Proposals for Improving Patient Access to Orphan Medicines

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01
Objective

The key objective of this document is to contribute to achieving guaranteed access to medicines needed by Spanish patients with rare diseases and, in turn, that the Spanish National Health System has a system in place for decision-making which guarantees the technical quality of these decisions and the inclusion of all relevant factors specific to these diseases.

With this document, Farmaindustria aims to positively contribute to align patients' needs, integration of the best technical criteria, participation of the Spanish NHS at all levels (autonomous regions included) and its guaranteed sustainability.

02
Availability of orphan medicines in Spain

Some three million people in Spain suffer diseases which – individually considered – have a very low incidence, with only 5% having some form of potential treatment. Because of their very nature, these are diseases whose handling, diagnosis, and treatment deserve a specialised approach.

Bodies of the European Union recognised this circumstance upon adopting a regulation (Regulation 141/2000) in the year 2000 specific to the so-called "orphan medicines" (OMs), which have, over the last twenty years, increased in number from eight to over one hundred.

Recognition of the characteristics specific to these medicines in Spanish law became established through Royal Legislative Decree 1/2015, Article 3.3 of which provides for the possibility of adopting special measures relating to OMs as regards their manufacture, importation, distribution and dispensation, as well as those measures concerning the economic and fiscal regime of these medicines, in addition to the aforementioned measures.

Indicators for Availability and Time to Patient Access

According to the annual Patients W.A.I.T. (Waiting to Access Innovative Therapies) Indicator report prepared by the IQVIA consultancy for EFPIA (European Federation of Pharmaceutical Industries and Associations), access to OMs in Spain diverges from trends in countries with similar socio-economic environments. The most recent study was conducted with OMs authorised from 2017-2020, with their availability being measured on 31 December 2021. The result shows that in Spain, 40 of every 100 medicines are available, whereas France and Italy have over 70% and in Germany, over 90%.

Availability is even lower for non-oncology OMs (40%), with 60% not included in the reimbursement list. This means that as of December 2021, there are 25 authorised medicines not available in Spain.

The W.A.I.T. indicator report measures the average time it takes for a medicine to be included on the reimbursement list after it receives the European marketing authorisation. More precisely, it measures the average time taken from the Spanish Medicines Agency's (AEMPS) authorisation of a medicine – the time at which a company notifies of its intent to market in Spain – until the medicine is included on the reimbursement list (*nomenclatór*). At year-end 2021, this time had increased to 572 days, meaning that the administrative deadline of 6 months was not met. And this number is even higher for non-oncology medicines at 613 days.

Additionally, 48% of OMs that have received a reimbursement decision are subject to restrictions for the patient population for which they should be available according to the authorised indications. Studies coming from other sources also show a peculiar and restrictive situation in Spain as regards availability of OMs reimbursed by the NHS. This situation may have some effect in terms of improving respect for state-of-the-art science in treatment decisions for these diseases. But this could also trigger other noticeable negative consequences, two of which we will mention.

Firstly, in a global market, it should be highlighted that the amount of OMs rejected for inclusion in the reimbursement system discourages prioritisation of the Spanish market during the launch phase of new products. In fact, 13% of OMs authorised in Europe do not have a national code in Spain. That is to say, market authorisation holders have not notified their intention to market the product in Spain.

Secondly, a slow, complicated process with an unpredictable outcome when it comes to managing the inclusion of an OM into the NHS creates uncertainty among regional healthcare management services and even prescribers, especially in the period immediately following approval of a product by the EMA and prior to a decision on reimbursement. This leads to a scattering of individual resolutions which creates asymmetry in access across different regions, as well as inefficient management.

In order to put the situation on access to OMs into context, the different aspects related to availability of these medicines in Spain should be briefly recapped, differentiating between the five factors which make up the process.

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1. Marketing Authorisation Stage

In Europe, the specific regulation on OMs has had a very positive effect on the development of new treatments. Considering that this designation is not permanent as of December 2022 there are 146 authorised OMs in Europe, of which 123 already have a national code (84%). In 2022 alone, 24 new OMs were authorised out of 52 medicines with new active pharmaceutical ingredients, 41% of the total.

In 2022 alone, 24 new orphan medicines were authorised out of 52 medicines with new active pharmaceutical ingredients

Once a medicine, orphans included, is authorised by EMA, the quality, efficacy and safety requirements are fulfilled, requiring the gathering and submission of information subsequent to the authorisation.

