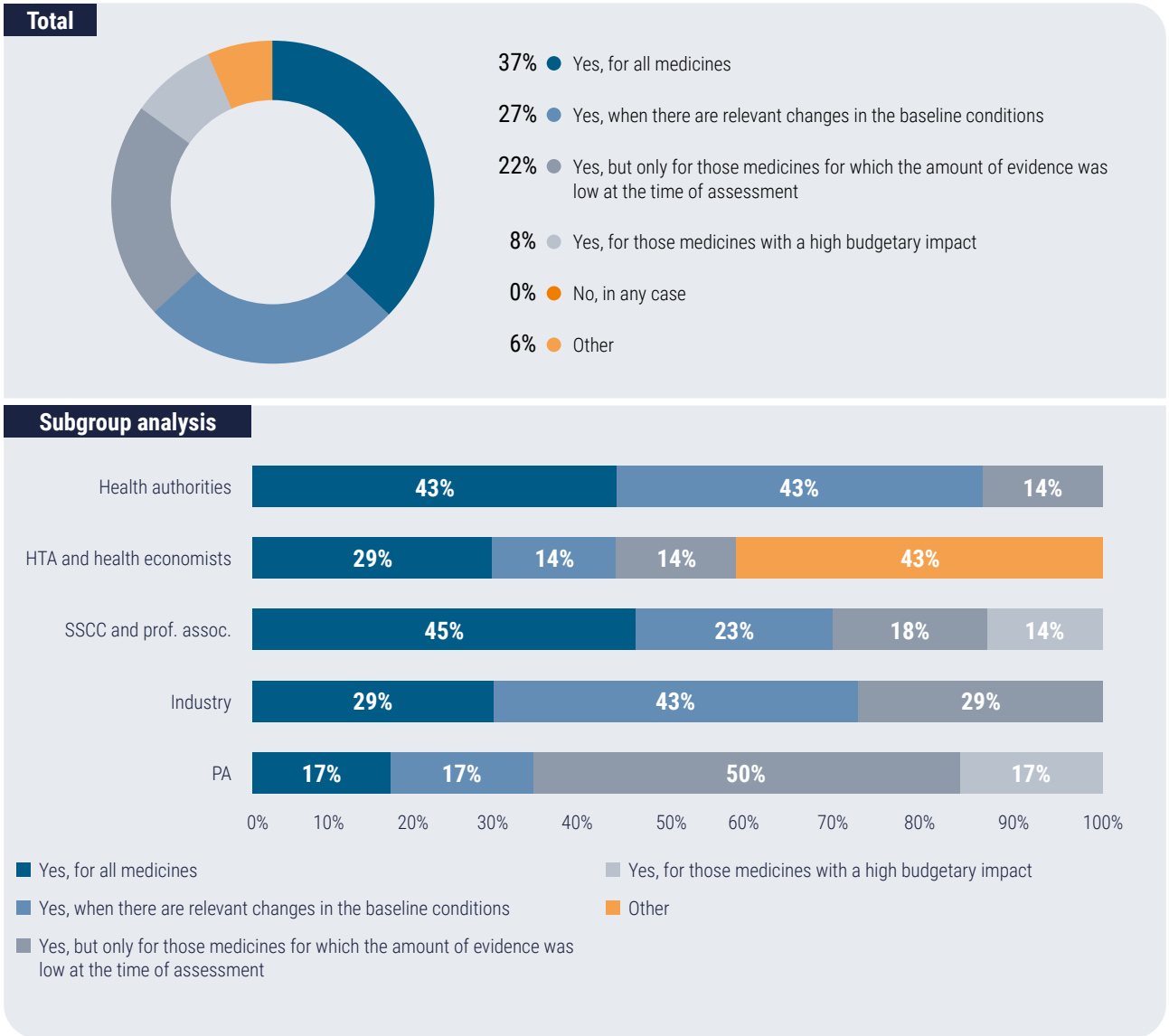
Figure 97. In what ways do you consider that the use of Valtermed could be optimised? (% of responses)



Regarding the need to re-evaluate funding or positioning decisions based on real-life data, **37%** believe that this should be done for all medicines, **27%** when there are relevant changes in baseline conditions, **22%** only for medicines for which the quality of evidence was low at the time of the assessment and **8%** for medicines with high budgetary impact. None believe that funding or positioning decisions should not be reassessed based on real-life data.

By subgroups, the majority of representatives of scientific societies (**45%**) believe that reassessment should be done for all medicines. Among industry members, reassessment should be done when there are relevant changes in the baseline conditions. Health authorities are ambivalent between the two options. On the other hand, for most patient representatives, reassessment would make more sense only for those medicines for which the quality of evidence was low at the time of assessment. Economists highlight reassessment for managed entry arrangements and a mix of several of the options put forward (Figure 98).

Figure 98. Do you consider that funding or positioning decisions should be reassessed on the basis of real-life data?

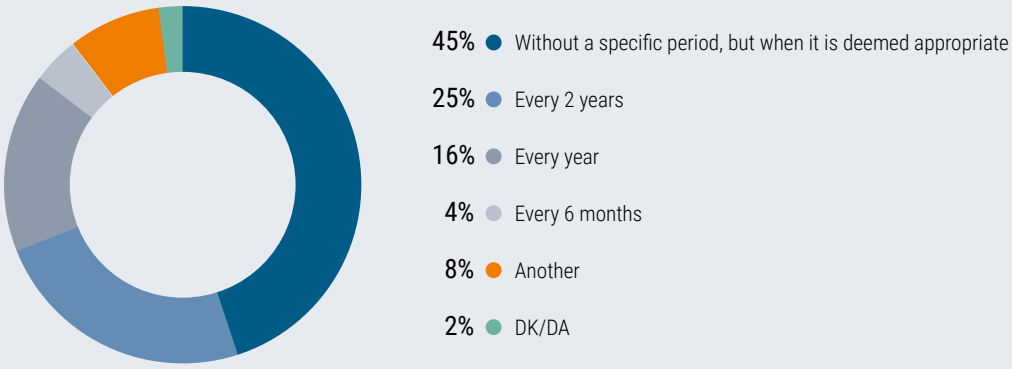


Agents were asked how often they think drug reassessment should be carried out. A total of **45%** specified that a specific period should not be established, but that reassessment should be carried out when it is considered appropriate. Another **45%** opted for a specific period, either every **6** months (**4%**), 1 year (**16%**) or 2 years (**25%**). Four respondents (**8%** of the total) specify other options for reassessment.

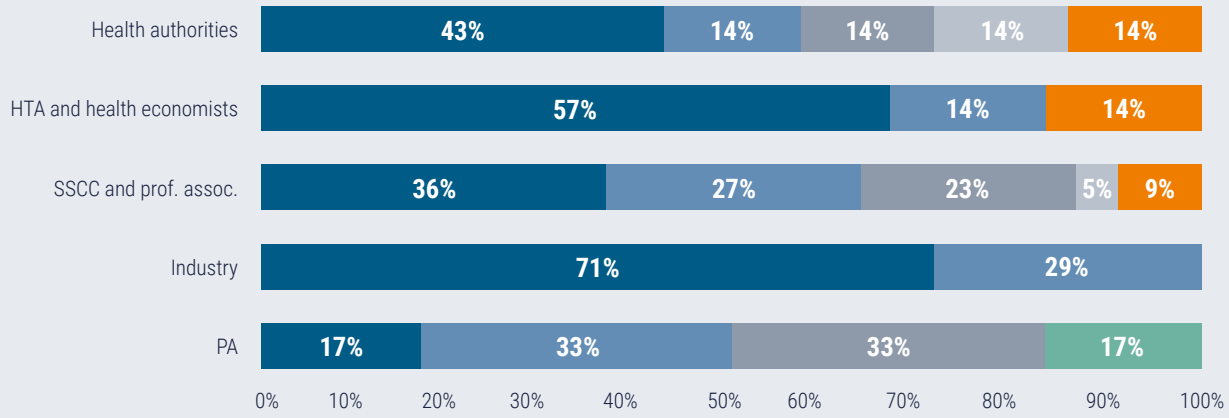
By subgroups, most health economists and industry representatives prefer not to specify a specific period for reassessment, but to decide on a case-by-case basis. Among scientific societies and patient associations, most prefer to reassess every year or every 2 years. Among health authorities, opinions are very divided (Figure 99).

Figure 99. How often do you consider that such a reassessment should be carried out?

Total



Subgroup analysis



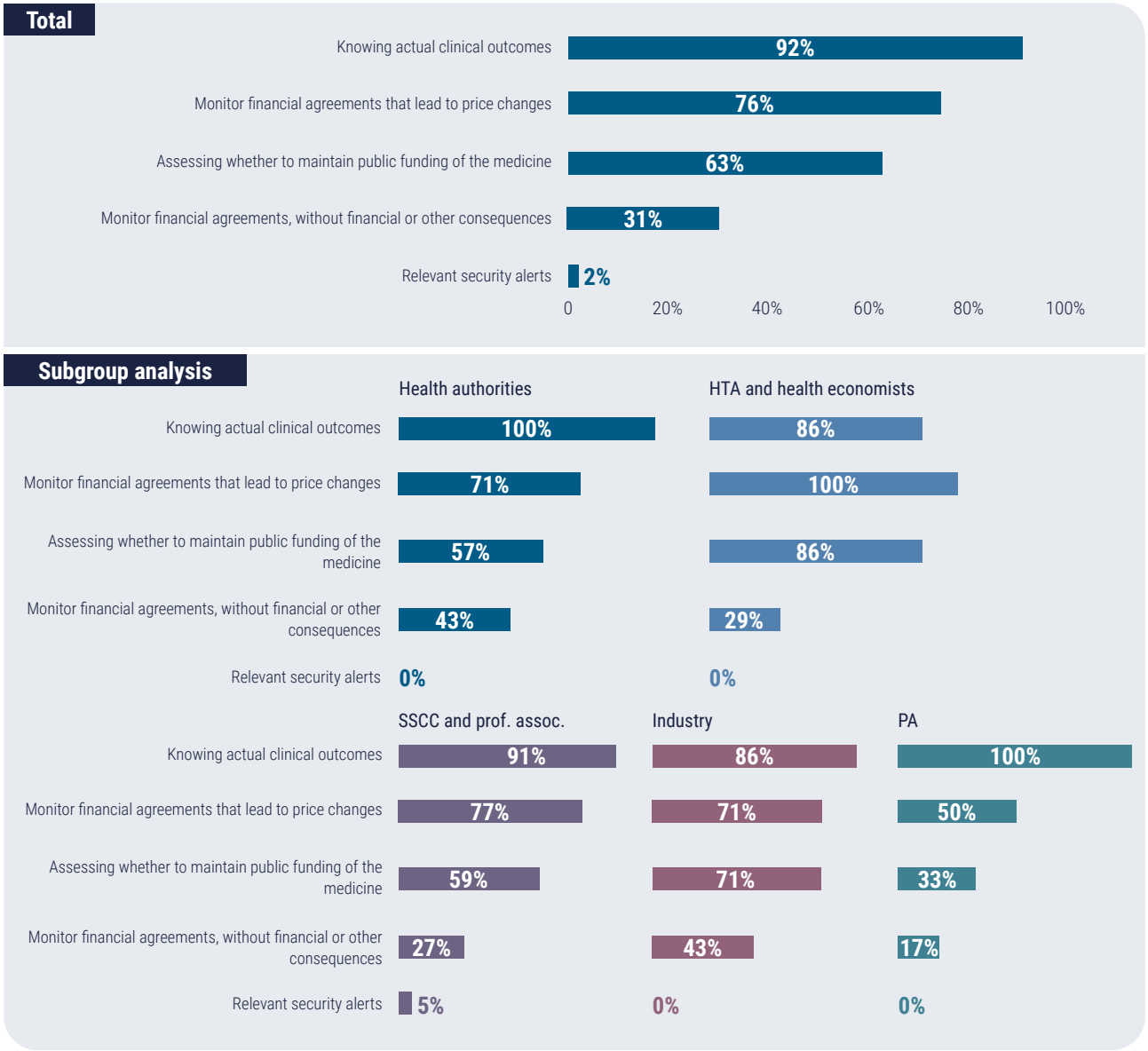
Note: the category "other" includes options not covered in the other categories, such as: it depends on the drug and the disease; in the specific period for data collection, not longer than 3 or 5 years; annual at the beginning, then when deemed appropriate for each particular drug; the period should be decided one by one, not when deemed appropriate but according to pre-specified criteria depending on the drug/disease.

- Without a specific period, but when it is deemed appropriate
- Every 2 years
- Every year
- Every 6 months
- Another
- DK/DA

The vast majority of respondents are of the opinion that the aim of drug reassessment should be to learn about the actual clinical outcomes of the drug. A large proportion also think that it should be used to monitor financial agreements: either with changes in price (**76%**) or without financial consequences (**31%**). Meanwhile, **63%** believe that reassessment should be used to assess whether to continue public funding of the medicine.

There is little variability between the different subgroups of respondents. All except health economists put the objective of knowing actual clinical outcomes first. For the economists, it is more important that the arrangements provide monitoring of the financial agreements, with consequences on price, which is supported by only **50%** of the patients. At the same time, the subgroup of economists is also the most supportive of assessment being used to decide whether to continue public funding of a medicine (Figure 100).

Figure 100. What do you consider should be the objective of the reassessment of a medicine? (Multiple options available)



CONCLUSIONS

4

Throughout this report, it has been shown how different developed countries, including Spain, approach the complex task of assessing the value of innovative medicines and subsequently deciding on their price and public funding. There are different trends and ways of doing things, and it is useful to understand them in detail in order to learn about possible good practices that can ultimately be applied in our country, even though the idiosyncrasies and organisation of each system are an important and differentiating starting point.

In Spain there have been notable recent changes in the process, with some clear examples. The planning of the TPRs aims for greater systematisation and agility of the evaluation, carried out in a network between different agents in the system. The systematic incorporation of economic evaluation in TPRs is a clear sign of the importance of this efficiency criterion in decision-making. The launch of Valtermed advocates unifying the determination of the real therapeutic value of high-impact medicines.

Despite the progress made, there are areas for improvement that it is desirable to explore. To this end, we have consulted around fifty agents from different areas of the healthcare system to find out their opinions on the current situation and possible options for improvement. The experts consulted are in agreement on some aspects, but have different opinions on others. More than **90%** believe that the evaluation processes for innovative medicines in Spain should be reformed, with more urgent changes in the evaluation part than in the pricing part. Two thirds believe that the current process times are too long, with major bottlenecks that need to be addressed. Health authorities tend to be the subgroup of respondents most satisfied with the current system, although they also suggest some lines of progress.

Among the challenges to be addressed are uncertainty in the measurement of clinical benefit and/or effectiveness, time agility and transparency of the process. The problem does not seem to be so much one of political leadership, but rather of a lack of resources (human and financial) available for the implementation of the process, as well as a lack of efficiency of the process, with excessive bureaucracy.

Based on the review of processes in other countries and the questionnaire to stakeholders on the situation in Spain, it is possible to identify the following trends and good practices to follow regarding the assessment and funding processes of medicines:

- **It must be rigorous and consistent.** For the sake of consistency of decisions, a procedure based on clear and homogeneous criteria on relevance and incremental clinical benefit should be agreed upon for the clinical assessment, with a consensus decision on which comparator to use. The economic evaluation should be carried out by professionals with proven experience and expertise in this field and should be based on clear and endorsed standards and methodologies, as is the case in Canada, England or Sweden. The evaluation should incorporate all cost variations beyond pharmacological variations and in health outcomes or QALYs, ideally using a dual perspective (health funder and societal). A binding nationwide assessment could avoid duplication and generate efficiencies. Finally, the funding decision should be based on relevant and explicit criteria (being the biggest challenge of the evaluation pointed out by respondents), probably more than those established in the law, where the specific weight of each of them in the final decision is also known in advance.

- **Capable of separating assessment and funding.** Ideally, the body in charge of leading the scientific-technical assessment of the medicine should have no responsibility regarding the allocated budget, in order to avoid conflict of interest in relation to the funding part of the decision-making process.

Thus, it would be desirable to separate the technical part of the funding decision (supported by **63%** of the actors interviewed), with different actors involved, as is the case in most of the countries analysed. Another option would be to follow the example of France, where, in addition to separate the evaluative part from the decision-making part, the clinical assessment is also separated from the economic evaluation.

- **Adjusted to the legally established timeframe.** Compared to countries such as Sweden, Austria, England or Italy, in Spain there seems to be scope for reducing the time between EMA authorisation of the medicine and its effective availability, a view supported by **90%** of the agents consulted.The streamlining of time planned in the new TPRs (**20** days for the clinical assessment + **10** days for the economic evaluation) is a step in the right direction, although it does not seem entirely feasible given the current TPR preparation times, especially if combined with the expected thoroughness of the evaluation. Thus, the objective to be pursued would be the effective fulfilment of the legally established deadlines (in RD 852/2021 and the European directive 89/105), of **180** days for the entire assessment and funding processes. Other lines of action to improve the agility of the process include prioritisation of the drugs to be assessed, with emphasis on serious diseases (largely supported by respondents), drugs with greater expected clinical benefit and health system needs; a fast-track process for certain diseases with significant unmet needs (as in Italy, England or France) with subsequent reassessment; or a binding national assessment at regional level (something that is particularly supported by industry representatives and the HTA agencies consulted, but not so much by the health authorities).

