Analysis of the THERAPEUTIC POSITIONING REPORTS 2013-2022*

*Analysis of the Therapeutic Positioning Reports initiated between 2013 and March 2022 and with a publication date prior to 13/05/2022.

Report elaborated by:

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the working group of:

aelmhu
asociación española de laboratorios de medicamentos huérfanos y ultrahuérfanos

and collaboration of:

LASKER

POSITIONING THERAPEUTIC REPORTS

- The sustainability of the National Health System (NHS) is essential for its medium and long term survival. Because of the limited resources, the efficient use of the NHS includes the selective public reimbursement of drugs. For this reason, after the marketing authorization of a new drug, a decision process on its public financing is initiated taking into account its "therapeutic utility" or "positioning" in the pharmaceutical provision, that is, its effectiveness compared to other available alternatives, its efficiency and the budgetary impact which would cause.

- In this context, on May 21, 2013, the so-called "Therapeutic Positioning Reports" (IPT - because of its Spanish acronym) were born in the Interterritorial Council of the National Health System (CISNS - because of its Spanish acronym), with the consensus of the Autonomous Communities (AA.CC.), the Spanish Agency for Medicines and Health Products (AEMPS - because of its Spanish acronym) and the General Directorate for the Common Portfolio of the National Health System and Pharmacy Services (DGCCSYF - because of its Spanish acronym), and approved by the Permanent Commission of Pharmacy (CPF - because of its Spanish acronym).

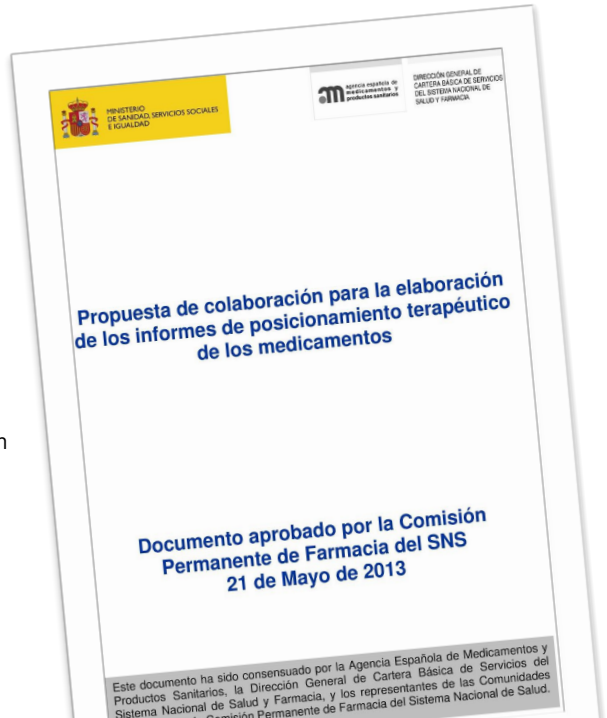
MINISTERIO DE SANIDAD

agencia española de medicamentos y productos sanitarios

Source: Spanish Agency for Medicines and Health Products. General Directorate for the Common Portfolio of the National Health System and Pharmacy Services. Proposal of collaboration for the elaboration of the Therapeutic Positioning Reports. May 21, 2013. Available in aemps.gob.es.

IPT ELABORATION

Thus, the "Proposal for collaboration for the elaboration of the Therapeutic Positioning Reports of medicines" was published. It defines a network evaluation system through the Therapeutic Positioning Coordination Group (GCPT - because of its Spanish acronym) - coordinated by the AEMPS and with the representation of the DGCCSYF and the CC.AA.-, whichpurpose is the preparation of reports based on scientific evidence as a tool for NHS price and reimbursement decision.