Upon recognition of the importance of these medicines by all regulatory agencies (FDA, EMA, …), and in order to provide faster access to patients, regulatory mechanisms are put in place through special authorisations (conditional, accelerated, exceptional) which should never be perceived as a weakness, but rather as a special characteristic when it comes to taking decisions which have an impact on the access regime of these medicines.

Spain plays an important role in this process through a large investment in clinical trials. According to the Spanish Clinical Studies Registry (REec), in 2022 there were 230 clinical trials registered for OMs (87 of which were for the paediatric population), which makes up 25.4% of

the total conducted in Spain. Taking the phases into account, 55% correspond to Phase I and II clinical trials and another 44% corresponds to Phase III clinical trials. In 96% of the cases, sponsors are pharmaceutical companies. The total number of OM clinical trials in increased by 22.6% in 2021, and has continued to increase in 2022.

These figures cannot be considered anything less than extremely positive for the Spanish NHS given that they imply the early availability of an alternative treatment for patients with rare diseases. Additionally, it entails an opportunity for specialists and the NHS to expand their knowledge of both the natural history of the disease and patient management, as well as new medicines.

According to the Spanish Clinical Studies Registry (REec), in 2022 there were 230 clinical trials registered for orphan medicines

In accordance with Royal Decree 1302/2006, the Spanish NHS provides for Healthcare Centre and Reference Units ("CSURs") and other specialised healthcare centres at its disposal which make it possible to provide specific treatments to patients with rare diseases. This situation, along with the intense participation in clinical trials previously mentioned, better treatment is made possible for patients and, furthermore, a source of experience that should not be underestimated in decision-making phases affecting access to these medicines.

2. Procedure and Financing Criteria

Orphan medicines have specific characteristics by the type of pathology they treat and their epidemiology. However, reimbursement evaluation tends to be carried out through the same, common-practice administrative procedure put in place for the rest of medicines since Spain, unlike other neighbouring countries, does not have a specific pricing and reimbursement procedure for OMs.

It has previously been mentioned that international indicators show that the situation in Spain compares unfavourably with that of neighbouring countries as regards administrative decisions regulating the market launch of these medicines.

W.A.I.T. indicators for a resolution show that the administrative deadline of six months for a resolution provided for by law is often not met. Moreover, the absence of an agile and efficient process triggers the use of alternative channels not intended for this purpose, as is the case with medicines in special situations which in turn leading to greater uncertainty and in some cases, more unequal access – even territorial.

Lastly, the current process has a high level of opacity for stakeholders, which can have a disincentivising effect that could lead to negative consequences for patients, healthcare professionals, and the NHS itself.

3. Assessment of Orphan Medicines

EMA approval determines, by definition, the quality, efficacy and safety of OMs. This should be recognised in the assessment phase for the purposes of pricing and reimbursement decision-making.

Currently, aside from the recent Therapeutic Positioning Report scheme (IPTs), neither patient associations nor experts in the rare disease the medicine is intended to treat participate in any of the processes. The Medicines Assessment Network (RevalMed) hub for rare diseases does not urgently address this need.

By their very nature, OMs have shortcomings as regards the evidence that can be generated during their development and the marketing-authorisation phase:

- The number of patients included in clinical trials due to the limitations presented by the epidemiology of the disease itself.
- Lack of comparators (single-arm studies) as these are most often diseases with no existing therapeutic alternative, unless pharmaceutical compounding or off-label medicines are to be taken into consideration to this end, which is clearly inadvisable and even with less regulatory evidence.

- Submission of data in early stages, given the urgent need to make treatments for rare diseases available.

- Despite the intrinsic nature of these characteristics in OMs, it has been observed that payers regard their results as uncertain, thus hindering their approval.

4. Monitoring Systems and Information Gathering

At present, Valtermed – the Spanish monitoring system for real-world patients receiving treatment, allows for financial agreements to be reached between the Government and stakeholders. Although this has been in use for a relatively short period of time, options for this tool's improvement have already been identified.

Pharmaco-clinical protocols must help in reaching financing agreements on OMs, establishing clinical criteria for the use of OMs, and in accomplishing their purpose as regards predictability and avoiding inequalities among Spanish regions.