- **Adequately resourced.** Among the main challenges identified by the agents interviewed were the lack of human and economic resources for the execution of the process, and the lack of professionalisation of the evaluation processes. Thus, in order to ensure the rigour of evaluation, reduce voluntarism and minimise the excessive workload of professionals, the design of the current evaluation circuits and the training of evaluation staff must be optimised, with greater human, economic, technical and training resources. One possible course of action would be to overcome the lack of evaluators with health economists from other fields (such as academia or health technology assessment agencies). The training provided by health technology assessment agencies in countries such as England, Germany and Canada can serve as a reference, although it should be borne in mind that the size and functions of each agency are different.

- **Enhancing the involvement of other stakeholders.** Beyond health authorities and clinicians, consideration should be given about how to enhance the participation of patient representatives and scientific societies in the drug assessment process, not only by giving them the possibility to submit information, but also by including them in the meetings, as is the case in other countries such as France, Germany and England, among others. Ideally, patients would be represented by the patient association related to the pathology for which the drug under assessment is indicated, rather than by individual patients. For its part, the pharmaceutical industry should also play a more active role in the process, with the possibility of arranging an exploratory meeting with decision-makers to bring positions closer together before the assessment, something that is already happening in countries such as England and Canada, which is included in the new European HTA regulation[424] and which is also supported by the stakeholders consulted in this study.

- **With maximum transparency.** Information must be an elementary part of any evaluation and decision-making process. On the one hand, the standards and methodologies used in the clinical and, especially, economic evaluation process, as measured by the respondents' approval, should be clearly specified. On the other hand, the information taken into account during the evaluation process and the information

provided by the company should be published, as well as the clinical experts and patient groups consulted, the minutes of the meetings involving various stakeholders (scientific societies, patient associations, industry) and the final decision, as well as the criteria used and the arguments presented by the parties. In this respect, countries such as Australia, Canada or England can serve as a model, as they publish detailed reports on the decision taken, beyond the criteria used for the decision, and the information provided by the different stakeholders. It would also be interesting to increase transparency regarding the evaluation timetable and innovative financial agreements, while respecting the confidentiality of economic and commercial information where necessary.

- **Increasing the weight of efficiency in the funding decision.** Efficiency, beyond the cost of the pharmacological treatment, should be an important criterion on which to base the pricing and funding decision for a medicine, but it should not be the only one. Other issues should also be considered, such as the quality of the evidence, the health or social costs avoided, or ethical aspects. According to the agents surveyed, Spain should consider a cost-effectiveness threshold or thresholds, not necessarily explicit, with the possibility of being able to apply differential thresholds in certain cases or pathologies, such as rare diseases, gene therapies and/or end-of-life medicines, as is the case in other countries such as Canada, Scotland, France and England.

- **Promoting funding schemes that facilitate innovation and access for patients.** Seven out of ten stakeholders consulted are in favour of creating some kind of earmarked budget fund for specific treatments, whether they are innovative medicines in general, innovative cancer drugs, advanced therapies or drugs targeting rare diseases. The specific funds available in countries such as Scotland, England or Italy can serve as an example, and be used in part to generate evidence. In addition to such instruments, alternative funding schemes, such as payment by results agreements, should be applied for therapies with high therapeutic or budgetary uncertainty. Also, conditional funding schemes, such as those implemented in Scotland, Italy or the Netherlands, may be an avenue to explore. It would also be interesting to encourage public-private collaboration for priority drugs from the research stages of drug development.

- **Promoting continuous assessment of interventions and decisions.** Given the frequent uncertainty associated with real-life outcomes, dynamic assessment over time is essential to be able to measure outcomes in clinical practice, update the evaluation in the face of new evidence, and to monitor agreed financial agreements, information that can then be used to enable binding reassessment of funding or positioning decisions. This reassessment could take place after a certain period of time, as is the case in the Netherlands, or when new evidence is generated that influences the assessment, as is the case in France or Italy. In any case, it is important that the criteria for initiating a reassessment are fixed from the beginning of the process, with the possibility for any of the parties involved to request the reassessment. To this end, in addition to the need for adequate information systems, TPRs should be updated over time.

- **Promoting more integrated and interoperable monitoring mechanisms.** It is necessary to further improve the interoperability of monitoring mechanisms, to move towards a nationwide system that draws on the different mechanisms already in place, as pointed out by most of the actors consulted, in order to improve the information available in real life without duplicating efforts. It would be interesting if this new system refocused its objective from measuring processes (which will continueto be necessary) towards measuring health outcomes. In this sense, Valtermed could be optimised by improving its integration with other databases; increasing transparency in the variables collected, their results and their use; increasing

the participation of clinicians and scientific societies; improving funding and coordination; optimising the variables collected; and improving user accessibility. There are some international examples of this, such as the Italian national registry platform, supported by the regions, for monitoring medicines.

Decalogue of recommendations on the assessment and funding processes of medicines in Spain:

1. It must be rigorous and consistent
2. Capable of separating assessment and funding
3. Adjusted to the established times
4. Adequately resourced
5. Enhancing the involvement of other actors
6. With maximum transparency
7. Increasing the weight of efficiency in the funding decision
8. Promoting funding schemes that facilitate innovation and access for patients
9. Promoting continuous assessment of interventions and decisions
10. Promoting more integrated and interoperable monitoring mechanisms

REFERENCES

1. OECD. Health at a Glance 2021: OECD Indicators. 2021.
2. OECD, Pharmaceutical spending (indicator). doi: 10.1787/998febf6-en. [accessed 30 November 2021]. Available from: http://data.oecd.org/healthres/pharmaceutical-spending.htm.
3. Newton M, Scott K, Troein P. EFPIA Patients W.A.I.T. Indicator 2020 Survey. IQVIA. Available from: https://www.efpia.eu/media/602652/efpia-patient-wait-indicator-final-250521.pdf.
4. BOE. Instrucción de 13 de diciembre de 2002, de la Subsecretaría, por la que se coordinan los procedimientos administrativos relativos a autorización de comercialización y a financiación con fondos públicos de las especialidades farmacéuticas de uso humano. Ministerio de Sanidad y Consumo. 2002.
5. AIReF. Gasto hospitalario del sistema nacional de salud: farmacia e inversión en bienes de equipo. 2020.
6. BOE. Real Decreto 271/1990, de 23 de febrero, sobre la reorganización de la intervención de precios de las especialidades farmacéuticas de uso humano.1990
7. Ministerio de Sanidad. Circular Informativa No 4/91. [accessed 11 October 2021]. Available from: https://www.mscbs.gob.es/profesionales/farmacia/legislacion/economia/cir4_91.htm.
8. BOE. Real Decreto 735/2020, de 4 de agosto, por el que se desarrolla la estructura orgánica básica del Ministerio de Sanidad, y se modifica el Real Decreto 139/2020, de 28 de enero, por el que se establece la estructura orgánica básica de los departamentos ministeriales. [accessed 11 October 2021]. Available from: https://www.boe.es/buscar/act.php?id=BOE-A-2020-9139.
9. BOE. Real Decreto 852/2021, de 5 de octubre, por el que se modifican el Real Decreto 139/2020, de 28 de enero, por el que se establece la estructura orgánica básica de los departamentos ministeriales y el Real Decreto 735/2020, de 4 de agosto, por el que se desarrolla la estructura orgánica básica del Ministerio de Sanidad, y se modifica el Real Decreto 139/2020, de 28 de enero, por el que se establece la estructura orgánica básica de los departamentos ministeriales. 2021.
10. Ministerio de Sanidad. Plan para la consolidación de los Informes de Posicionamiento Terapéutico de los medicamentos en el Sistema Nacional de Salud. 2020.
11. Ministerio de Sanidad, Consumo y Bienestar. Preguntas y respuestas sobre el Plan para la consolidación de los Informes de Posicionamiento Terapéutico (IPT) de los medicamentos en el Sistema Nacional de Salud (SNS). 2020.
12. Ministerio de Sanidad. Documento informativo sobre la financiación y fijación de precio de los medicamentos en España. 2022.
13. AIReF. Anexo 7. Farmacia Hospitalaria. Estudio gasto hospitalario del sistema nacional de salud: farmacia e inversión en bienes de equipo. 2020. Available from: https://www.airef.es/wp-content/uploads/2020/10/SANIDAD/ANEXOS/Documento-Anexo-7.-Farmacia-Hospitalaria.pdf.
14. Ministerio de Sanidad, Consumo y Bienestar. Reglamento interno de la Comisión Interministerial de Precios de Medicamentos y Productos sanitarios (CIMP). 2019.
15. Ministerio de Sanidad, Consumo y Bienestar Social. Comisión Interministerial de Precios de Medicamentos y productos sanitarios. [accessed 1 July 2021]. Available from: https://www.mscbs.gob.es/profesionales/farmacia/CIPMyPS.htm.
16. Paz-Ares T, Cocina B. ¿Qué queda del artículo 100 de la ley del medicamento veinte años después? La libertad de precios, que no es poco. Cuadernos de Derecho Farmacéutico. 2020.
17. BOE. Real Decreto-ley 16/2012, de 20 de abril, de medidas urgentes para garantizar la sostenibilidad del Sistema Nacional de Salud y mejorar la calidad y seguridad de sus prestaciones. Ministerio de Sanidad, Servicios Sociales e Igualdad; 2012.
18. Ministerio de Sanidad, Consumo y Bienestar Social. Creación del Comité Asesor para la financiación de la prestación farmacéutica del SNS. Gabinete de Prensa. Notas de Prensa. [accessed 1 July 2021]. Available from: https://www.mscbs.gob.es/gabinete/notasPrensa.do?id=4545.
19. Consejo de Ministros de España. Acuerdo del Consejo de Ministros por el que se crea el Comité Asesor para la financiación de la prestación farmacéutica del SNS. 2019. https://www.sanidad.gob.es/profesionales/farmacia/pdf/20190322_Dilig_ACM_Com_Ases_PF_SNS.pdf

20. Ministerio de Sanidad, Consumo y Bienestar Social. Financiación y fijación de precios de medicamentos por el Sistema Nacional de Salud. @GESFARMA. [accessed 8 October 2021]. Available from: https://www.mscbs.gob.es/profesionales/farmacia/gesfarma/homegesfarma.htm.

21. Ministerio de Sanidad. Procedimiento normalizado de trabajo de evaluación clínica, evaluación económica y posicionamiento terapéutico para la redacción de Informes de Posicionamiento Terapéutico de medicamentos en el Sistema Nacional de Salud. 2020.

22. Ortega Eslava A, Marín Gil R, Fraga Fuentes MD, López-Briz E, Puigventós Latorre F. Guía de evaluación económica e impacto presupuestario en los informes de evaluación de medicamentos. SEFH. Sociedad Española de Farmacia Hospitalaria; 2016. Available from: https://gruposdetrabajo.sefh.es/genesis/genesis/Documents/GUIA_EE_IP_GENESIS-SEFH_19_01_2017.pdf

23. Sacristán JA, Oliva J, Campillo-Artero C, Puig-Junoy J, Pinto-Prades JL, Dilla T, et al. ¿Qué es una intervención sanitaria eficiente en España en 2020? Gaceta Sanitaria. 2020;34(2):189-93, doi: 10.1016/j.gaceta.2019.06.007.

24. Vallejo-Torres L, García-Lorenzo B, Serrano-Aguilar P. Estimating a cost-effectiveness threshold for the Spanish NHS. Health Econ. 2018;27(4):746-61, doi: 10.1002/hec.3633.

25. BOE. Real Decreto Legislativo 1/2015, de 24 de julio, por el que se aprueba el texto refundido de la Ley de garantías y uso racional de los medicamentos y productos sanitarios. 2015.

26. BOE. Ley 11/2020, de 30 de diciembre, de Presupuestos Generales del Estado para el año 2021. 2020.

27. Carlos Arganda. Precios notificados: cada año hay más y con mayor diferencia sobre el real. DiarioFarma. 2019. Available from: https://www.diariofarma.com/2019/02/12/precios-notificados-cada-ano-hay-mas-y-con-mayor-diferencia-sobre-el-real.

28. Jørgensen J, Hanna E, Kefalas P. Outcomes-based reimbursement for gene therapies in practice: the experience of recently launched CAR-T cell therapies in major European countries. Journal of Market Access & Health Policy. 2020;8(1):1715536, doi: 10.1080/20016689.2020.1715536.

29. Redacción Médica. El Ministerio anuncia que Valtermed «puede abrirse a fármacos de uso común». Redacción Médica. [accessed 9 July 2021]. Available from: https://www.redaccionmedica.com/secciones/ministerio-sanidad/valtermed-un-sistema-dinamico-que-puede-abrirse-a-farmacos-de-uso-comun--5725.

30. Ministerio de Sanidad, Consumo y Bienestar Social. Preguntas y respuestas frecuentes sobre el sistema de información para determinar el valor terapéutico en la práctica clínica real de los medicamentos de alto impacto sanitario y económico en el sistema nacional de salud (Valtermed). 2019.

31. Ministerio de Sanidad, Consumo y Bienestar Social. Sistema de Información para determinar el Valor Terapéutico en la Práctica Clínica Real de los Medicamentos de Alto Impacto Sanitario y Económico en el SNS (VALTERMED). Available from: https://www.mscbs.gob.es/profesionales/farmacia/valtermed/home.htm.

32. DiarioFarma. Publicados los primeros protocolos farmacoclínicos de evaluación y seguimiento en tumores sólidos. [accessed 13 September 2021]. Available from: https://www.diariofarma.com/2021/08/31/publicados-los-primeros-protocolos-farmacoclinicos-de-evaluacion-y-seguimiento-en-tumores-solidos.

33. Ministerio de Sanidad, Consumo y Bienestar Social. Seguimiento para el abastecimiento de medicamentos en el mercado nacional. (SEGUIMED). [accessed 9 July 2021]. Available from: https://sede.mscbs.gob.es/ciudadanos/procAdministrativos.do?tipo=detallar&cod=993591.

34. BOE. Real Decreto-ley 9/2011, de 19 de agosto, de medidas para la mejora de la calidad y cohesión del sistema nacional de salud, de contribución a la consolidación fiscal, y de elevación del importe máximo de los avales del Estado para 2011. 2011.

35. Secretaría de Estado de Sanidad. Acuerdos de la reunión de la comisión interministerial de precios de los medicamentos. Sesión 213. Available from: https://www.mscbs.gob.es/profesionales/farmacia/pdf/ACUERDOS_DE_LA_CIPM_2132_web.pdf.

36. Ministerio de Sanidad, Servicios Sociales e Igualdad. Informe de situación del plan estratégico para el abordaje de la hepatitis C crónica presentado al Consejo Interterritorial del SNS. 2017.

37. EMA. El sistema europeo de regulación de medicamentos. 2016.

38. AEMPS. Cómo se regulan los Medicamentos y Productos Sanitarios en España. 2014.

39. CEE. Directiva del consejo 89/105 relativa a la transparencia de las medidas que regulan la fijación de precios de los medicamentos para uso humano y su inclusión en el ámbito de los sistemas nacionales del seguro de enfermedad. 1988.

40. Reglamento (CE) No 726/2004 del Parlamento Europeo y del Consejo de 31 de marzo de 2004 por el que se establecen los procedimientos comunitarios para la autorización y el control de los medicamentos de uso humano.

41. BOE. Real Decreto 1015/2009, de 19 de junio, por el que se regula la disponibilidad de medicamentos en situaciones especiales. Ministerio de Sanidad y Política Social.

42. VFA. Tratamiento con medicamentos que aún no han sido aprobados. [accessed 18 October 2021]. Available from: https://www.vfa.de/de/patienten/artikel-patienten/behandlung-mit-medikamenten-die-noch-nicht-zugelassen-sind.html.

43. BASG. Compassionate Use Programme in Österreich. Available from: https://www.basg.gv.at/fileadmin/redakteure/01_Formulare_Listen/I/L_I216_Compassionate_use_AT__de.pdf.

44. BASG. Compassionate Use und Heilversuch/Named Patient Use. [accessed 26 October 2021]. Available from: https://www.basg.gv.at/fuer-unternehmen/arzneimittel-informationen/compassionate-use-1.

45. Gov.UK. Off-label or unlicensed use of medicines: prescribers' responsibilities. [accessed 18 October 2021]. Available from: https://www.gov.uk/drug-safety-update/off-label-or-unlicensed-use-of-medicines-prescribers-responsibilities.

46. MHRA. The supply of unlicensed medicinal products ("specials"). Available from: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/373505/The_supply_of_unlicensed_medicinal_products__specials_.pdf.

47. PSNC. Unlicensed specials and imports. PSNC Main Site. [accessed 18 October 2021]. Available from: https://psnc.org.uk/dispensing-supply/dispensing-a-prescription/unlicensed-specials-and-imports/.

48. HAS. Autorisations temporaires d'utilisation (ATU). Ministère des Solidarités et de la Santé. [accessed 23 June 2021]. Available from: https://solidarites-sante.gouv.fr/soins-et-maladies/medicaments/professionnels-de-sante/autorisation-de-mise-sur-le-marche/article/autorisations-temporaires-d-utilisation-atu.

49. AIFA. Accesso precoce e uso off-label. [accessed 15 June 2021]. Available from: https://aifa.gov.it/accesso-precoce-uso-off-label.