5. Medicines in Special Situations

Authorisations in special situations make it possible for a medicine to be made available, on an individual basis, in cases where it is urgently needed, as provided for by Royal Decree 1015/2009, of 19 June 2009, on the regulation of availability of medicines in special situations. Moreover, this allows for real-world experience with OMs to be gained even prior to a decision on reimbursement.

Although this could, in theory, be an alternative channel for the case at hand, at present the chronic delay in reimbursement decision-making puts a strain on a process intended for individual requests, a condition which does not happen when a medicine is intended to cover a therapeutic gap for the entirety of a rare disease. In these situations, it becomes quite complicated for the NHS to balance the management of individual requests with the financing uncertainties and, at the same time, to prevent any significant equity disparities.

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03

Proposals for improving access to orphan medicines

Once the AEMPS grants an orphan medicine's marketing authorisation, it is within the purview of the Ministry of Health to issue a decision on pricing and reimbursement.

Designation as an OM is defined by EU law (Regulation (EC) No 141/2000 of the European Parliament and of the Council, of 16 December 1999). Practical experiences shows that OMs are regarded differently based on what is deemed a necessity by the NHS.
In this document, medicines for therapeutic areas where no alternative treatment is available are viewed as meriting a specific model for the decision-making process on pricing and reimbursement.

This differential approach to access to OMs is a reality in many European countries, as has been laid out in some publications[1] analysing the HTA process, coming to the conclusion that 78% of the 32 European countries, Canada and New Zealand account for OMs differently. Essentially, they recognise that conventional evaluation approaches may not be appropriate for assessing the value of treatments intended for rare diseases.

In another publication[2], a comparison is conducted at the European level on the implementation of different value assessment approaches for OMs, which has contributed to disparities in access for patients of rare diseases.

Therefore, there is overwhelming evidence supporting the convenience of a specific access procedure for these medicines.

It is this line of thought that has inspired the following proposed model, which simply aims to integrate the peculiarities intrinsic to OMs into decision-making, and by no means aims to give a privileged approach

[1] Elena Nicod, Amanda Whittal, Michael Drummond and Karen Facey. *Are supplemental appraisal/reimbursement processes needed for rare disease treatments? An international comparison of country approaches.* Orphanet Journal of Rare Diseases (2020).

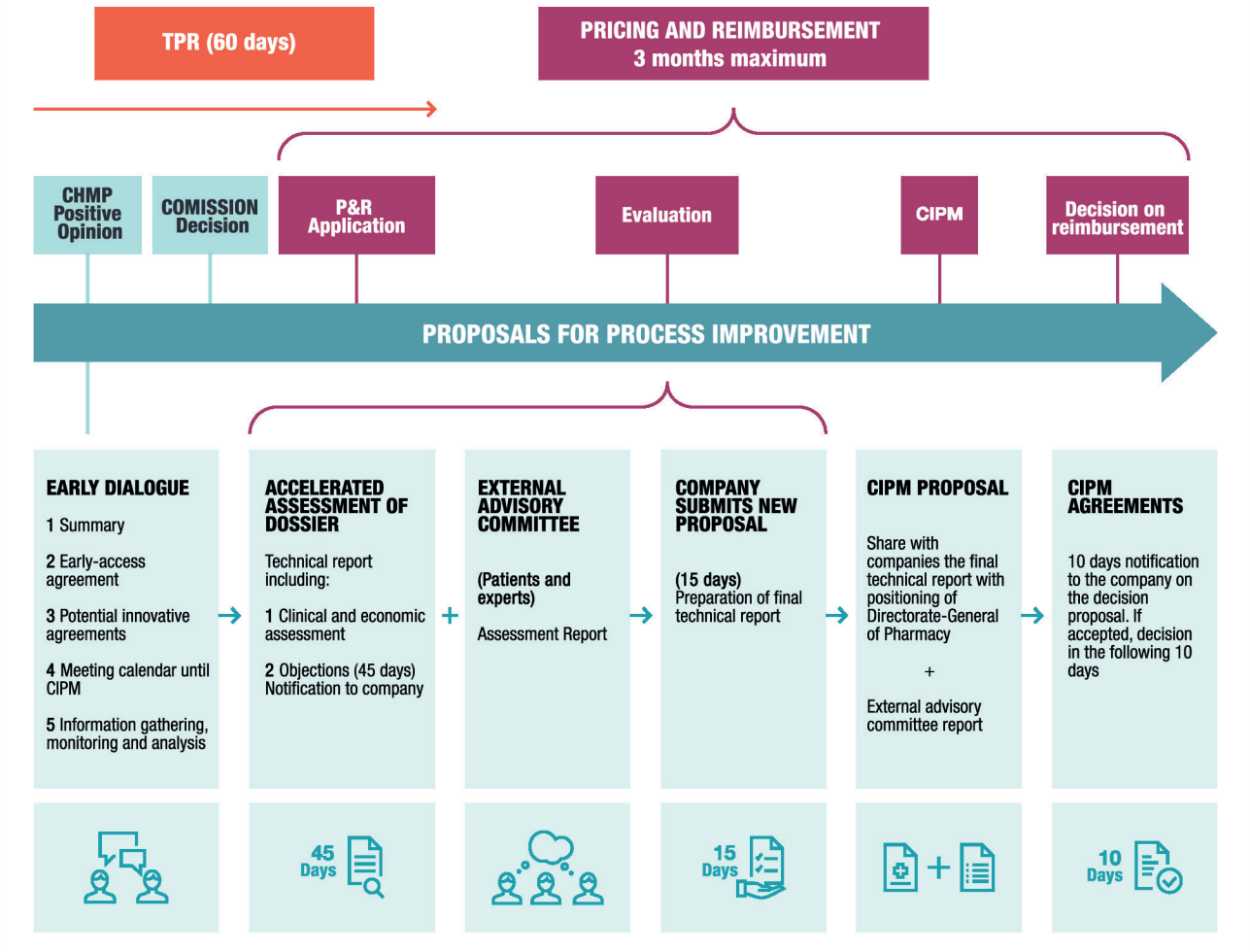
[2] Alessandra Blonda, Yvonne Denier, Isabelle Huys and Steven Simoens. *How to Value Orphan Drugs? A Review of European Value Assessment Frameworks. Frontiers in pharmacology.*

There is overwhelming evidence supporting the convenience of a specific access procedure for these medicines

to OMs over other medicines.

Prior to listing the specific proposals, a diagram is provided which lays out some of the most relevant aspects of the process:

Current Steps in the P&R Process of Orphan Medicines in Spain



First:

From the moment a pharmaceutical company receives a positive opinion from the CHMP (Committee for Medicinal Products for Human Use) for an OM and communicates its intention to market it in Spain, **early dialogue** will be established with the Ministry of Health. To this end, a calendar of meetings will be outlined through to the time at which the dossier is submitted to the CIPM (Inter-Ministerial Medicine Prices Committee), which would give predictability, trust, and transparency to the assessment process.

The content of this early dialogue would be:

- Consideration for the unmet medical need, value proposition of the product, epidemiology & patient profiles, and the estimated budgetary impact.

- Agreement on early access for exceptional cases provided for by law in accordance with Royal Decree 1015/2009, of 19 June 2009, on the regulation of availability of medicines in special situations. Hence, potential provisional agreements (conditional upon the final result of the procedure).

- For cases in which it is possible, prior consideration of the potential innovative approaches with shared-risk agreements or those of an economic-financial nature.

Second:

An **accelerated reimbursement assessment procedure** is proposed to provide a comprehensive response to the unmet medical need which these medicines are intended to treat.

The procedure must lead to decisions being made in a period of time not exceeding three months from the beginning of the pricing and reimbursement procedure.

Adoption of specific financing criteria for orphan medicines is proposed

Third:

As has been indicated in the context analysis covered in this document, OMs have characteristics which cover their scientific, clinical and economic assessment.

With the aim of guaranteeing that this particularity is included in the decision-making process, and without wishing to address other provisions aimed at regulating clinical and pharmaco-economic assessment of the pricing and reimbursement dossiers, the setting up of a specific **external Advisory Committee** is proposed. This committee, through involvement of scientific societies, patient associations, and experts of renowned prestige in the given disease, will guarantee that none of the varying specific circumstances presented by these medicines are omitted from the analysis.

This committee will prepare a report with their findings, which shall be submitted to the CIPM along with all other documentation and could also occasionally provide and specific counsel should the CIPM so require.

Fourth:

Adoption of **specific financing criteria** for OMs is proposed. These should take into account the repeatedly mentioned particularities of these medicines and should be designed with the aim of balancing the added value to patients with the Government's concern over covering their cost.