50. Parlamento italiano. Conversión en ley del decreto-ley de 21 de octubre de 1996, no 536, que contiene medidas para la contención del gasto farmacéutico y la redeterminación del tope de gasto para el año 1996. 1996.

51. KNMG. Off-label voorschrijven. [accessed 3 November 2021]. Available from: https://www.knmg.nl/advies-richtlijnen/dossiers/off-label-voorschrijven.htm.

52. INFARMED. Autorização de Utilização Excecional (AUE). 2021, Available from: https://www.infarmed.pt/web/infarmed/entidades/medicamentos-uso-humano/avaliacao-tecnologias-saude/avaliacao-terapeutica-e-economica/autorizacao-de-utilizacao-excecional.

53. Ministério da Saúde de Portugal. Decreto-Lei n.o 115/2017. Diário da República, 1.a série — N.o 173. 2017.

54. INFARMED. Programa de Acesso Precoce a Medicamentos (PAP). 2021, Available from: https://www.infarmed.pt/web/infarmed/avaliacao-terapeutica-e-economica/programa-de-acesso-precoce-a-medicamentos.

55. Swedish Medical Products Agency. Licens för läkemedel. [accessed 3 November 2021]. Available from: https://www.lakemedelsverket.se/sv/behandling-och-forskrivning/forskrivning/licenser.

56. IQWiG. Aprobación de medicamentos y evaluación temprana de beneficios en Alemania. [accessed 7 September 2021]. Available from: https://www.iqwig.de/presse/im-fokus/neue-arzneimittel-zulassung-nutzenbewertung-erstattung/1-arzneimittel-zulassung-und-fruehe-nutzenbewertung-in-deutschland/.

57. Global Legal Insights. Pricing & Reimbursement Laws and Regulations. Germany. [accessed 6 August 2021]. Available from: https://www.globallegalinsights.com/practice-areas/pricing-and-reimbursement-laws-and-regulations/germany.

58. OCDE. Pharmaceutical reimbursement and pricing in Germany. Available from: https://www.oecd.org/els/health-systems/Pharmaceutical-Reimbursement-and-Pricing-in-Germany.pdf.

59. Gaceta de Leyes Federales. Código Social. Libro Quinto (V). Seguro médico legal. 1988.

60. Institute for German and European Studies. Reimbursement of Pharmaceuticals in Germany. Available from: https://www.iges.com/e15094/e15095/e15096/e17469/IGES_Reimbursement_Pharmaceuticals_Germany_2020_2021_WEB_ger.pdf.

61. GKV-Spitzenverband. Wir über uns - GKV-Spitzenverband. [accessed 7 September 2021]. Available from: https://www.gkv-spitzenverband.de/gkv_spitzenverband/der_verband/wir_ueber_uns.jsp.

62. G-BA. AMNOG - Evaluación de beneficios de medicamentos de acuerdo con § 35a SGB V - Comité Conjunto Federal. [accessed 7 September 2021]. Available from: https://www.g-ba.de/themen/arzneimittel/arzneimittel-richtlinie-anlagen/nutzenbewertung-35a/.

63. Información para empresas farmacéuticas. Federal Joint Committee. [accessed 10 September 2021]. Available from: https://www.g-ba.de/themen/arzneimittel/arzneimittel-richtlinie-anlagen/nutzenbewertung-35a/informationen-fuer-unternehmen/.

64. G-BA. Directriz sobre la participación recíproca en reuniones de consulta en el Comité Federal Conjunto y en el Instituto Federal de Medicamentos y Productos Sanitarios o Instituto Paul Ehrlich. Available from: https://www.g-ba.de/downloads/17-98-4342/Leitfaden%20gem%20Beratung_BfArM_PEI_G-BA_final.pdf.

65. BfArM. Evaluación de tecnologías sanitarias (HTA). [accessed 9 September 2021]. Available from: https://www.bfarm.de/DE/Das-BfArM/Aufgaben/HTA/_node.html.

66. G-BA. Expediente de evaluación de beneficios. Available from: https://www.g-ba.de/downloads/17-98-4824/2018-03-16_2018-08-16_Anl2_5_Modul3.pdf.

67. HealthEcon. AMNOG procedure is the name of the German HTA procedure. [accessed 9 September 2021]. Available from: https://www.healthecon.com/amnog/index_eng.html.

68. IQWIG. General Methods. Version 6.0.

69. G-BA. Expediente de evaluación de beneficios para medicamentos que son farmacológica y terapéuticamente comparables con medicamentos de precio fijo.

70. EMA. Reflection paper on the regulatory guidance for the use of health-related quality of life (HRQL) measures in the evaluation of medicinal products. 2005.

71. Patientenvertretung. Cómo trabajamos. [accessed 10 September 2021]. Available from: https://patientenvertretung.g-ba.de/was-wir-tun/wie-wir-arbeiten/.

72. G-BA. Criterios de designación de las organizaciones relevantes para representantes de pacientes en el G-BA. Available from: https://patientenvertretung.g-ba.de/media/dokumente/benennungskriterien-fuer-patv.pdf.

73. GBA. Recopilación de datos relacionados con la aplicación de nuevos medicamentos. [accessed 8 September 2021]. Available from: https://www.g-ba.de/themen/arzneimittel/arzneimittel-richtlinie-anlagen/anwendungsbegleitende-datenerhebung/.

74. Robinson JC, Panteli D, Ex P. Reference Pricing in Germany: Implications for U.S. Pharmaceutical Purchasing. The Commonwealth Fund Issue Brief February 2019.

75. Precios de referencia. [accessed 13 October 2021]. Available from: https://www.dimdi.de/dynamic/en/drugs/reference-pricing/.

76. Schremser K, Butzke B, Wilman N, Brandes A, Rogowski W. Managed Entry Agreements in Deutschland: Konzepte, rechtliche Grundlagen und systematischer Review. Gesundheitsökonomie & Qualitätsmanagement. 2017;22(1):20-34, doi: 10.1055/s-0042-109798.

77. Federal Register of Legislation. Therapeutic Goods Act 1989. Attorney-General's Department; 1989.

78. Administration AGD of HTG. TGA basics. Therapeutic Goods Administration (TGA). [accessed 19 October 2021]. Available from: https://www.tga.gov.au/tga-basics.

79. Australian Government. Department of Health AGD of HTG. Prescription medicines: registration of new chemical entities in Australia. Therapeutic Goods Administration (TGA). [accessed 19 October 2021]. Available from: https://www.tga.gov.au/prescription-medicines-registration-new-chemical-entities-australia.

80. Australian Government. Department of Health. Medicines and TGA classifications. Therapeutic Goods Administration (TGA). [accessed 19 October 2021]. Available from: https://www.tga.gov.au/medicines-and-tga-classifications.

81. Kim H, Byrnes J, Goodall S. Health Technology Assessment in Australia: The Pharmaceutical Benefits Advisory Committee and Medical Services Advisory Committee. Value in Health Regional Issues. 2021;24:6-11, doi: 10.1016/j.vhri.2020.09.001.

82. NPW Medicine Wise. How medicines are approved for use in Australia. [accessed 19 October 2021]. Available from: https://www.nps.org.au/consumers/how-medicines-are-approved-for-use-in-australia.

83. Australian Government. Department of Health. Guidelines for preparing a submission to the Pharmaceutical Benefits Advisory Committee, Version 5.0. Available from: https://pbac.pbs.gov.au/content/information/files/pbac-guidelines-version-5.pdf.

84. Lopert R, Viney R. Revolution then evolution: The advance of health economic evaluation in Australia. ZEFQ. 2014;108(7):360-6, doi: 10.1016/j.zefq.2014.08.020.

85. Australian Government. Department of Health and Aged Care. Pharmaceutical Benefits Scheme (PBS). Finalisation of the budget. Available from: https://www.pbs.gov.au/info/industry/listing/procedure-guidance/8-procedures-positive-recommendation-list/8-5-finalisation-of-the-budget-impact

86. Australian Government Department of Health Therapeutic Goods. Australian prescription medicine decision summaries. Therapeutic Goods Administration (TGA). [accessed 25 October 2021]. Available from: https://www.tga.gov.au/australian-prescription-medicine-decision-summaries.

87. Australian Government. Department of Health. Pharmaceutical Benefits Scheme (PBS). Pharmaceutical Benefits Advisory Committee (PBAC) Membership. [accessed 19 October 2021]. Available from: https://www.pbs.gov.au/info/industry/listing/participants/pbac.

88. Federal Register of Legislation. National Health Act 1953. Attorney-General's Department; 1953.

89. Australian Government. Department of Health. Esquema de beneficios farmacéuticos (PBS). 6.1 Subcomités PBAC. [accessed 19 October 2021]. Available from: https://www.pbs.gov.au/pbs/industry/listing/procedure-guidance/6-consideration-submissions/6-1-pbac-subcommittees.

90. Pharmaceutical Benefits Scheme (PBS). Drug Utilisation Sub Committee (DUSC). [accessed 19 October 2021]. Available from: https://www.pbs.gov.au/info/industry/listing/participants/drug-utilisation-subcommittee.

91. Australian Government Department of Health. Procedure guidance for listing medicines on the Pharmaceutical Benefits Scheme. 2020.

92. Australian Government. Department of Health. Pharmaceutical Benefits Scheme (PBS) Economics Sub Committee (ESC). [accessed 20 October 2021]. Available from: https://www.pbs.gov.au/info/industry/listing/participants/economics-subcommittee-esc.

93. Australian Government. Department of Health. PBAC Guidelines. [accessed 20 October 2021]. Available from: https://pbac.pbs.gov.au/.

94. Australian Government Department of Health. About the Life Saving Drugs Program. [accessed 25 October 2021]. Available from: https://www.health.gov.au/initiatives-and-programs/life-saving-drugs-program/about-the-lsdp.

95. Australian Government. Department of Health. Life Saving Drugs Program Expert Panel. [accessed 15 November 2021]. Available from: https://www.health.gov.au/committees-and-groups/life-saving-drugs-program-expert-panel.

96. Pharmaceutical Benefits Scheme (PBS). 6.7 Consumer input. [accessed 20 October 2021]. Available from: https://www.pbs.gov.au/pbs/industry/listing/procedure-guidance/6-consideration-submissions/6-7-consumer-input.

97. Pricing & Reimbursement Laws and Regulations. Australia. GLI. Global Legal Insights International legal business solutions. [accessed 25 October 2021]. Available from: https://www.globallegalinsights.com/practice-areas/pricing-and-reimbursement-laws-and-regulations/australia.

98. Donovan P. Access to unregistered drugs in Australia. Aust Prescr. 2017;40(5):194-6, doi: 10.18773/austprescr.2017.062.

99. Lybrand S, Wonder M. Analysis of PBAC submissions and outcomes for medicines (2010–2018). International Journal of Technology Assessment in Health Care. 2020;36(3):224-31, doi: 10.1017/S026646232000029X.

100. Australian Government. Department of Health. Esquema de beneficios farmacéuticos (PBS). [accessed 19 October 2021]. Available from: https://www.pbs.gov.au/info/industry/listing/elements/deeds-agreement/b-background.

101. Australian Government. Application No. 1519. Tisagenlecleucel (CTL019) for treatment of refractory CD19-positive leukaemia and lymphoma. Available from: http://www.msac.gov.au/internet/msac/publishing.nsf/content/BE2E1EB50ED57442CA2581F4000C1723/$File/1519-Final%20PSD-April%202019_redacted.pdf.

102. Kim H, Comey S, Hausler K, Cook G. A real world example of coverage with evidence development in Australia. Ipilimumab for the treatment of metastatic melanoma. Journal of Pharmaceutical Policy and Practice. 2018;11(1):4, doi: 10.1186/s40545-018-0131-4.

103. Australian Government Department of. Pharmaceutical Benefits Scheme (PBS). PBS Statistics. [accessed 28 October 2021]. Available from: https://www.pbs.gov.au/info/browse/statistics.

104. Portal de salud pública de Austria. Sistema de salud. Asistencia sanitaria. Gesundheitsportal. [accessed 29 September 2021]. Available from: https://www.gesundheit.gv.at/gesundheitsleistungen/gesundheitswesen/gesundheitssystem.

105. System der Pflichtversicherung (ASVG, GSVG, FSVG, BSVG). oesterreich.gv.at. Österreichs digitales Amt. [accessed 29 September 2021]. Available from: https://www.oesterreich.gv.at/themen/arbeit_und_pension/pension/1/Seite.270110.html.

106. Pharmaceutical Pricing and Reimbursement Information. PPRI Pharma Brief: Austria. Available from: https://jasmin.goeg.at/1129/1/PPRI_Pharma_Brief_AT_2019_April2020.pdf.

107. Ley de Medicamentos. [accessed 28 September 2021]. Available from: https://www.ris.bka.gv.at/GeltendeFassung.wxe?Abfrage=Bundesnormen&Gesetzesnummer=10010441.

108. European Parliament. Towards a harmonized EU assessment of the added therapeutic value of medicines. Study for the ENVI Committee. 2015.

109. Wolf S, Zechmeister-Koss I, Grössmann N, Wild C. Evaluating options for decision making on costly hospital drugs in Austria. Int J Technol Assess Health Care. 2020;36(3):277-84, doi: 10.1017/S0266462320000276.

110. PHARMIG. Reembolso de medicamentos. [accessed 30 September 2021]. Available from: https://www.pharmig.at/arzneimittel/erstattung-von-arzneimitteln/.

111. Servicios e información para la Comisión de Evaluación de Productos Terapéuticos. [accessed 30 September 2021]. Available from: https://www.sozialversicherung.at/cdscontent/?contentid=10007.844491&portal=svportal.

112. Asociación Principal de Organismos de Seguridad Social de Austria. Documento de trabajo del Código de reembolso. Available from: https://www.sozialversicherung.at/cdscontent/load?contentid=10008.555012.

113. Asociación Principal de Instituciones de Seguridad Social de Austria. Procedimiento para emitir el código de reembolso. [accessed 23 September 2021]. Available from: https://www.ris.bka.gv.at/Dokumente/Avsv/AVSV_2004_0047/AVSV_2004_0047.pdfsig.

114. Nueva Seguridad social. [accessed 30 September 2021]. Available from: https://www.sozialversicherung.at/cdscontent/?contentid=10007.846560&portal=svportal.

115. Schlößl M. Reglamento interno de la Comisión de Precios del Ministerio Federal de Trabajo, Asuntos Sociales, Sanidad y Protección del Consumidor.

116. Bundesministerium für Soziales, Gesundheit, Pflege und Konsumentenschutz (BMSGPK). Descripción del sistema LKF. 2021.

117. Rawson NSB. Regulatory, Reimbursement and Pricing Barriers to Accessing Rare Disorder Drugs in Canada. 2018.

118. Canada H. Prescription drug insurance coverage. [accessed 4 October 2021]. Available from: https://www.canada.ca/en/health-canada/services/health-care-system/pharmaceuticals/access-insurance-coverage-prescription-medicines.html.

119. Canada H. How Drugs are Reviewed in Canada. [accessed 20 September 2021]. Available from: https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/fact-sheets/drugs-reviewed-canada.html.

120. Mittmann N, Evans WK, Rocchi A, Longo CJ, Au H-J, Husereau D, et al. Guidelines for Health Technologies: Specific Guidance for Oncology Products in Canada. Value in Health. 2012;15(3):580-5, doi: 10.1016/j.jval.2011.12.006.

121. George Wyatt. Drug Reimbursement in Canada. Regulatory Affairs Professionals Society. Available from: https://www.innomar-strategies.com/insights/drug-reimbursement-in-canada.

122. Canadian Agency for Drugs and Technologies in Health. About CADTH. [accessed 3 September 2021]. Available from: https://www.cadth.ca/index.php/about-cadth.

123. PWC. Canadian Agency for Drugs and Technologies in Health. 2020.

124. CADTH. Procedures for CADTH Reimbursement Reviews. 2021.

125. Canadian Drug Expert Committee (CDEC). CADTH. [accessed 22 September 2021]. Available from: https://www.cadth.ca/canadian-drug-expert-committee-cdec.

126. Canadian Agency for Drugs and Technologies in Health. The pCODR Expert Review Committee (pERC). CADTH. [accessed 18 August 2021]. Available from: https://www.cadth.ca/pcodr-expert-review-committee-perc.

127. CADTH. Process for Drugs with Expanded Health System Implications. [accessed 16 September 2021]. Available from: https://cadth.ca/sites/default/files/pdf/Drugs_Health_System_Implications.pdf.

128. Gouvernment of Canada. Patented Medicine Prices Review Board. [accessed 29 July 2021]. Available from: http://pmprb-cepmb.gc.ca.

129. Patented Medicine Prices Review Board. Roles and Responsiblities of Board Members. [accessed 21 April 2022]. Available from: https://www.canada.ca/en/patented-medicine-prices-review/corporate/organizational-structure/roles-responsiblities-board-members.html.

130. Canada PMPRB. Regulatory Process. [accessed 22 September 2021]. Available from: https://www.canada.ca/en/patented-medicine-prices-review/services/regulatory-process.html.

131. PMPRB. Scientific Review. [accessed 22 September 2021]. Available from: http://pmprb-cepmb.gc.ca.

132. PMPRB. Investigations. [accessed 22 September 2021]. Available from: http://pmprb-cepmb.gc.ca.

133. PMPRB. Voluntary Compliance Undertakings. [accessed 22 September 2021]. Available from: http://pmprb-cepmb.gc.ca.

134. PCPA. About pCPA. [accessed 18 August 2021]. Available from: https://www.pcpacanada.ca/about.

135. CADTH. Guidelines for the Economic Evaluation of Health Technologies: Canada (4th Edition). 2017.

136. Waxman. International Reference Pricing: How it Works and Considerations. 2019.

137. Ruggeri K, Nolte E. Pharmaceutical pricing: The use of external reference pricing. Rand Health Q. 2013;3(2):6. eCollection Summer 2013.

138. Guerreiro CA, Daley BR, Wall K. PMPRB Update: delayed implementation of Patented Medicines Regulations amendments and new Guidelines. [accessed 22 September 2021]. Available from: https://www.pharmainbrief.com/2021/07/pmprb-update-delayed-implementation-of-patented-medicines-regulations-amendments-and-new-guidelines/.

139. Government of Canada. Patented Medicine Price Review Board. Price Review. [accessed 22 September 2021]. Available from: http://pmprb-cepmb.gc.ca.

140. Balijepalli C, Gullapalli L, Druyts E, Yan K, Desai K, Barakat S, et al. Can Standard Health Technology Assessment Approaches Help Guide the Price of Orphan Drugs in Canada? A Review of Submissions to the Canadian Agency for Drugs and Technologies in Health Common Drug Review. Clinicoecon Outcomes Res. 2020;12:445-57, doi: 10.2147/CEOR.S264589.

141. The Patented Medicine Prices Review Board. PMPRB Guidelines. 2021.

142. Bourassa Forcier M, Noël F. Product Listing Agreements (PLAs): A New Tool for Reaching Quebec's Pharmaceutical Policy Objectives? Healthc Policy. 2013;9(1):65-75.

143. Canada Reimbursement Profile. [accessed 5 October 2021]. Available from: https://www.raps.org/regulatory-focusTM/news-articles/2017/10/canada-reimbursement-profile.

144. Health Canada. A Prescription for Canada: Achieving Pharmacare for All. 2019:184.

145. Kyle Choi K, Lee Y. Pricing & Reimbursement Laws and Regulations 2021 / Korea. Global Legal Insights. 2021, Available from: https://www.globallegalinsights.com/practice-areas/pricing-and-reimbursement-laws-and-regulations/korea.

146. Jang S, Byun J, Song I, Cho H. PPRI Pharma Profile South Korea 2018. Pharmaceutical Pricing and Reimbursement Information (PPRI), College of Pharmacy, Gachon University, National Health Insurance Service. 2019.

147. Bae E-Y. Role of Health Technology Assessment in Drug Policies: Korea. Value Health Reg Issues. 2019;18:24-9, doi: 10.1016/j.vhri.2018.03.009.

148. Liu G, Wu EQ, Ahn J, Kamae I, Xie J, Yang H. The Development of Health Technology Assessment in Asia: Current Status and Future Trends. Value Health Reg Issues. 2020;21:39-44, doi: 10.1016/j.vhri.2019.08.472.

149. HIRA. Health Insurance Review & Assessment Service. Korea. Pharmaceutical management procedure. [accessed 22 October 2021]. Available from: https://www.hira.or.kr/dummy.do?pgmid=HIRAJ010000009001.

150. HIRA. Health Insurance Review & Assessment Service. Korea. Drug price. [accessed 22 October 2021]. Available from: https://www.hira.or.kr/eng/about/05/02/02/index.html.

151. Park HK, Chae JY, So SM. Effect of Parallel Review Processes for the Marketing Authorization and Reimbursement to Patients and Budget. Value in Health. 2015;18(7):A518, doi: 10.1016/j.jval.2015.09.1579.

152. Kim S, Lee JH. Price-Cutting Trends in New Drugs after Listing in South Korea: The Effect of the Reimbursement Review Pathway on Price Reduction. Healthcare. 2020;8(3):233, doi: 10.3390/healthcare8030233.

153. Lee E-K, Kim B-Y, Lim J-Y, Park M-H. Different Policy Outcomes of the New Drugs and Currently Listed Drugs under the Positive List System in South Korea. Value in Health. 2012;15(1, Supplement):S100-3, doi: 10.1016/j.jval.2011.11.017.

154. Health Insurance Review & Assessment Service (HIRA). A people centered approach. 2020.

155. HIRA. Health Insurance Review & Assessment Service. Korea. Organizational Chart. [accessed 22 October 2021]. Available from: https://www.hira.or.kr/eng/about/04/organization.html.

156. HIRA. Health Insurance Review & Assessment Service. Korea. Drug Benefit Coverage Assessment Committee. 2021, Available from: https://www.hira.or.kr/dummy.do?pgmid=HIRAA030051000006.

157. HIRA. Health Insurance Review & Assessment Service. Korea. Guidelines for Pharmaceutical Economic Evaluation (First version 2006). 2006.

158. HIRA. Health Insurance Review & Assessment Service. Korea. Guidelines for Pharmaceutical Economic Evaluation (Revision 2011). 2011.

159. HIRA. Health Insurance Review & Assessment Service. Korea. Guidelines for Pharmaceutical Economic Evaluation (Revision 2021). 2021.

160. Bae S, Lee S, Bae EY, Jang S. Korean guidelines for pharmacoeconomic evaluation (second and updated version) : consensus and compromise. Pharmacoeconomics. 2013;31(4):257-67, doi: 10.1007/s40273-012-0021-6.

161. International Society For Pharmacoeconomics and Outcomes Research (ISPOR). Third Version of the Korean Economic Evaluation Guidelines. 2020. Available from: https://www.ispor.org/publications/journals/value-outcomes-spotlight/vos-archives/issue/view/september-2020-supplement-spotlight-on-asia-pacific/third-version-of-the-korean-economic-evaluation-guidelines.

162. Mesana L, Syed IA, Constantin J, Tardivel C, Wang X, Pruce D, et al. Patient Involvement in Health Technology Assessments: An International Comparison. Value in Health. 2018;21:S54, doi: 10.1016/j.jval.2018.07.407.

163. Bae E-Y, Kim HJ, Lee H-J, Jang J, Lee SM, Jung Y, et al. Role of economic evidence in coverage decision-making in South Korea. PLoS One. 2018;13(10):e0206121, doi: 10.1371/journal.pone.0206121.

164. The World Bank. GDP per capita (current US$). Korea. 2020, Available from: https://data.worldbank.org/indicator/NY.GDP.PCAP.CD?end=2020&locations=KR&start=2014.

165. Lee B, Bae E-Y, Bae S, Choi H-J, Son K-B, Lee Y-S, et al. How can we improve patients' access to new drugs under uncertainties? South Korea's experience with risk sharing arrangements. BMC Health Services Research. 2021;21(1):967, doi: 10.1186/s12913-021-06919-x.

166. Kwon S-H, Park H-S, Na Y-J, Park C, Shin J-Y, Kim H-L. Price Reduction of Anticancer Drugs from 2007 to 2019 in South Korea: The Impact of Pharmaceutical Cost-Containment Policies. Appl Health Econ Health Policy. 2021;19(3):439-50, doi: 10.1007/s40258-020-00604-6.

167. HIRA. Health Insurance Review & Assessment Service. Korea. Monitoring and Feedback. DUR Service Procedure and Operational Performance. 2020, Available from: https://www.hira.or.kr/dummy.do?pgmid=HIRAJ010000009002.

168. Jang S, Jeong S, Kang E, Jang S. Impact of a nationwide prospective drug utilization review program to improve prescribing safety of potentially inappropriate medications in older adults: An interrupted time series with segmented regression analysis. Pharmacoepidemiol Drug Saf. 2021;30(1):17-27, doi: 10.1002/pds.5140.

169. UK government. Medicines, medical devices and blood regulation and safety: Marketing authorisations, variations and licensing guidance. Detailed information. [accessed 19 July 2021]. Available from: https://www.gov.uk/topic/medicines-medical-devices-blood/marketing-authorisations-variations-licensing.

170. SMC. Guide to the Scottish Medicines Consortium. Available from: https://www.scottishmedicines.org.uk/media/3574/20180712-a-guide-to-the-scottish-medicines-consortium.pdf.

171. Healthcare Improvement Scotland. About us. [accessed 14 October 2021]. Available from: https://www.healthcareimprovementscotland.org/about_us.aspx.

172. NHS Scotland. Organisations. [accessed 14 October 2021]. Available from: https://www.scot.nhs.uk/organisations/.

173. SMC. Access to newly licensed medicines. Available from: https://archive2021.parliament.scot/S4_HealthandSportCommittee/Inquiries/ANM023_Scottish_Medicines_Consortium.pdf.

174. SMC. Working with SMC. A Guide for Manufacturers. Available from: https://www.scottishmedicines.org.uk/media/5498/working-with-smc-updated-october-2020.pdf.

175. SMC. A Guide for Patient Group Partners. Available from: https://www.scottishmedicines.org.uk/media/2724/patient-group-partner-guide.pdf.

176. SMC. Who we are. Scottish Medicines Consortium. [accessed 5 August 2021]. Available from: https://www.scottishmedicines.org.uk/about-us/who-we-are/.

177. SMC. Policies & publications. Scottish Medicines Consortium. [accessed 5 August 2021]. Available from: https://www.scottishmedicines.org.uk/about-us/policies-publications/.

178. SMC. Meetings. Scottish Medicines Consortium. [accessed 5 August 2021]. Available from: https://www.scottishmedicines.org.uk/about-us/meetings/.

179. SMC. Interim acceptance decision option. Scottish Medicines Consortium. [accessed 21 April 2022]. Available from: https://www.scottishmedicines.org.uk/how-we-decide/interim-acceptance-decision-option/.

180. SMC. Patient and Clinician Engagement (PACE) Meetings Overview. Available from: https://www.scottishmedicines.org.uk/media/5423/pace-overview-document-v32.pdf.

181. SMC. Guidance to Submitting Companies for Completion of New Product Assessment Form (NPAF). Supplement for medicines for extremely rare conditions (ultra-orphan medicines). Available from: https://www.scottishmedicines.org.uk/media/6168/guidance-supplement-ultra-orphan.pdf.

182. SMC. Guidance to submitting companies on abbreviated submissions. Available from: https://www.scottishmedicines.org.uk/media/5974/guidance-to-submitting-companies-on-abbreviated-submissions-may-2021.pdf.

183. SMC. New Product Assessment Form. Available from: https://www.scottishmedicines.org.uk/media/6159/20210728-new-product-assessment-form-npaf.docx.

184. SMC. Guidance to submitting companies for completion of New Product Assessment Form. Available from: https://www.scottishmedicines.org.uk/media/6161/20210728-guidance-on-npaf.pdf.

185. SMC. Attending a virtual Patient and Clinician Engagement (PACE) meeting. Available from: https://www.scottishmedicines.org.uk/media/6009/20201013-patient-group-participation-at-a-pace-meeting-v41_final.pdf.

186. SMC. SMC modifiers used in appraising new medicines. Available from: https://www.scottishmedicines.org.uk/media/3565/modifiers.pdf.

187. ABPI. Pharmaceutical companies give NHS Scotland £1 million a week to help fund new treatments. [accessed 1 September 2021]. Available from: https://www.abpi.org.uk/media-centre/news/2020/january/pharmaceutical-companies-give-nhs-scotland-1-million-a-week-to-help-fund-new-treatments/.

188. NHS Scotland. Patient Access Scheme (PAS) Guidance. Available from: https://www.scottishmedicines.org.uk/media/5635/pas801-018-v9-nhsscotland-pas-guidance.pdf.

189. NHS Scotland. Ultra-orphan medicines. National Services Scotland. [accessed 5 August 2021]. Available from: https://www.nss.nhs.scot/specialist-healthcare/financial-risk-share/ultra-orphan-medicines/.

190. NHS Scotland. Inherited metabolic disorders. National Services Scotland. [accessed 5 August 2021]. Available from: https://www.nss.nhs.scot/specialist-healthcare/financial-risk-share/inherited-metabolic-disorders/.

191. Scottish Goverment. New Medicines Fund and Rare Conditions Medicines Fund information: FOI release. [accessed 26 April 2022]. Available from: http://www.gov.scot/publications/foi-202200287608/.

192. NHS Scotland. National Data Catalogue | National Datasets | ISD Scotland | Information Services Division. [accessed 6 August 2021]. Available from: https://www.ndc.scot.nhs.uk/National-Datasets/data.asp?ID=1&SubID=31.

193. Légifrance. Chapitre 1 bis : Haute Autorité de santé (Articles L161-37 à L161-46). [accessed 21 June 2021]. Available from: https://www.legifrance.gouv.fr/codes/id/LEGISCTA000006156027/.

194. ANSES. Procedimientos de autorización de comercialización nacionales, europeos descentralizados y centralizados. [accessed 18 October 2021]. Available from: https://www.anses.fr/fr/content/pr%C3%A9sentation-de-lanses.

195. HAS. La HAS en bref. [accessed 7 April 2022]. Available from: https://www.has-sante.fr/jcms/c_452559/fr/la-has-en-bref.

196. CLEISS. El sistema sanitario en Francia. [accessed 18 October 2021]. Available from: https://www.cleiss.fr/particuliers/venir/soins/ue/systeme-de-sante-en-france.html.

197. HAS. Service médical rendu (SMR) Le médicament a-t-il suffisamment d'intérêt clinique pour être pris en charge par la solidarité nationale ? 2017.

198. HAS. Commission de la Transparence. [accessed 21 June 2021]. Available from: https://www.has-sante.fr/jcms/c_412210/fr/commission-de-la-transparence.

199. Journal officiel de la République française. Article R163-15. Code de la sécurité sociale. 2018.

200. France Assos Santé. Qui sommes-nous ? France Assos Santé. 2019, Available from: https://www.france-assos-sante.org/presentation/qui-sommes-nous/.

201. HAS. Comprendre l'évaluation des médicaments. [accessed 24 June 2021]. Available from: https://www.has-sante.fr/jcms/c_412115/fr/comprendre-l-evaluation-des-medicaments.

202. HAS. Commission d'évaluation économique et de santé publique. [accessed 21 June 2021]. Available from: https://www.has-sante.fr/jcms/c_419565/fr/commission-d-evaluation-economique-et-de-sante-publique.

203. HAS. Règlement intérieur de la commission d'évaluation économique et de santé publique. Available from: https://www.has-sante.fr/upload/docs/application/pdf/2018-10/reglement_interieur_ceesp.pdf.

204. HAS. Comprendre l'évaluation économique des produits de santé. [accessed 21 June 2021]. Available from: https://www.has-sante.fr/jcms/r_1502595/fr/comprendre-l-evaluation-economique-des-produits-de-sante.

205. HAS. CEPS (Comité économique des produits de santé). Ministère des Solidarités et de la Santé. [accessed 21 June 2021]. Available from: https://solidarites-sante.gouv.fr/ministere/acteurs/instances-rattachees/article/ceps-comite-economique-des-produits-de-sante.

206. Journal officiel de la République française. Artículo D162-2-5. Code de la sécurité sociale. 2018.

207. Journal officiel de la République française. Article L162-17-3. Code de la sécurité sociale. 2016.

208. LabCorp. Pricing & Reimbursement in France. Available from: https://drugdevelopment.labcorp.com/content/dam/covance/

assetLibrary/salessheets/Pricing-Reimbursement-France-SSCMA053.pdf.

209. HAS. Procédures d'évaluation anticipée « Fast - Tracking » par la Commission de la Transparence.

210. HAS. Déposer un dossier d'évaluation d'un médicament. Haute Autorité de Santé. [accessed 22 June 2021]. Available from: https://www.has-sante.fr/jcms/c_1046750/fr/deposer-un-dossier-d-evaluation-d-un-medicament.

211. HAS. Choix méthodologiques pour l'évaluation économique à la HAS. [accessed 25 June 2021]. Available from: https://www.has-sante.fr/jcms/p_3197550/fr/guide-2020-choix-methodologiques-pour-l-evaluation-economique-a-la-has.

212. Marsh K, IJzerman M, Thokala P, Baltussen R, Boysen M, Kaló Z, et al. Multiple Criteria Decision Analysis for Health Care Decision Making. Emerging Good Practices: Report 2 of the ISPOR MCDA Emerging Good Practices Task Force. Value in Health. 2016;19(2):125-37, doi: 10.1016/j.jval.2015.12.016.

213. Angelis A, Kanavos P. Value-Based Assessment of New Medical Technologies: Towards a Robust Methodological Framework for the Application of Multiple Criteria Decision Analysis in the Context of Health Technology Assessment. Pharmacoeconomics. 2016;34:435-46, doi: 10.1007/s40273-015-0370-z.

214. Mühlbacher AC, Kaczynski A. Making Good Decisions in Healthcare with Multi-Criteria Decision Analysis: The Use, Current Research and Future Development of MCDA. Appl Health Econ Health Policy. 2016;14(1):29-40, doi: 10.1007/s40258-015-0203-4.

215. GLOBALHealthPR. France.Market Access Pharma. [accessed 21 June 2021]. Available from: https://www.globalhealthpr.com/services/france/.