In addition to being public, they should also go beyond the simple approach based on budgetary impact and cost effectiveness as criteria for reimbursement, given that the Royal Legislative Decree 1/2015 itself includes other criteria, such as the severity of the disease, needs of certain collectives, and the social value of the medicine.

As laid out in the document of findings prepared by the Health Technology Assessment Agency of the Carlos III Health Institute on criteria for the reimbursement of OMs, the efficiency criteria are not, and must not, be the sole criteria for determining the public reimbursement of these medicines. New funding instruments are being launched and different multi-criteria decision-making frameworks are being discussed to help reconcile social preference and the sustainability of the NHS[3].

This proposed approach should be the basis for possible reviews of pricing and reimbursement conditions which, lawfully, should be executed based on the use of real-world outcomes as well as with new available evidence in mind subsequent to their inclusion in the pharmaceutical provision.

[3] Zozaya N., Villoro R., Hidalgo Á., Sarria A. Criterios de financiación y reembolso de los medicamentos huérfanos. Agencia de Evaluación de Tecnologías Sanitarias (AETS). Instituto de Salud Carlos III - Ministerio de Economía y Competitividad.

Fifth:

Establish criteria for defining **longitudinal funding models,** which take into account the reality of pricing and reimbursement not as just a one-off decision, but rather as an evolving flexible and versatile feedback process, which will reduce the effect of the medicine's sophistication on the healthcare authorities' annual accounting system.

To this end:

- In situations of epidemiological uncertainty - and thus uncertainty in the budgetary impact a new OM could entail for the Government - evaluate financial agreements such as expenditure caps, discounts based on required volume, or similar.

- In situations of uncertainty regarding the efficacy offered by the new OM, evaluate a staggered payment scheme over a period of time or conditional on reaching efficacy milestones over time.

Sixth:

As regards the **analysis of clinical evidence** conducted in the financing procedure, accepting the particularities and limitations of OMs is strongly suggested as regards the level of data which, by their very nature, they can provide. In Europe, it could prove impossible to recruit the necessary number of patients in an acceptable period of time in order to reach the level of significance usually sought for other medicines. On the other hand, the absence of comparators in the case of the first treatment in a specific disease is quite frequent, and in these cases the comparator chosen could simply be a supplementary treatment.

Having accepted this, adoption of transparent, specific, and strict evaluation criteria – tailored to the peculiarities of these medicines – determining what should be included in the value dossier is proposed.

In this clinical assessment it is important to include all available information, including evidence that could have been provided after the conduction of trials in the authorisation phase.

Seventh:

The pharmaco-economic assessment should include the particular

Accepting the particularities and limitations of orphan medicines is strongly suggested as regards the level of data which, by their very nature, they can provide

nature of the diseases that these medicines treat and which, as a general rule, have a higher social burden resulting from the personal care needs, decreased labour productivity and patients' quality of life & that of those close to them. Therefore, in the pharmaco-economic analyses there is a need to move beyond the oversimplified approach of budgetary impact and integrate the societal standpoint, in addition to indirect costs.

It would be difficult for the majority of OMs to be cost-effective based on the traditional threshold for acceptability used for medicines intended for prevalent diseases. On the other hand, society does not feel that the efficiency criterion should prevail when substantiating reimbursement and access to an orphan or ultra-orphan medicine, citing reasons such as social fairness and equality, among others[4].

There is a primary methodological guide to economic assessment applied to OMs, developed in collaboration with the RADEEV expert group, which should be taken into consideration as a model in the pharmaco-economic assessment of OMs[5].

Moreover, the Spanish Society of Hospital Pharmacy's Rare Diseases and Orphan Medicines Working Group (ORPHAR-SEFH) has developed a guidebook for the development of orphan medicines' assessment reports which employ the MCDA (Multi-Criteria Decision Analysis) method[6].

At regional level, the Catalan Healthcare Service (CatSalut) was selected to launch a pilot project intended to test MCDA usefulness. The positive results obtained through the use of this framework led to MCDA being included in the 2016-2020 Health Plan for Cataluña[7].

It is critical that the therapeutic assessment is carried out first, followed by the economic assessment.

Eighth:

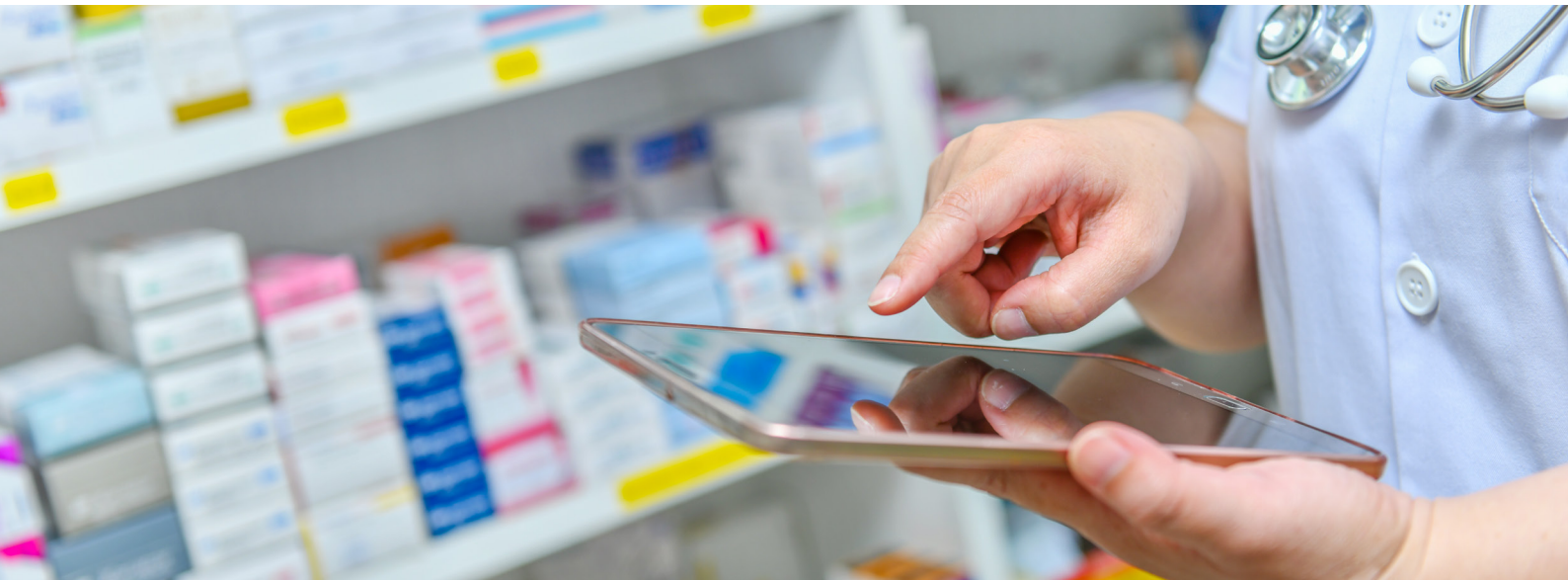
With reference to **Therapeutic Positioning Reports,** this document does not aim to make a broad proposal thereof nor in relation to the most recent and relevant modifications to its procedure adopted over

[4] Drummond MF, Wilson DA, Kanavos P, Ubel P, Rovira J. *Assessing the economic challenges posed by orphan drugs*. Int J Technol Assess Health Care. Winter 2007;23(1):36-42.

[5] https://weber.org.es/publicacion/guia-metodologica-de-evaluacion-economica-aplicada-a-medicamentos-huerfanos.

[6] https://gruposdetrabajo.sefh.es/orpharsefh/images/stories/documentos/Manual_MCDA_Orphar_SEFH_060520.pdf.

[7] Guarga, L., Badia, X., Obach, M. et al. *Implementing reflective multicriteria decision analysis (MCDA) to assess orphan drugs value in the Catalan Health Service (CatSalut)*. Orphanet J Rare Dis 14, 157 (2019). https://doi.org/10.1186/s13023-019-1121-6.



recent months.

However, it is strongly recommended that considerations relating to any previously carried out **evidence analysis** be taken into account in the preparation of the TPRs.

Should the inclusion of economic assessments in Therapeutic Positioning Reports continue to be considered, which is particularly difficult for this kind of medicines as there is a frequent lack of available comparators, it is recommendable that they be made once the price of reimbursement is determined in order to avoid unnatural theoretical economic assessment scenarios.

Ninth:

As a result of many of the arguments used in this document, it seems obvious that the gathering of effectiveness data is particularly relevant to this kind of medicines.