216. Rémuzat C, Toumi M, Falissard B. New drug regulations in France: what are the impacts on market access? Part 1 – Overview of new drug regulations in France. Journal of Market Access & Health Policy. 2013;1(0), doi: 10.3402/jmahp.v1i0.20891.

217. Journal officiel de la République française. Artículo L165-2. Code de la sécurité sociale. 2019.

218. Vogler S. PPRI Pharma Brief: France. Available from: https://jasmin.goeg.at/1686/1/PPRI_Pharma_Brief_FR_2020_final_Oct2020.pdf.

219. BioPharma. Market Access in France. [accessed 21 June 2021]. Available from: https://mapbiopharma.com/demo/market-access-in-france/.

220. HAS. Notice de dépôt Modalités de dépôt d'un dossier d'évaluation économique auprès de la CEESP. Available from: https://www.has-sante.fr/upload/docs/application/pdf/2013-08/notice_de_depot.pdf.

221. HAS. Étapes d'élaboration d'un avis économique. Available from: https://www.has-sante.fr/upload/docs/application/pdf/2013-08/etapes_delaboration_des_avis_defficience.pdf.

222. HAS. Associations de patients, votre avis nous intéresse. [accessed 10 September 2021]. Available from: https://www.has-sante.fr/jcms/p_3056102/fr/associations-de-patients-votre-avis-nous-interesse.

223. Toumi M, Motrunich A, Millier A, Rémuzat C, Chouaid C, Falissard B, et al. Analysis of health economics assessment reports for pharmaceuticals in France – understanding the underlying philosophy of CEESP assessment. Journal of Market Access & Health Policy. 2017;5(1):1344088, doi: 10.1080/20016689.2017.1344088.

224. Forest J. L'accès au marché des médicaments en France au travers des contrats de paiement à la performance: solution crédible et extrapolable? Sciencespharmaceutiques. 2020.

225. HAS. Analyse d'impact budgétaire : la HAS enrichit l'évaluation médico-économique des produits de santé. [accessed 18 October 2021]. Available from: https://www.has-sante.fr/jcms/c_2747893/fr/analyse-d-impact-budgetaire-la-has-enrichit-l-evaluation-medico-economique-des-produits-de-sante.

226. HAS. Choix méthodologiques pour l'analyse de l'impact budgétaire à la HAS. Available from: https://www.has-sante.fr/upload/docs/application/pdf/2016-12/guide_methodologique__choix_methodologiques_pour_lanalyse_de_limpact_budgetaire_a_la_has_.pdf.

227. PPRI Pharma. PPRI Pharma Brief: France. Available from: https://ppri.goeg.at/sites/ppri.goeg.at/files/inline-files/PPRI_Pharma_Brief_FR_2020_final_Oct2020.pdf.

228. Moutie AS, Sales JP, Planel MP, Rodrigues J. PDG57 DRUG PRICING PREDICTABILITY IN FRANCE: WHICH MANAGED ENTRY AGREEMENT SUITS THE BEST? Value in Health. 2019;22:S606, doi: 10.1016/j.jval.2019.09.1071.

229. CESP. Rapport d'activité 2019. Available from: https://solidarites-sante.gouv.fr/IMG/pdf/ceps_rapport_d_activite_2019_20201001.pdf.

230. APMnews. Contrats de performance CEPS/laboratoires. [accessed 26 July 2021]. Available from: https://www.apmnews.com/freestory/0/255481/contrats-de-performance-ceps-laboratoires-il-faut-travailler-sur-le-realisme-et-la-confiance-%28dominique-giorgi%29.

231. Décision & Stratégie Santé. Jean-Patrick Sales (CEPS)* : « Les deux inconvénients du paiement étalé ». Décision & Stratégie Santé. [accessed 26 July 2021]. Available from: https://www.decision-sante.com/medecine-pharmacie/actualites/jean-patrick-sales-ceps-les-deux-inconvenients-du-paiement-etale.

232. SNDS. Composantes du Système National des Données de Santé. [accessed 26 July 2021]. Available from: https://www.snds.gouv.fr/SNDS/Composantes-du-SNDS.

233. HAS. Plan d'action pour l'évaluation des médicaments innovants. Available from: https://www.has-sante.fr/upload/docs/application/pdf/2020-01/plan_daction_pour_les_medicaments_innovants_27.01.2020.pdf.

234. UK government. European Commission (EC) Decision Reliance Procedure. GOV.UK. [accessed 19 July 2021]. Available from: https://www.gov.uk/guidance/european-commission-ec-decision-reliance-procedure.

235. UK government. 150-day assessment for national applications for medicines. GOV.UK. [accessed 19 July 2021]. Available from: https://www.gov.uk/guidance/guidance-on-150-day-assessment-for-national-applications-for-medicines.

236. UK government. Rolling review for marketing authorisation applications. GOV.UK. [accessed 21 July 2021]. Available from: https://www.gov.uk/guidance/rolling-review-for-marketing-authorisation-applications.

237. UK government. Decentralised and mutual recognition reliance procedure for marketing authorisations. GOV.UK. [accessed 19 July 2021]. Available from: https://www.gov.uk/guidance/decentralised-and-mutual-recognition-reliance-procedure-for-marketing-authorisations.

238. MS Trust. Drug approval process. [accessed 14 October 2021]. Available from: https://mstrust.org.uk/a-z/drug-approval-process.

239. Global Legal Insights. Pricing & Reimbursement Laws and Regulations. United Kingdom. [accessed 21 July 2021]. Available from: https://www.globallegalinsights.com/practice-areas/pricing-and-reimbursement-laws-and-regulations/united-kingdom.

240. Gov.UK. National Institute for Health and Care Excellence. [accessed 14 October 2021]. Available from: https://www.gov.uk/government/organisations/national-institute-for-clinical-excellence.

241. NICE. National Institute for Health and Care Excellence Annual Report and Accounts 2019/20. 2020.

242. Ben Collins. Access to new medicines in the English NHS. The King's Fund. 2020, Available from: https://www.kingsfund.org.uk/publications/access-new-medicines-english-nhs.

243. NICE. Introduction. Guide to the methods of technology appraisal. [accessed 21 July 2021]. Available from: https://www.nice.org.uk/process/pmg9/chapter/introduction.

244. NICE. Guide to the processes of technology appraisal. [accessed 21 July 2021]. Available from: https://www.nice.org.uk/process/pmg19/chapter/the-appraisal-process#evidence-review-group-report.

245. NICE. Technology Appraisals Committee Terms of Reference and Standing Orders. 2017.

246. University of Sheffield. NICE Decision Support Unit. [accessed 23 July 2021]. Available from: http://nicedsu.org.uk/.

247. NICE. Introduction. Guide to the processes of technology appraisal. [accessed 23 July 2021]. Available from: https://www.nice.org.uk/process/pmg19/chapter/introduction.

248. NICE. NICE technology appraisal guidance. [accessed 21 July 2021]. Available from: https://www.nice.org.uk/about/what-we-do/our-programmes/nice-guidance/nice-technology-appraisal-guidance.

249. NICE. Technology appraisal data: appraisal recommendations. Technology appraisal data. NICE technology appraisal guidance. NICE guidance. Our programmes. What we do. About. [accessed 27 July 2021]. Available from: https://www.nice.org.uk/about/what-we-do/our-programmes/nice-guidance/nice-technology-appraisal-guidance/data/appraisal-recommendations.

250. NICE. The reference case. [accessed 22 July 2021]. Available from: https://www.nice.org.uk/process/pmg9/chapter/the-reference-case.

251. NICE. Technology appraisal and highly specialised technologies appeals. [accessed 21 July 2021]. Available from: https://www.nice.org.uk/about/what-we-do/our-programmes/nice-guidance/nice-technology-appraisal-guidance/technology-appraisal-and-highly-specialised-technologies-appeals.

252. NICE. Developing the scope. Guide to the methods of technology appraisal. [accessed 28 July 2021]. Available from: https://www.nice.org.uk/process/pmg9/chapter/developing-the-scope.

253. NICE. Evidence. Guide to the methods of technology appraisal. [accessed 28 July 2021]. Available from: https://www.nice.org.uk/process/pmg9/chapter/evidence.

254. NICE. NICE highly specialised technologies guidance. [accessed 21 July 2021]. Available from: https://www.nice.org.uk/about/what-we-do/our-programmes/nice-guidance/nice-highly-specialised-technologies-guidance.

255. NICE. Incorporating economic evaluation. [accessed 21 July 2021]. Available from: https://www.nice.org.uk/process/pmg20/chapter/incorporating-economic-evaluation.

256. NICE. Changes we're making to health technology evaluation. [accessed 28 July 2021]. Available from: https://www.nice.org.uk/about/what-we-do/our-programmes/nice-guidance/nice-technology-appraisal-guidance/changes-to-health-technology-evaluation.

257. NICE. Patient and public involvement policy. Public Involvement Programme. Public involvement. NICE and the public. NICE Communities. [accessed 10 September 2021]. Available from: https://www.nice.org.uk/about/nice-communities/nice-and-the-public/public-involvement/public-involvement-programme/patient-public-involvement-policy.

258. NICE. NICE strategy 2021 to 2026: Dynamic, Collaborative, Excellent. Available from: https://static.nice.org.uk/NICE%20strategy%202021%20to%202026%20-%20Dynamic,%20Collaborative,%20Excellent.pdf.

259. Department of Health and Social Care. The 2019 voluntary scheme for branded medicines pricing and access: chapters and glossary. Available from: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/761834/voluntary-scheme-for-branded-medicines-pricing-and-access-chapters-and-glossary.pdf.

260. Finance and NHS/Medicines, Pharmacy and Industry Group. The Pharmaceutical Price Regulation Scheme 2014. 2014:135.

261. Department of Health and Social Care. The 2019 voluntary scheme for branded medicines pricing and access: payment percentage for 2021. GOV.UK. [accessed 14 October 2021]. Available from: https://www.gov.uk/government/publications/voluntary-scheme-for-branded-medicines-payment-percentage-for-2021/the-2019-voluntary-scheme-for-branded-medicines-pricing-and-access-payment-percentage-for-2021.

262. Matar M, Tatham G, Calderwood S, Girn S. NICE's Highly Specialized Technologies. Simon-Kucher. [accessed 27 July 2021]. Available from: https://www.simon-kucher.com/en/blog/nices-highly-specialized-technologies.

263. Genetic Alliance UK. Changes to the HST programme. [accessed 28 July 2021]. Available from: https://geneticalliance.org.uk/gauk-news/news/changes-to-the-hst-programme/.

264. NICE. Consideration of the evidence. Cerliponase alfa for treating neuronal ceroid lipofuscinosis type 2. [accessed 14 October 2021]. Available from: https://www.nice.org.uk/guidance/hst12/chapter/4-Consideration-of-the-evidence#applying-qaly-weighting-2.

265. ABPI. NICE Methods Review. [accessed 12 January 2022]. Available from: https://www.abpi.org.uk/value-and-access/nice-methods-review/.

266. Rudd A. What is NICE's new QALY shortfall? Remap Consulting. 2021, Available from: https://remapconsulting.com/the-qaly-shortfall/.

267. Pauwels K, Huys I, Vogler S, Casteels M, Simoens S. Managed Entry Agreements for Oncology Drugs: Lessons from the European Experience to Inform the Future. Front Pharmacol. 2017;8:171, doi: 10.3389/fphar.2017.00171.

268. NHS. NHS commercial framework for new medicines. Available from: https://www.england.nhs.uk/wp-content/uploads/2021/02/

B0255-nhs-commercial-framework-for-new-medicines.pdf.

269. NICE. Patient access schemes liaison unit. What we do. About. [accessed 21 July 2021]. Available from: https://www.nice.org.uk/about/what-we-do/patient-access-schemes-liaison-unit.

270. NICE. Cancer Drugs Fund. NICE. [accessed 21 July 2021]. Available from: https://www.nice.org.uk/about/what-we-do/our-programmes/nice-guidance/nice-technology-appraisal-guidance/cancer-drugs-fund.

271. NHS England. NHS England announces new Innovative Medicines Fund to fast-track promising new drugs. [accessed 22 Diciembre 2021]. Available from: https://www.england.nhs.uk/2021/07/nhs-england-announces-new-innovative-medicines-fund-to-fast-track-promising-new-drugs/.

272. NICE. Data collection agreement to treating cystic fibrosis patients. NICE. [accessed 21 July 2021]. Available from: https://www.nice.org.uk/about/what-we-do/our-programmes/nice-guidance/nice-technology-appraisal-guidance/data-collection-agreement.

273. NICE. Managed Access Agreement Niraparib. Available from: https://www.nice.org.uk/guidance/ta673/resources/managed-access-agreement-pdf-9014549581.

274. Bright CJ, Lawton S, Benson S, Bomb M, Dodwell D, Henson KE, et al. Data Resource Profile: The Systemic Anti-Cancer Therapy (SACT) dataset. International Journal of Epidemiology. 2020;49(1):15-15l, doi: 10.1093/ije/dyz137.

275. AIFA. Negoziazione e rimborsabilità. [accessed 11 June 2021]. Available from: https://aifa.gov.it/negoziazione-e-rimborsabilit%C3%A0.

276. AIFA. L'Agenzia Italiana del Farmaco. [accessed 11 June 2021]. Available from: https://aifa.gov.it/l-agenzia.

277. Ministerio de Salud. Boletín Oficial. Criterios para la negociación de los precios de los medicamentos reembolsados por el Servicio Nacional de Salud. [accessed 9 June 2021]. Available from: https://www.gazzettaufficiale.it/eli/id/2020/07/24/20A03810/sg.

278. AIFA. Commissioni tecnico-consultive. [accessed 9 June 2021]. Available from: https://aifa.gov.it/commissioni-tecnico-consultive.

279. AIFA. Reglamento de organización y funcionamiento del Comité Consultivo Técnico y Científico y del Comité de Precios y Reembolsos. 2014.

280. Camera dei deputati. Classificazione dei farmaci e regime di rimborsabilità. [accessed 14 June 2021]. Available from: https://temi.camera.it/leg17/post/classificazione_dei_farmaci_e_regime_di_rimborsabilit_.html.

281. AIFA. L'AIFA approva le nuove linee guida per la contrattazione dei prezzi e rimborsi dei farmaci. [accessed 14 June 2021]. Available from: https://aifa.gov.it/-/l-aifa-approva-le-nuove-linee-guida-per-la-contrattazione-dei-prezzi-e-rimborsi-dei-farmaci.

282. AIFA. Linee guida per la compilazione del dossier a supporto della domanda di rimborsabilità e prezzo di un medicinale. 2019.

283. AIFA. Criteri per la valutazione dell'innovativita'. 2017.

284. What is GRADE? [accessed 29 June 2017]. Available from: http://clinicalevidence.bmj.com/x/set/static/ebm/learn/665072.html.

285. AIFA. Farmaci innovativi. [accessed 9 June 2021]. Available from: https://aifa.gov.it/farmaci-innovativi.

286. AIFA. Farmaci orfani. [accessed 18 October 2021]. Available from: https://aifa.gov.it/farmaci-orfani.

287. AIFA. Valutazioni economiche. [accessed 15 June 2021]. Available from: https://aifa.gov.it/valutazioni-economiche.

288. AIFA. Linee guida per la compilazione del Dossier a supporto della domanda di rimborsabilità e prezzo di un medicinale. 2020.

289. AIFA. Analisi registri di monitoraggio. [accessed 15 June 2021]. Available from: https://aifa.gov.it/analisi-registri-di-monitoraggio.

290. AIFA. Comunicazioni Managed Entry Agreements (MEA). [accessed 23 July 2021]. Available from: https://aifa.gov.it/comunicazioni-managed-entry-agreements-mea-1.

291. OECD. Pharmaceutical Expenditure Tracking, Budgeting and Forecasting in 23 OECD and EU countries. 2019.

292. European Observatory on Health Systems and, OCDE. State of Health in the EU: Italy. 2019.

293. European Commission. Italy Health Care & Long-Term Care Systems. 2019.

294. Gobierno de Italia. Ley no 232 del 11 dicembre 2016 sobre Presupuesto estatal para el año 2017 y presupuesto plurianual para el trienio 2017-2019. [accessed 15 June 2021]. Available from: https://www.gazzettaufficiale.it/eli/id/2016/12/21/16G00242/sg.

295. AIFA. Elenchi farmaci innovativi ai sensi dell'art. 1, commi 402, 403 e 404, della legge 11/12/2016, n. 232 (Legge di Bilancio 2017). 2021.

296. Irma D'Aria. Tumori: "Sfondato di 464 milioni di euro il fondo dei farmaci innovativi. Servono più risorse". la Repubblica. 2021.

297. AIFA. Fondo Nazionale. [accessed 15 June 2021]. Available from: https://aifa.gov.it/fondo-nazionale-aifa.

298. AIFA. Sospensione accesso al Fondo nazionale AIFA 5%. [accessed 29 April 2022]. Available from: https://www.aifa.gov.it/-/sospensione-accesso-al-fondo-nazionale-aifa.

299. AIFA. Registri farmaci sottoposti a monitoraggio. [accessed 9 June 2021]. Available from: https://www.aifa.gov.it/registri-farmaci-sottoposti-a-monitoraggio.

300. AIFA. Appropriatezza prescrittiva. 2013

301. Murri G. Registri AIFA come strumento di appropriatezza e sostenibilità. 2017.

302. PKE. Quanti medici ci sono in Italia? [accessed 12 July 2021]. Available from: http://www.pkegroup.it/quanti-medici-ci-sono-in-italia.asp.

303. Tanaka M, Idei M, Sakaguchi H, Kato R, Sato D, Sawanobori K, et al. Evolving Landscape of New Drug Approval in Japan and Lags from International Birth Dates: Retrospective Regulatory Analysis. Clin Pharmacol Ther. 2021;109(5):1265-73, doi: 10.1002/cpt.2080.

304. Shiroiwa T. Cost-effectiveness evaluation for pricing medicines and devices: A new value-based price adjustment system in Japan. International Journal of Technology Assessment in Health Care. 2020;36(3):270-6, doi: 10.1017/S0266462320000264.

305. Core2Health. Precios de medicamentos y dispositivos médicos. [accessed 29 October 2021]. Available from: https://c2h.niph.go.jp/assessment/price-setting/.

306. Hasegawa M, Komoto S, Shiroiwa T, Fukuda T. Formal Implementation of Cost-Effectiveness Evaluations in Japan: A Unique Health Technology Assessment System. Value in Health. 2020;23(1):43-51, doi: 10.1016/j.jval.2019.10.005.

307. Kamae I, Thwaites R, Hamada A, Fernandez JL. Health technology assessment in Japan: a work in progress. Journal of Medical Economics. 2020;23(4):317-22, doi: 10.1080/13696998.2020.1716775.

308. Fukuda T, Shiroiwa T. Application of economic evaluation of pharmaceuticals and medical devices in Japan. 2019:7.

309. Shiroiwa T, Fukuda T, Ikeda S, Takura T, Moriwaki K. Development of an Official Guideline for the Economic Evaluation of Drugs/Medical Devices in Japan. Value in Health. 2017;20(3):372-8, doi: 10.1016/j.jval.2016.08.726.

310. Core2Health. Guideline for Preparing Cost-Effectiveness Evaluation to the Central Social Insurance Medical Council. 2019.

311. MHLW. Esquema del sistema de designación de productos como medicamentos huérfanos, dispositivos médicos para enfermedades raras y medicina regenerativa para enfermedades raras. [accessed 28 October 2021]. Available from: https://www.mhlw.go.jp/stf/seisakunitsuite/bunya/0000068484.html.

312. Kobayashi M. Introduction of Japanese Pricing System. ISPOR Asia-Pacific 2018, Tokyo, Japan. Available from: https://www.ispor.org/docs/default-source/conference-ap-2018/makoto.pdf?sfvrsn=47ae4e02_0

313. Yumoto T. Update of Drug Pricing System in Japan. Japan. Ministry of Health, Labour and Welfare 2018. Available from: https://www.pmda.go.jp/files/000226220.pdf

314. Fernández de Piérola J. Estudio de mercado. El marcado farmacéutico en Japón 2020. ICEX España Exportación e Inversiones

315. Kang S-Y, Bai G, DiStefano MJ, Socal MP, Yehia F, Anderson GF. Comparative Approaches to Drug Pricing. Annu Rev Public Health. 2020;41(1):499-512, doi: 10.1146/annurev-publhealth-040119-094305.

316. Yamate M. Update of Drug Pricing System in Japan. Ministry of Health, Labour and Welfare 2020. Available from: https://www.pmda.go.jp/files/000226220.pdf

317. Wenzl M, Chapman S. Performance-based managed entry agreements for new medicines in OECD countries and EU member states: How they work and possible improvements going forward. OECD Health Working Paper No. 115, 2019. Available from: https://health.ec.europa.eu/system/files/2020-01/2019_entryagreements_newmedicines_oecdeu_en_0.pdf

318. Matsushita S, Tachibana K, Kondoh M. The Clinical Innovation Network: a policy for promoting development of drugs and medical devices in Japan. Drug Discovery Today. 2019;24(1):4-8, doi: 10.1016/j.drudis.2018.05.026.

319. CIN. Red de innovación clínica. 2021. Available from: https://cinc.ncgm.go.jp/.

320. CIN. Introducción al registro. 2021. Available from: https://cinc.ncgm.go.jp/?page_id=194.

321. Ministry of Health, Welfare and Sport. Healthcare in the Netherlands. 2016.

322. National Healthcare Institute. Advising on and clarifying the contents of the standard health care benefit package. 2021. Available from: https://english.zorginstituutnederland.nl/about-us/tasks-of-the-national-health-care-institute/advising-on-and-clarifying-the-contents-of-the-standard-health-care-benefit-package.

323. Kloeke K van L, Artz L. Pricing & Reimbursement Laws and Regulations 2021. Netherlands. Global Legal Insights. 2021, Available from: https://www.globallegalinsights.com/practice-areas/pricing-and-reimbursement-laws-and-regulations/netherlands.

324. National Healthcare Institute. Assessment of outpatient medicines for the benefit of the Medicine Reimbursement System (GVS). 2021. Available from: https://english.zorginstituutnederland.nl/about-us/tasks-of-the-national-health-care-institute/assessment-of-outpatient-medicines-for-the-benefit-of-the-medicine-reimbursement-system-gvs.

325. National Healthcare Institute. Reimbursement of outpatient medicines. 2021. Available from: https://english.zorginstituutnederland.nl/about-us/tasks-of-the-national-health-care-institute/assessment-of-outpatient-medicines-for-the-benefit-of-the-medicine-reimbursement-system-gvs/reimbursement-of-outpatient-medicines.

326. Ophuis RH, Diemer FS. Specialist medicinal products assessment procedure. National Healthcare Institute. 2020.

327. Dutch Association for Innovative Medicines. Medicines Monitor Edition. 2021. Available from: https://publicaties.vereniginginnovatievegeneesmiddelen.nl/magazine/mm2021uk/access/#c007uk.

328. National Healthcare Institute. The Medicines Evaluation Board and the National Health Care Institute start pilot to accelerate access to innovative medicines. 2019. Available from: https://english.zorginstituutnederland.nl/latest/news/2019/05/09/cbg-meb-and-zin-have-started-the-%E2%80%9Ccbg-zin-parallel-procedures-pilot%E2%80%9D-to-accelerate-access-to-innovative-medicines.

329. National Healthcare Institute. Pilot Parallel Procedures for registration and reimbursement processes. 2021, Available from: https://www.zorginstituutnederland.nl/werkagenda/parallelle-procedures-cbg-zin.

330. National Healthcare Institute. Working committees and members of the committees from the Scientific Advisory Board (WAR). 2021. Available from: https://www.zorginstituutnederland.nl/over-ons/commissies/wetenschappelijke-adviesraad-war/werkcommissies-en-leden.

331. National Healthcare Institute. Package Advisory Committee (ACP). 2021, Available from: https://www.zorginstituutnederland.nl/over-ons/commissies/adviescommissie-pakket-acp.

332. National Healthcare Institute. Composition of the Package Advisory Committee (ACP). 2021. Available from: https://www.zorginstituutnederland.nl/over-ons/commissies/adviescommissie-pakket-acp/samenstelling-acp.

333. Dutch Healthcare Authority. NZa Duties and Roles in brief. 2021.

334. ACM. Authority for Consumers and Markets. 2021. Available from: https://www.acm.nl/en.

335. National Healthcare Institute. Overview of dossier requirements for drug assessments. 2021.

336. National Healthcare Institute. Pharmacotherapeutic dossier template. 2016. Available from: https://www.zorginstituutnederland.nl/over-ons/publicaties/publicatie/2016/08/29/format-farmacotherapeutisch-dossier-voor-herbeoordeling-in-het-kader-van-pakketbeheer-specialistische-geneesmiddelen.

337. National Healthcare Institute. Pharmaco-economic dossier template. 2016. Available from: https://www.zorginstituutnederland.nl/over-ons/publicaties/publicatie/2016/07/25/template-farmaco-economisch-dossier.

338. National Healthcare Institute. Assessment of established medical science and medical practice. 2015. Available from: https://english.zorginstituutnederland.nl/about-us/publications/reports/2015/01/19/assessment-of-established-medical-science-and-medical-practice.

339. National Healthcare Institute. Criteria for the assessment of therapeutic value. 2014. Available from: https://www.zorginstituutnederland.nl/over-ons/publicaties/publicatie/2014/07/01/criteria-voor-beoordeling-therapeutische-waarde.

340. National Healthcare Institute. Guideline for economic evaluations in healthcare. 2016. Available from: https://english.zorginstituutnederland.nl/about-us/publications/reports/2016/06/16/guideline-for-economic-evaluations-in-healthcare.

341. Drummond MF, Sculpher MJ, Claxton K, Stoddart GL, Torrance GW. Methods for the economic evaluation of health care programmes. Fourth. Oxford University Press; 2015.

342. National Healthcare Institute. Package advice in practice. Deliberations for arriving at a fair package. 2018, Available from: https://english.zorginstituutnederland.nl/about-us/publications/reports/2018/09/05/package-advice-in-practice---deliberations-for-arriving-at-a-fair-package.

343. Bærøe K, Baltussen R. Legitimate Healthcare Limit Setting in a Real-World Setting: Integrating Accountability for Reasonableness and Multi-Criteria Decision Analysis. Public Health Ethics. 2014;7(2):98-111, doi: 10.1093/phe/phu006.

344. Government of the Netherlands. Keeping medicines affordable. 2019. Available from: https://www.government.nl/topics/medicines/keeping-medicines-affordable.

345. National Healthcare Institute., Zwaap J, Knies S, van der Meijden C, Staal P, van der Heiden L. Cost-effectiveness in practice. 2015. Available from: https://english.zorginstituutnederland.nl/about-us/publications/reports/2015/06/16/cost-effectiveness-in-practice.

346. Office of Health Economics. Clarifying meanings of absolute and proportional shortfall with examples. 2013.

347. National Healthcare Institute. Budget impact analysis dossier template. 2020. Available from: https://www.zorginstituutnederland.nl/over-ons/publicaties/publicatie/2020/07/22/format-budgetimpactanalyse.

348. Makady A, van Veelen A, de Boer A, Hillege H, Klungel OH, Goettsch W. Implementing managed entry agreements in practice: The Dutch reality check. Health Policy. 2019;123(3):267-74, doi: 10.1016/j.healthpol.2018.09.016.

349. National Healthcare Institute. Advice on the reassessment of axicabtagene ciloleucel (Yescarta®). 2021.

350. National Healthcare Institute. Package advice for the lock procedure drug betibeglogene autotemcel (Zynteglo®). 2021. Available from: https://english.zorginstituutnederland.nl/publications/reports/2021/07/21/package-advice-on-betibeglogene-autotemcel-zynteglo.

351. National Healthcare Institute. Conditional inclusion procedure for medicinal products. 2020.

352. National Healthcare Institute. Conditional inclusion of orphan drugs, conditionals and exceptionals in basic health care. 2020. Available from: https://english.zorginstituutnederland.nl/about-us/tasks-of-the-national-health-care-institute/conditional-inclusion-of-orphan-drugs-conditionals-and-exceptionals.

353. National Healthcare Institute. Working method for the Zinnige Zorg (appropriate care) Programme. 2018. Available from: https://english.zorginstituutnederland.nl/zinnige-zorg/publications/leaflets/2018/08/27/working-method-for-the-zinnige-zorg-appropriate-care-programme.

354. EIT Health Scandinavia. Overview of Health Data Registries in The Netherlands. 2020. Available from: https://www.eithealth-scandinavia.eu/biobanksregisters/registers/netherlands/.

355. Ministério da Saúde de Portugal. Decreto-Lei n.o 97/2015. Diário da República nº 105/2015. 2015.

356. Martins J, Rodrigues J, Antunes M, Ferrador F, Ramos I, Ramos R, et al. Sistema Nacional de Avaliação de Tecnologías de Saúde para Portugal (SiNATS). Criar o futuro. INFARMED: Autoridade Nacional do Medicamento e Produtos de Saúde; 2014.

357. INFARMED. Comissão de Avaliação de Tecnologias de Saúde (CATS). 2021. Available from: https://www.infarmed.pt/web/infarmed/

institucional/estrutura-e-organizacao/comissoes-tecnicas-especializadas/comissao-de-avaliacao-de-tecnologias-de-saude.

358. Ministerio da Saúde de Portugal. Despacho n.o 5847/2016, Diário da República, 2.a série nº 84. 2016.

359. Ministerio da Saúde de Portugal. Despacho n.o 7069/2016. Diário da República, 2.a série nº 103. 2016.

360. Ministerio da Saúde de Portugal. Despacho n.o 1878/2017. Diário da República, 2.a série nº 46. 2017.

361. INFARMED. Direção de Avaliação das Tecnologias de Saúde (DATS). 2021. Available from: https://www.infarmed.pt/web/infarmed/institucional/estrutura-e-organizacao/dats.

362. INFARMED. Conselho Diretivo (CD). 2021, Available from: https://www.infarmed.pt/web/infarmed/institucional/estrutura-e-organizacao/conselho-diretivo.

363. INFARMED. Perguntas frequentes: avaliação terapéutica e econômica. 2021. Available from: https://www.infarmed.pt/web/infarmed/perguntas-frequentes-area-transversal/medicamentos_uso_humano/avaliacao_economica_e_comparticipacao.

364. Ministerio da Saúde de Portugal. Portaria n.o 195-A/2015. Diário da República, 1.a série n.o 125. 2015.

365. Ministerio da Saúde de Portugal. Portaria n.o 270/2017. Diário da República, 1.a série n.o 176. 2017.

366. Ministério da Saúde de Portugal. Portal da Transparência. 2021.

367. INFARMED. Indicadores de atividade. 2021. Available from: https://www.infarmed.pt/web/infarmed/indicadores-de-atividade.

368. INFARMED. Resultados da Avaliação para Financiamento de Medicamentos (janeiro – dezembro 2019). 2019.

369. Comissão de Avaliação de Tecnologías de Saúde (CATS). Metodología para Avaliação Farmacoterapéutica. 2016.

370. INFARMED. Relatórios de avaliação de financiamento público. 2021, Available from: https://www.infarmed.pt/web/infarmed/relatorios-de-avaliacao-de-financiamento-publico.

371. Direção de Avaliação de Tecnologías de Saúde (DATS). Relatório Público de Avaliação: YESCARTA (AXICABTAGENE CILOLEUCEL). 2021.

372. INFARMED. Avaliação terapêutica e económica. 2021. Available from: https://www.infarmed.pt/web/infarmed/entidades/medicamentos-uso-humano/avaliacao-tecnologias-saude/avaliacao-terapeutica-e-economica.

373. Perelman J, Soares M, Mateus C, Duarte A, Faria R, Ferreira L, et al. Orientações Metodológicas para Estudos de Avaliação Económica. INFARMED: Autoridade Nacional do Medicamento e Produtos de Saúde; 2019.

374. Oliveira M. Projeto INCLUIR: Patient involvement in health tecnhnology assessment in Portugal. 2019.

375. Ministério da Saúde de Portugal. Portaria n.o 297/2020. Diário da República, 1.a série, no 248. 2020.

376. INFARMED. Atribuição de preços. 2021. Available from: https://www.infarmed.pt/web/infarmed/entidades/medicamentos-uso-humano/avaliacao-economica/regulamentacao-preco-medicamentos/atribuicao_precos.

377. Ministério da Saúde de Portugal. Portaria n.o 195-C/2015. Diário da República, 1.a série n.o 125. 2015.

378. INFARMED. Alterações e revogações de preços de medicamentos. 2021. Available from: https://www.infarmed.pt/web/infarmed/entidades/medicamentos-uso-humano/avaliacao-economica/regulamentacao-preco-medicamentos/notificacoes_revogacoes.

379. INFARMED. Regulamentação de preços. 2021. Available from: https://www.infarmed.pt/web/infarmed/entidades/medicamentos-uso-humano/avaliacao-tecnologias-saude/regulamentacao-de-precos.

380. INFARMED. Revisões de preços. 2021. Available from: https://www.infarmed.pt/web/infarmed/entidades/medicamentos-uso-humano/avaliacao-economica/regulamentacao-preco-medicamentos/revisao_precos.

381. República Portuguesa Saúde, Serviço Nacional de Saúde, INFARMED. Methodological guidelines for economic evaluation studies of health technologies. 2019.

382. Gonçalves FR, Santos S, Silva C, Sousa G. Risk-sharing agreements, present and future. Ecancermedicalscience. 2018;12, doi: 10.3332/ecancer.2018.823.

383. Ferrario A, Kanavos P. Managed entry agreements for pharmaceuticals: the European experience. Brussels; 2013.

384. INFARMED. Vemurafenib. Relatório de avaliação prévia do medicamento para uso humano em meio hospitalar. 2014.

385. INFARMED. Certolizumab Pegol. Relatório de avaliação prévia do medicamento para uso humano em meio hospitalar. 2014.

386. INFARMED. Relatório de Atividades do Sistema Nacional de Avaliação de Tecnologias de Saúde (SiNATS). 2015.

387. INFARMED. Pertuzumab. Relatório de avaliação prévia do medicamento para uso humano em meio hospitalar. 2015.

388. INFARMED. Canacinumab. Relatório de avaliação prévia do medicamento para uso humano em meio hospitalar. 2016.

389. INFARMED. Monitorização das condições de financiamento. 2021. Available from: https://www.infarmed.pt/web/infarmed/entidades/medicamentos-uso-humano/avaliacao-tecnologias-saude/avaliacao-terapeutica-e-economica/monitorizacao.