For this reason, **information gathering systems** on treatment effectiveness should:

- Be optimised and automized to avoid manual data management and to incorporate all potential opportunities which result from the implementation of the upcoming Strategy on Digital Health, with the clear objective being to serve as a basis for a robust structure for gathering real-world evidence.
- Facilitate data entry to doctors, reviewing the need for the number of variables collected; improve technological supports; and review follow-up times in order to avoid irrelevant exhaustiveness.
- Be able to share information with clinicians, patients and pharmaceutical companies, bringing transparency to the tool.
- Support approval of analysis results by a follow-up committee comprising the Government and the Marketing Authorisation Holder. Where necessary, seek technical advice from a clinical disease expert.
- With the aim of increasing the level of evidence available, data could be gathered during the authorisation procedures in special situations (mentioned in the first proposal of this document) during the period spanning from approval of the European Commission to the decision on reimbursement, which could provide more certainty in the decision on pricing and reimbursement using real-world data available in Spanish population.
- Include data originating from patients with rare diseases that are not receiving treatment, with a view to being able to gain the strongest evidence possible on the natural history of the disease to compare with data gathered from clinical studies, thus avoiding omission of beneficial effects of the treatments under consideration.

“Should the inclusion of economic assessments in Therapeutic Positioning Reports continue to be considered it is recommendable that they be made once the price of reimbursement is determined

- Similarly, for purposes of comparing real-world effectiveness, collect data of patients with rare diseases being treated with other therapeutic options, including other non-authorised treatments or supplementary alternatives for the disease being studied.

Tenth:

When deciding on adoption of **pharmaco-clinical protocols**, these should:

- Be based on tools for the effective management of OMs.
- Provide for the particularity of OMs as a basis for strengthening clinical criteria of PROs (Patient Reported Outcomes), which are especially relevant given the difficulty of conducing clinical trials for these diseases using the usual efficacy parameters[8].
- Include clinical disease experts in the protocol development.
- Be simple, agile, easily applied, and available prior to the agreement on reimbursement, being consistent with this agreement.
- Be dynamic, gradually including the developments recorded in the management of the disease.

Eleventh:

An OM must be subject to a special reimbursement framework, and should therefore not be included in the Reference Price System together with other medicines which lack these peculiarities.

[8] Katy Benjamin, Margaret K Vernon, Donald L Patrick, Eleanor Perfetto, Sandra Nestler-Parr, Laurie Burke. *Patient-Reported Outcome and Observer-Reported Outcome Assessment in Rare Disease Clinical Trials: An ISPOR COA Emerging Good Practices Task Force Report.* Value Health. Jul-Aug 2017;20(7):838-855. doi: 10.1016/j.jval.2017.05.015.

Twelfth:

OMs and the diseases they target, due to their low prevalence and level of specialisation, entail treatment in reference centres or CSURs which – together with the territorial concentration of epidemiological incidences resulting from some of these diseases' genetic predisposition – suggests that a specific economic-compensation process be approved by the Inter-Territorial Council of the NHS, with the aim of providing equitable healthcare assistance among Spanish regions created by these medicines.

> **An orphan medicine must be subject to a special reimbursement framework**

04

List of abbreviations

AEMPS	Spanish Medicines Regulatory Agency *Agencia Española de Medicamentos y Productos Sanitarios*
CIPM	Inter-Ministerial Medicine Prices Commission *Comisión Interministerial Precios de los medicamentos*
CHMP	Committee for Medicinal Products for Human Use *Comité de Medicamentos de Uso Humano*
CSUR	*Centros, Servicios y Unidades de Referencia*
EMA	European Medicines Agency Agencia Europea del Medicamento
FDA	U.S. Food and Drug Administration *Administración de Alimentos y Medicamentos de los Estados Unidos*
HTA	Health Technology Assessment
MCDA	Multi-Criteria Decision Analysis *Análisis de Decisión Multi-Criterio*
PROs	Patient-Reported Outcome Measure
REEC	Spanish Clinical Studies Registry *Registro Español de Estudios Clínicos*
RevalMed	Medicines Assessment Network *Red Evaluación de Medicamentos*
NHS	National Health System
TPR	Therapeutic Positioning Report *Informe de Posicionamiento Terapéutico (IPT)*
Valtermed	Registry system for collecting real-world clinical data through a web-based tool to reduce the uncertainty associated with new therapies and the benefit observed in clinical practice *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*

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