390. INFARMED. Monitorização do mercado. 2021. Available from: https://www.infarmed.pt/web/infarmed/entidades/medicamentos-uso-humano/monitorizacao-mercado.

391. Pontén J, Rönnholm G, Skiöld P. Pharma Profile Sweden. Pharmaceutical Pricing and Reimbursement Information. 2017.

392. The Dental and Pharmaceutical Benefits Agency TLV. The pharmaceutical market. 2021. Available from: https://www.tlv.se/lakemedel/lakemedelsmarknaden.html.

393. The Dental and Pharmaceutical Benefits Agency TLV. Pricing and reimbursement of medicines. 2020, Available from: https://www.tlv.se/in-english/medicines/pricing-and-reimbursement-of-medicines.html.

394. The Dental and Pharmaceutical Benefits Agency TLV. Types of reimbursement. 2020. Available from: https://www.tlv.se/in-english/medicines/pricing-and-reimbursement-of-medicines/types-of-reimbursement.html.

395. The Dental and Pharmaceutical Benefits Agency TLV. Pharmaceutical reviews. 2020. Available from: https://www.tlv.se/in-english/medicines/pharmaceutical-reviews.html.

396. The Dental and Pharmaceutical Benefits Agency TLV. Annual Report 2020 (Årsredovisning). 2020.

397. Heintz E, Arnberg K, Levin L-Å, Liliemark J, Davidson T. The impact of health economic evaluations in Sweden. Zeitschrift Für Evidenz, Fortbildung Und Qualität Im Gesundheitswesen. 2014;108(7):375-82, doi: 10.1016/j.zefq.2014.09.006.

398. The Dental and Pharmaceutical Benefits Agency TLV. Processing time. 2020. Available from: https://www.tlv.se/in-english/medicines/apply-for-reimbursement/processing-time.html.

399. The Dental and Pharmaceutical Benefits Agency TLV. Apply for reimbursement. 2020. Available from: https://www.tlv.se/in-english/medicines/apply-for-reimbursement.html.

400. The Dental and Pharmaceutical Benefits Agency TLV. Health economics assessment of Sarclisa in multiple myeloma (isatuximab). 2021.

401. The Dental and Pharmaceutical Benefits Agency TLV. Health economic assessment of Strensiq in patients with hypophosphatasia. 2021.

402. The Dental and Pharmaceutical Benefits Agency TLV. Health economic assessment of Zolgensma in spinal muscle atrophy. 2021.

403. The Dental and Pharmaceutical Benefits Agency TLV. General guidelines for economic evaluations from the Pharmaceutical Benefits Board. [accessed 27 September 2021]. Available from: https://www.tlv.se/download/18.2e53241415e842ce95514e9/1510316396792/Guidelines-for-economic-evaluations-LFNAR-2003-2.pdf.

404. The Dental and Pharmaceutical Benefits Agency TLV. Patient participation. 2020. Available from: https://www.tlv.se/om-oss/om-tlv/patientmedverkan.html.

405. Swarting O, Hedman P. Pricing & Reimbursement Laws and Regulations. Sweden. Global Legal Insights. [accessed 23 September

2021]. Available from: https://www.globallegalinsights.com/practice-areas/pricing-and-reimbursement-laws-and-regulations/sweden.

406. Dylst P, Vulto AG, Simoens S. Reference pricing systems in Europe: characteristics and consequences. Generics and Biosimilars Initiative Journal. 2012;1:127-31, doi: 10.5639/gabij.2012.0103-4.028.

407. Ministry of Health and Social Affairs, Sweden. The Health and Medical Service Act (1982:763). 1982.

408. Ministry of Health and Social Affairs, Sweden. Act on Pharmaceutical Benefits (2002:160). 2002.

409. Ministry of Health and Social Affairs, Sweden. Health Care Act (2017:30). [accessed 24 September 2021]. Available from: https://www.riksdagen.se/sv/dokument-lagar/dokument/svensk-forfattningssamling/halso--och-sjukvardslag_sfs-2017-30.

410. Beletsi A, Koutrafouri V, Karampli E, Pavi E. Comparing Use of Health Technology Assessment in Pharmaceutical Policy among Earlier and More Recent Adopters in the European Union. Value in Health Regional Issues. 2018;16:81-91, doi: 10.1016/j.vhri.2018.08.002.

411. Epstein D, Espín J. Evaluation of new medicines in Spain and comparison with other European countries. Gaceta Sanitaria. 2020;34(2):133-40, doi: 10.1016/j.gaceta.2019.02.009.

412. Angelis A, Lange A, Kanavos P. Using health technology assessment to assess the value of new medicines: results of a systematic review and expert consultation across eight European countries. Eur J Health Econ. 2018;19(1):123-52, doi: 10.1007/s10198-017-0871-0.

413. Svensson M, Nilsson FOL, Arnberg K. Reimbursement Decisions for Pharmaceuticals in Sweden: The Impact of Disease Severity and Cost Effectiveness. Pharmacoeconomics. 2015;33(11):1229-36, doi: 10.1007/s40273-015-0307-6.

414. The Dental and Pharmaceutical Benefits Agency TLV. The development of pharmaceutical expenditure in Sweden. 2017.

415. The Dental and Pharmaceutical Benefits Agency TLV. Monitoring drug costs. [accessed 24 September 2021]. Available from: https://www.tlv.se/download/18.607390731743754877745d35/1598963091875/uppfoljning_av_lakemedelskostnader%202020.pdf.

416. The Dental and Pharmaceutical Benefits Agency TLV. Price reduction according to the 15-year rule. 2020. Available from: https://www.tlv.se/lakemedel/prissankning-enligt-15-arsregeln.html.

417. The Swedish Dental and Pharmaceutical Benefits Agency TLV. Reassessment of drugs. 2020. Available from: https://www.tlv.se/lakemedel/omprovning-av-lakemedel.html.

418. The Dental and Pharmaceutical Benefits Agency TLV. Completed reassessment of medicines. 2021. Available from: https://www.tlv.se/lakemedel/omprovning-av-lakemedel/avslutade-omprovningar-av-lakemedel.html?start=20210101-00000000-AM&end=20211231-235959999-PM.

419. The Dental and Pharmaceutical Benefits Agency TLV. Ongoing Reassessment of medicines. 2021. Available from: https://www.tlv.se/lakemedel/omprovning-av-lakemedel/pagaende-omprovningar-av-lakemedel.html.

420. The Office for National Quality Registers (Nationela Kvalitetsregister, NKL). Background to the National Quality Register. 2020. Available from: https://www.kvalitetsregister.se/kvalitetsregister/omnationellakvalitetsregister/bakgrundtillnationellakvalitetsregister.54308.html.

421. The Office for National Quality Registers (Nationela Kvalitetsregister, NKL). National Quality Registries. 2020. Available from: https://www.kvalitetsregister.se/en/kvalitetsregister/omnationellakvalitetsregister.52218.html.

422. EIT Scandinavia. Overview of Health Data Registers in Sweden. 2021. Available from: https://www.eithealth-scandinavia.eu/biobanksregisters/registers/sweden/.

423. The Office for National Quality Registers (Nationela Kvalitetsregister, NKL). Current situation report on National Quality Registers. 2020.

424. Parlamento Europeo, Consejo de la UE. Reglamento (UE) 2021/2282 del Parlamento Europeo y del Consejo sobre evaluación de las tecnologías sanitarias y por el que se modifica la Directiva 2011/24/UE. 2021.

ANNEX 1 Questionnaire on the assessment and funding processes of innovative medicines in Spain

General situation

1. In general, do you consider that changes should be made to the way innovative medicines are assessed in Spain? Please give reasons for your answer

   a. Yes, a number of urgent reforms are needed as soon as possible

   b. Yes, there is a need to think about some long-term reforms

   c. No, the current system is adequate

   d. My knowledge does not allow me to answer the question

2. In general, do you consider that changes should be made to the way in which the price and public funding of innovative medicines is set in Spain? Please give reasons for your answer

   a. Yes, a number of urgent reforms are needed as soon as possible

   b. Yes, there is a need to think about some long-term reforms

   c. No, the current system is adequate

   d. My knowledge does not allow me to answer the question

3. Rate from 0 to 10 the importance of the following challenges in the assessment and funding processes of innovative medicines in the NHS (0 being the minimum and 10 the maximum, and knowing that you have available the option do not know or do not answer: DK/DA)

   ○ Regulatory aspects

   ○ Uncertainty in measuring clinical benefit and/or effectiveness

   ○ Lack of transparency of processes

   ○ Duplicity of evaluations

   ○ Excessive bureaucracy

   ○ Poor timeliness

   ○ Lack of process efficiency

   ○ Lack of equity in access to treatment

   ○ Lack of human resources for the implementation of the process

   ○ Lack of financial resources for the implementation of the process

   ○ Legitimacy of decisions

- ○ Lack of governance in the decision-making process
- ○ Lack of political leadership
- ○ Excessive voluntarism and lack of professionalisation in evaluation processes
- ○ Lack of explicit guidance on economic evaluation
- ○ Other (open answer)

Agents and processes

4. Do you consider that there should be a separation between scientific/technical processes (assessment) and management/policy decisions (pricing and funding)? Please give reasons for your answer

- **a.** Yes, there should be a clear separation between the medicine assessment and the pricing and funding decision
- **b.** Yes, although it may lead to problems of concordance between the two processes
- **c.** No, because the disadvantages outweigh the benefits
- **d.** No, under no circumstances should assessment and pricing and funding be integrated into the same process
- **e.** DK/DA

5. Who do you consider that should lead the technical part of the assessment process in Spain? (Multiple options available)

- ☐ Spanish Agency of Medicines and Medical Devices
- ☐ Commission on the Prices of Medicines and Health Products
- ☐ Directorate-General of the Basic Portfolio of National Health System and Pharmacy Services
- ☐ Spanish Network of Agencies for the Evaluation of Health Technologies and Services of the National Health System (RedETS)
- ☐ A new specific agency in charge of the assessment
- ☐ Other (please specify)

6. What type of actors do you consider that should be involved in the assessment process of a new medicine in Spain? Select all that apply

- ☐ Ministry of Health
- ☐ Clinicians

- ☐ Scientific societies
- ☐ Representatives of patients' associations
- ☐ Representatives of the Autonomous Communities
- ☐ Pharmaceutical industry
- ☐ Others:

7. Do you consider interesting the possibility of a rapprochement meeting including scientific advice between the pharmaceutical laboratory and the decision-makers to bring their positions closer together? Please give reasons for your answer

- **a** Yes, there should be a meeting before the assessment
- **b** Yes, there should be a meeting prior to the pricing decision
- **c** Yes, there could be a rapprochement meeting limited to certain cases (e.g. where there is a lot of uncertainty about results or budgetary impact, or where an innovative clinical trial design has been used)
- **d** I do not consider necessary to have a rapprochement meeting between the two parties
- **e** Other (specify)
- **f** DK/DA

8. What type of actors do you consider that should be involved in the process of pricing and funding a new medicine in Spain? Select all that apply

- ☐ Ministry of Health
- ☐ Ministry of Finance
- ☐ Ministry of Industry
- ☐ Clinicians
- ☐ Scientific societies
- ☐ Representatives of the Autonomous Communities
- ☐ Patient representatives
- ☐ Pharmaceutical industry
- ☐ Others:

9. Of the actors selected above, which ones do you consider that should have a vote in the pricing and funding decision? Select all that apply

Transparency and timing of the process

10. What is your opinion on the current timing of the assessment process for innovative therapies in Spain? Please give reasons for your answer

a. They are reasonable, given their casuistry

b. They are reasonable, but we should try to shorten them

c. They are too long, with major bottlenecks that need to be addressed

d. My knowledge does not allow me to answer the question

11. What is your opinion on the current timing of pricing and funding decisions for innovative therapies in Spain? Please give reasons for your answer

a. They are reasonable, given their casuistry

b. They are reasonable, but we should try to shorten them

c. They are too long, with major bottlenecks that need to be addressed

d. My knowledge does not allow me to answer the question

12. What measures do you consider that would help to speed up assessment times? Rate the following elements on a scale of 0 to 10, where 0 means that it would not help at all, and 10 means that it would help considerably

- ○ Existence of fast-track processes for diseases with significant unmet needs
- ○ Prioritisation of medicines to be assessed, taking into account issues such as the needs of the health system, the severity of the pathology, unmet needs, or the opinion of clinicians and patients
- ○ Tighter timing system, stipulating maximum times for each phase of the process
- ○ Legislative regulation of the maximum time limits for each part of the process
- ○ Linking non-compliance with time limits to certain penalties
- ○ Binding national assessment at regional level
- ○ Other (open answer):

13. Rate from 0 to 10 your degree of agreement with the following points rrelating to the transparency of the current assessment process in the NHS (0 being the minimum and 10 the maximum and DK/DA option)

- ○ The information (except for confidential information), which has been taken into account during the assessment process, and that provided by the actors involved, as well as the final decision, should be published
- ○ There should be transparency on the profile of the members of the assessment committees, as well as their CV and possible conflicts of interest

- ○ A draft of the assessment should be published so that anyone who wishes to comment on it can do so
- ○ A clear and detailed methodological guide on the main issues to be taken into account in the assessment should be published

14. Rate from 0 to 10 your degree of agreement with the following points relating to the transparency of the current pricing and funding decision process in the NHS (0 being the minimum and 10 the maximum and option of DK/DA)

- ○ There should be transparency on the profile of the members of the price and funding decision committees, as well as their CV and possible conflicts of interest
- ○ The information (except for confidential information), which has been taken into account in the decision, should be published
- ○ The criteria taken into account in the decision should be specified in detail
- ○ The relative weight given to each of the criteria taken into account in the decision should be explicitly stated

Documentation

15. What is your opinion on the information currently required from the laboratory to carry out the medicine assessment? Please give reasons for your answer

- **a.** It is sufficient and necessary for a correct assessment to be made
- **b.** It is sufficient, but some obsolete or unnecessary information is also requested that does not benefit the process
- **c.** It is insufficient for a proper assessment to be made and more information should be requested
- **d.** My knowledge does not allow me to answer this question

16. Which of the following elements do you consider should be required from the sponsor laboratory as documentation for the assessment and pricing and funding of a medicine in Spain? (Note that requiring a lot of information may increase access times for medicines)

- ☐ Marketing approval document
- ☐ Scientific documentation supporting the potential therapeutic value of the drug in comparison to the main treatments used in routine practice in Spain
- ☐ Information on therapies that could be substituted with the entry of the medicine into the country (main comparators)
- ☐ Information on the medical need covered by the medicine
- ☐ Incidence and prevalence of the pathology targeted by the therapy

- ☐ Effects on patients' quality of life as a result of drug use
- ☐ Systematic review of the therapeutic arsenal available in Spain for the indication
- ☐ Economic evaluation of the drug (cost-effectiveness or cost-utility)
- ☐ Economic evaluation of the drug (cost minimisation)
- ☐ Time horizon used in the economic evaluation
- ☐ Discount rate used in the economic evaluation
- ☐ Sensitivity analysis of the economic evaluation results
- ☐ Estimated annual market shares in the indicated market segment
- ☐ Quantification of the economic and financial impact (budgetary impact)
- ☐ Information on price, marketing, consumption and funding status in other countries
- ☐ Other therapeutic indications of the drug in Spain
- ☐ If available, Therapeutic Positioning Report of the medicine in other indications
- ☐ Other (please specify):
- ☐ My knowledge does not allow me to answer this question

Clinical assessment

17. **Rate from 0 to 10 your degree of agreement with the following points regarding the clinical assessment of medicines in Therapeutic Positioning Reports (TPRs) (0 being the minimum and10 the maximum, with the option of DK/DA available)**

- ○ The therapeutic value of the assessed medicine should be categorised based on different levels of added therapeutic value over available alternatives
- ○ The quality of the evidence shown by the assessed medicine should be graded
- ○ The medical need to be covered by the assessed medicine should be ranked using a matrix that stipulates different levels of unmet medical needs in the NHS
- ○ A consensus decision must be reached between the industry and the assessors on the choice of the comparator
- ○ The process should follow national public guidelines/procedures endorsed by the scientific community

18. The Therapeutic Positioning Reports (TPRs), recently reformulated by the Ministry of Health, aim to improve the therapeutic and economic evaluation of medicines approved in Spain. Rate from 0 to 10 your degree of agreement with the following statements about the TPRs (0 being the minimum and 10 the maximum, with the option of DK/DA available)

- ○ New TPR methodology aids pricing and funding decisions
- ○ New TPRs are methodologically rigorous
- ○ The new TPR methodology should be homogeneous for all therapeutic alternatives
- ○ New TPRs help manage uncertainty about the evidence for some therapies
- ○ New TPRs will speed up assessment times
- ○ A TPR must be carried out for each new medicine

19. What is your opinion on the times set in the TPRs for clinical (20 days) and economic (10 days) evaluation? Rate from 0 to 10 your degree of agreement with the following statements about the TPRs (0 being the minimum and 10 the maximum, with the option DK/DA available)

- ○ The times set for conducting the clinical assessment are adequate
- ○ The times set for conducting the clinical assessment are adequate and feasible
- ○ The times set for conducting the economic evaluation are adequate
- ○ The times set for conducting the economic evaluation are adequate and feasible

20. Do you consider that there should be a prioritisation on the development of TPRs for medicines?

- **a.** Yes
- **b.** No, the realisation of TPRs should be done according to the starting date of the pricing and funding procedure
- **c.** My knowledge does not allow me to answer this question

21. Since you consider that a prioritisation should be made on the development of TPRs, please specify how much weight each of the following criteria should have in this prioritisation, where 0 is the minimum value and 10 is the maximum value

- ○ Therapeutic position (covers some therapeutics in severe pathology)
- ○ Potential incremental clinical benefit over funded alternatives
- ○ Similar clinical benefit, but better safety profile
- ○ New indications for medicines already funded and marketed
- ○ Potential interest for the NHS
- ○ Other (please specify):

22. How do you consider that drugs for rare diseases (pathologies of low prevalence, less than 5 per 10,000 inhabitants) should be assessed in general in Spain?

a. In the same way as other medicines

b. Using the same process as for other medicines, but with certain different rules that take into account the characteristics of these therapies

c. With a differentiated assessment process and an *ad hoc* committee to assess and set the price of these therapies

d. Other (please specify):

e. My knowledge does not allow me to answer this question

Economic evaluation

23. What is your view on the role of economic evaluation (efficiency or cost-effectiveness) in informing pricing and funding decisions for a new medicine?

a. It must be the fundamental criterion on which the decision is based

b. It should be an important criterion on which the decision is based

c. It should be just one more criterion on which to make a decision

d. Depends on the type of medicine evaluated

e. It should not play a major role in the decision

f. It should have no role in the decision

g. My knowledge does not allow me to answer this question

24. Rate from 0 to 10 your level of agreement with the following points regarding the economic evaluation of innovative therapies (0 being the minimum and 10 the maximum, with the option of DK/DA available)

○ It should be carried out by experts recognised by the scientific community

○ It should be methodologically rigorous, and based on endorsed methodological guidelines

○ The current economic evaluation methods applied in Spain are valid for the evaluation of medicinal products

○ They should incorporate all cost variations beyond pharmacological and variations in healt houtcomes/QALY

○ It should be conducted from the dual perspective of payer and society, i.e. also considering their impact on indirect costs

○ It should incorporate mechanisms for the appropriate management of uncertainty

25. To what extent do you consider that the economic evaluation is currently taken into account when deciding on the price and funding of innovative medicines in Spain?

- **a.** To a large extent, for all cases
- **b.** To a large extent, for most cases
- **c.** To some extent, for some cases
- **d.** To a low extent, only for a few cases
- **e.** Nothing
- **f.** I do not know
- **g.** My knowledge does not allow me to answer this question

26. Do you consider that the current economic evaluation is conducted in a rigorous manner, with established methodological rules and standards for all evaluated medicines? Please give reasons for your answer

- **a.** Yes, the current methodological rules and standards are clear and rigorously applied
- **b.** Yes, the current methodological rules and standards are clear, but they are not rigorously applied
- **c.** No, the standards and methodologies established in the evaluation processes should be more clearly specified and more rigorously applied
- **d.** I do not know
- **e.** My knowledge does not allow me to answer this question

27. Do you think that a threshold of willingness to pay for a drug in Spain (cost-effectiveness threshold or euros per QALY gained threshold) should be considered? Please give reasons for your answer

- **a.** Yes, there should be a single explicit threshold
- **b.** Yes, there should be a range of explicit thresholdss
- **c.** Yes, there should be a single implicit threshold
- **d.** Yes, there should be a range of implicit thresholds
- **e.** There should be no cost-effectiveness threshold
- **f.** I do not have a clear opinion on this issue
- **g.** My knowledge does not allow me to answer this question

28. If you answered yes to the previous question, where do you consider that this threshold(s) should be in terms of euros per quality-adjusted life year (QALY) gained?

29. Do you consider that there should be differentiated thresholds in some cases, such as rare diseases, gene therapies or end-of-life treatments? Please give details of your answer, including which values could be considered

Involvement of patients and scientific societies

30. How do you consider that scientific societies should be involved in the medicines assessment process? Select all that apply

- ☐ They should not participate
- ☐ Being able to comment (in writing) on the draft TPR, prior to its publication
- ☐ Being present during the assessment meetings, bringing their experiences to the debate
- ☐ I do not know
- ☐ My knowledge does not allow me to answer this question
- ☐ Other (please specify)

31. How do you consider that the patient should be involved in the assessment process? Select all that apply

- ☐ They should not participate
- ☐ Being able to comment (in writing) on the draft TPR, prior to its publication
- ☐ Being present during the assessment meetings, bringing their experiences to the debate
- ☐ I do not know
- ☐ My knowledge does not allow me to answer this question
- ☐ Other (please specify)

32. On patient participation in the assessment process, what do you consider the patient profile should be like?

- **a.** Patient with expertise in the pathology for which tthe medicine under assessment is indicated
- **b.** Representative of a patient association related to the pathology for which the medicine under assessment is indicated isindicated
- **c.** Representative of a patient association not related to the pathology for which the medicine under assessment is indicated
- **d.** Member of the society without any pathology
- **e.** None, the patient should not be involved in this phase
- **f.** My knowledge does not allow me to answer this question

33. On patient involvement in the decision on pricing and public funding, how do you consider that the profile of such a patient should be?

- **a.** Patient with expertise in the pathology for which the medicine under assessment is indicated
- **b.** Representative of a patient association related to the pathology for which the the medicine under assessment is indicated
- **c.** Representative of a patient association not related to the pathology for whichthe medicine under assessment is indicated
- **d.** Member of the society without any pathology
- **e.** None, the patient should not be involved in this phase
- **f.** My knowledge does not allow me to answer this question

34. WWhat role do you consider the sponsor laboratory should play in the medicine assessment process?

- **a.** They should not participate
- **b.** Being able to comment (in writing) on the draft TPR, prior to its publication
- **c.** Being present during the assessment meetings, bringing their experiences to the debate
- **d.** Actively participating, e.g. through an approach meeting with the assessing agency
- **e.** Other (please specify)
- **a.** I do not know
- **b.** My knowledge does not allow me to answer this question

P&R decision elements

35. According to your experience or based on your vision, do you consider the following elements to be relevant challenges in the area of medicine pricing and funding? Rate from 0 to 10, where 0 is not relevant at all and 10 is very relevant, with the option DK/DA available

- ○ Public health budgets are insufficient
- ○ There is uncertainty in terms of outcomes and number of patient candidates
- ○ There is a lack of explicit and transparent criteria for decision making
- ○ There is a lack of information systems to monitor results
- ○ The discussion is overly focused on price and not on the value of the medicine
- ○ There is difficulty in implementing innovative financial agreements
- ○ Other (open answer)

36. Currently, the inclusion of medicines in the funding of the NHS is made possible by taking into account the following criteria, set out in article 92 of Royal Legislative Decree 1/2015:

a) Severity, duration and sequelae of the different pathologies for which they are indicated

b) Specific needs of certain groupss

c) Therapeutic and social value of the medicine and incremental clinical benefit of the medicine taking into account its cost-effectiveness

d) Rationalisation of public spending on pharmaceutical benefits and budget impact on the NHS

e) Existence of medicines or other therapeutic alternatives for the same conditions at a lower price orlower treatment cost

f) Degree of innovation of the medicine

Do you agree that the pricing decision should be based solely on these criteria? Please give reasons for your answer

a. Yes, these should be the only criteria to be considered

b. No, only some of these criteria should be taken into account, but not all of them

c. No, only some of these criteria should be taken into account and others not specified in this list should be added

d. No, additional criteria should be taken into account in addition to all of these

e. No, criteria other than those mentioned above should be taken into account

f. I do not know

g. My knowledge does not allow me to answer this question

37. If you answered c) or d) in question 36, should additional criteria be taken into account in the funding decision? Select as many criteria as you consider necessary

☐ Size of the affected population

☐ Patient-reported or perceived drug outcomes

☐ Type of treatment benefit: symptomatic or curative

☐ Duration of treatment

☐ Appropriateness of treatment (oral route, improved adherence, etc.)

☐ New medicine or new indication for an existing medicine

☐ Health costs avoided

- ☐ Social costs avoided (job losses, social services, family care, etc.)
- ☐ Quality of evidence
- ☐ Ethical aspects (justice, solidarity)
- ☐ Contribution to GDP of the pharmaceutical company
- ☐ Other (open answer)

38. Do you consider that a specific weighting should be defined for each of the criteria specified in the Royal Legislative Decree mentioned above?

- **a.** Yes, the specific weight given to each criterion should be made explicit and publicised
- **b.** Yes, a specific or approximate weighting for each criterion should be considered, but only for the internal use of the committee
- **c.** No, in no way should each criterion be associated to a weight
- **d.** I do not know
- **e.** My knowledge does not allow me to answer this question

39. Specify a weighting for the criteria you expect to be considered in pricing and funding. Range from 0 to 10. (If you consider that any of the criteria should not be taken into account, score it with 0)

- ○ Severity, duration and sequelae of the different pathologies for which they are indicated
- ○ Specific needs of certain groups
- ○ Therapeutic and social value of the medicine and incremental clinical benefit of the medicine taking into account its cost-effectiveness
- ○ Rationalisation of public spending on pharmaceutical provision and budgetary impact on the NHS
- ○ Existence of medicines or other therapeutic alternatives for the same conditions at a lower price or lower treatment cost
- ○ Degree of innovation of the medicine
- ○ Size of the affected population
- ○ Patient-reported or perceived drug outcomes
- ○ Type of treatment benefit: symptomatic or curative
- ○ Duration of treatment
- ○ Appropriateness of treatment (oral route, improved adherence, etc.)

- ○ New medicine or new indication for an existing medicine
- ○ Health costs avoided
- ○ Social costs avoided (job losses, social services, family care, etc.)
- ○ Quality of evidence
- ○ Ethical aspects (justice, solidarity)
- ○ Contribution to GDP of the pharmaceutical company
- ○ Other (whichever you put in 38)

40. In which of the following cases do you consider that the innovative medicine could be allowed to have a higher price than the available alternatives? Select as many options as you consider appropriate

- ☐ Substantial improvement in terms of effectiveness and safety
- ☐ Incremental improvement in terms of effectiveness and safety
- ☐ Paediatric medicines
- ☐ Advanced therapies
- ☐ Orphan drugs
- ☐ End-of-life medicines
- ☐ Clinical trials in the Spanish population
- ☐ In no case should there be exceptions
- ☐ My knowledge does not allow me to answer this questiona
- ☐ Other (please specify)

Access to medicines authorised and not marketed in Spain that are pending or excluded from public funding

41. Do you consider that the current system of access to medicines pending marketing or not funded in Spain (compassionate use of investigational medicines, access to medicines under conditions other than those authorised and unauthorised medicines) fulfils its objective?

- **a.** Yes, it is the right one
- **b.** Yes, but it should be improved
- **c.** No, it is too restrictive and can lead to undesirable situations

d. I do not know

e. My knowledge does not allow me to answer this question

f. Other (please specify)

42. What actions would you take to improve the current system of access to medicines pending marketing or unfunded medicines mentioned in the previous question? Open answer

Financial agreements and their monitoring

43. What is your opinion on the financial agreements (expenditure ceilings, risk-sharing agreements, etc.) currently in place in Spain?

a. In general, they are reasonably applied

b. Fewer than desirable are applied

c. They are over-applied, and their use should be limited

d. I know they apply, but their opacity does not allow me to know more details about them

e. DK/DA

f. Other (please specify)

44. Rate from 0 to 10 your degree of agreement with the following points regarding the price and financial agreements for innovative medicines in Spain (0 being the minimum and 10 the maximum, with theoption of DK/DA available)

- ○ It is necessary to reformulate financial relations between the AACC and hospitals to improve access to medicines
- ○ It is recommended that therapies with a high budgetary impact be funded through financial agreements, such as rebates, expenditure ceilings or price-volume agreements
- ○ For therapies with high therapeutic or budgetary uncertainty, alternative financial schemes, such as risk-sharing or evidence-based financial agreements, should be applied
- ○ It would be necessary/appropriate to consider a longer-term vision in the financing of medicines
- ○ Public-private collaboration on priority drugs should be encouraged from the research stages of drug development, similar to that done for COVID-19 vaccines
- ○ Pharmaceutical companies should reimburse a percentage of their annual sales if a certain increase in drug spending in Spain is exceeded

45. Do you consider that earmarked budget funds should be created for the funding of certain therapies?

- **a.** Yes, for innovative medicines
- **b.** Yes, for innovative oncology medicines
- **c.** Yes, for medicines indicated for rare diseases
- **d.** Yes, for advanced therapies
- **e.** No, I am not in favour of the use of earmarked funds
- **f.** My knowledge does not allow me to answer this question
- **g.** Other (please specify):

46. Rate from 0 to 10 your degree of agreement with the following points regarding the monitoring of medicines in Spain (0 being the minimum and 10 the maximum, with the option DK/DA available)

- ○ Current monitoring systems (digital medical records, registers, etc.) are adequate
- ○ Valtermed is a suitable element to follow up therapies
- ○ Valtermed should be used to monitor all innovative therapies
- ○ More monitoring mechanisms need to be introduced to improve the agility and efficiency of funding decisions
- ○ The interoperability of existing monitoring mechanisms needs to be improved
- ○ There is a need for a national medicines monitoring system, building on the different monitoring mechanisms already in place
- ○ In cases where there are doubts about real-life outcomes, the funding of medicines should be linked to monitoring mechanisms

47. How do you consider that the use of Valtermed (information system to determine the therapeutic value in real clinical practice of medicines with a high health and economic impact on the NHS) could be optimised? Open answer

48. Do you consider that funding or positioning decisions should be reassessed on the basis of real-life data? Please give reasons for your answer

- **a.** Yes, for all medicines
- **b.** Yes, but only for those medicines for which the quality of evidence was low at the time of assessment
- **c.** Yes, when there are relevant changes in the baseline conditions (e.g. entry of a new competitor,changes in the price of the drug or alternatives, etc.)
- **d.** Yes, for those medicines with a high budgetary impact

e. No, in any case

f. I do not know

g. My knowledge does not allow me to answer this question

h. Other (please specify)

49. If the answer to the previous question is yes, how often do you consider that such a reassessment should be carried out?

a. Every 6 months

b. Every year

c. Every 2 years

d. Other (indicate period)

e. Without a specific period, but when it is deemed appropriate

f. DK/DA

50. What do you consider should be the objective of the reassessment of a medicine? Select all that you consider to be appropriate

☐ Knowing actual clinical outcomes in patients

☐ Monitor financial agreements, without financial or other consequences

☐ Monitor financial agreements that lead to price changes and/or penalties

☐ Assessing whether to maintain public funding of the medicine

☐ I do not know

☐ My knowledge does not allow me to answer this question

☐ Other (please specify)

ANNEX 2 Entities and persons participating in the questionnaire who agreed to have their participation reflected in the report

Entities	Participants
Spanish Academy of Dermatology and Venereology (AEDV)	Pablo de la Cueva Dobao
Andalusian Agency for Health Technology Assessment (AETSA)	-
Spanish Agency of Medicines and Medical Devices (AEMPS)	-
Alnylam Pharmaceuticals	Javier Ahuir Torres
Health Economics Association (AES)	-
Spanish Association of Gastroenterology (AEG)	Enrique de Madaria Pascual
Spanish Association of Biosimilar Medicines (BioSim)	-
Spanish Association of Generic Medicines (AESEG)	-
Confederation of Associations of Crohn's and Ulcerative Colitis Sufferers of Spain (ACCU)	-
Ministry of Universal Health and Public Health. Valencian Community	José Manuel Ventura Cerdá
General Council of Official Associations of Pharmacists	-
General Nursing Council	Jose Luis Cobos Serrano
Andalusian School of Public Health	Jaime Espín
Farmaindustria	-
Spanish Patients' Forum (FEP)	Andoni Lorenzo Garmendia
Spanish Cancer Patients Group (GEPAC)	Begoña Barragán García
Costa del Sol Hospital Marbella. Málaga	Angeles Perez Aisa
Ramón y Cajal Hospital. Madrid	Agustín Albillos
La Paz University Hospital. Madrid	Pedro Herranz
Marqués de Valdecilla University Hospital. Santander	Javier Crespo García
Puerta de Hierro University Hospital. Majadahonda	Cristina Avendaño Solá
Son Espases University Hospital. Mallorca	-
Aragonese Institute of Health Sciences	Sandra García Armesto
REU+.Catalan Rheumatology League	-
Canary Islands Health Service	Vicente Olmo Quintana
Evaluation Service of the Canary Islands Health Service (SESCS)	Lidia García Pérez
Murcian Health Service	Juan Antonio Marqués Espí
Spanish Society of Health Managers (SEDISA)	José Francisco Soto Bonel
Spanish Society of Haematology and Haemotherapy (SEHH)	Ramón García Sanz
Spanish Society for Family and Community Medicine (semFYC)	Miguel Ángel Hernández Rodríguez
Spanish Society of Primary Care Physicians (SEMERGEN)	-
-	Santiago Alfonso
-	Jonathan Galduf Cabañas
-	Francisco Marí Marí
-	José Luis Sánchez Chorro
-	Carmen Sanclemente Ansó

Carried out by:

Weber

Sponsored by:

abbvie