MINISTERIO DE SANIDAD, SERVICIOS SOCIALES E IGUALDAD

DIRECCIÓN GENERAL DE CARTERA BÁSICA DE SERVICIOS DEL SISTEMA NACIONAL DE SALUD Y FARMACIA

Propuesta de colaboración para la elaboración de los informes de posicionamiento terapéutico de los medicamentos

Documento aprobado por la Comisión Permanente de Farmacia del SNS 21 de Mayo de 2013

Este documento ha sido consensuado por la Agencia Española de Medicamentos y Productos Sanitarios, la Dirección General de Cartera Básica de Servicios del Sistema Nacional de Salud y Farmacia, y los representantes de las Comunidades

Source: Spanish Agency for Medicines and Health Products. General Directorate for the Common Portfolio of the National Health System and Pharmacy Services. Proposal of collaboration for the elaboration of the Reports of Therapeutic Positioning of the medicines. May 21, 2013. Available in aemps.gob.es.

THE PROCESS FRAMED IN THE 2013 PROPOSAL IS DIVIDED IN TWO PHASES:

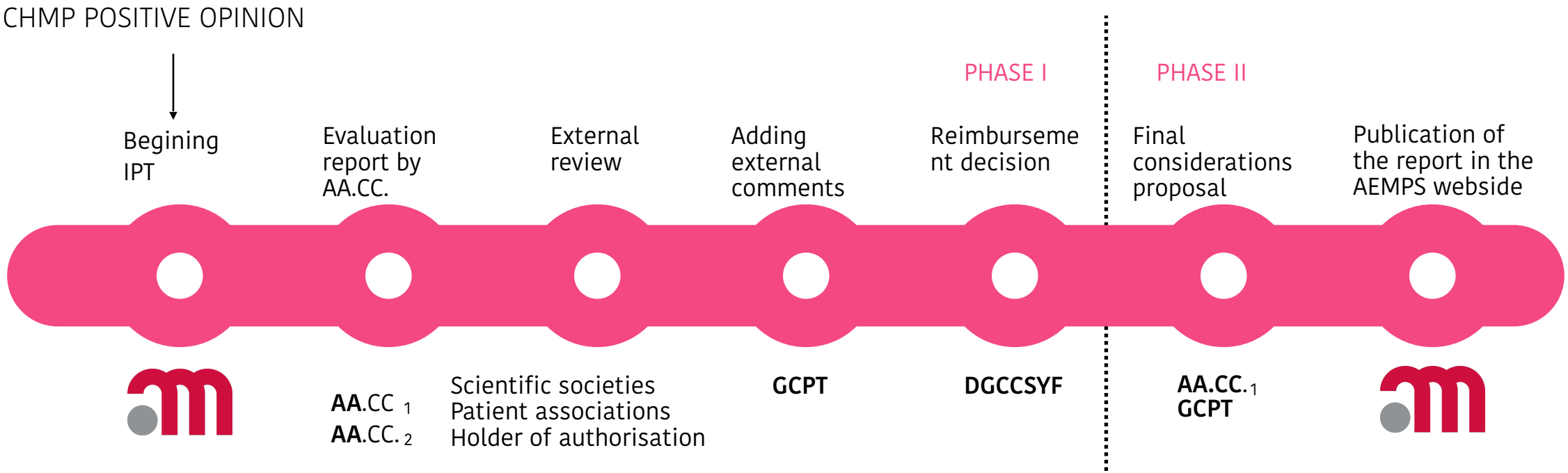
PHASE I: EVALUATION OF EFFECTIVENESS AND SAFETY

- The elaboration of the IPT (start of Phase I) begins when the medicine obtains the positive opinion of the Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency and after the laboratory communication of its intention to market the medicine in Spain. The first report is prepared by the AEMPS and, a posteriori, discussed with one or more Autonomous Communities through teleconferences. Once the draft is agreed, external associations can provide observations and comments, such as Scientific Societies, Patient Associations and the holder of the authorization himself.
- Once all the external contributions have been done, the GCPT includes them in the report. Phase I ends sending the report to the DGCCSYF for the reimbursement decision.

PHASE II: PROPOSAL OF FINAL CONSIDERATIONS

- One of the CC.AA. that has participated in the previous phase makes a proposal of final considerations on the use of the drug and sends it to the GCPT.
- Finally, the report is published on the AEMPS website (public and accessible).

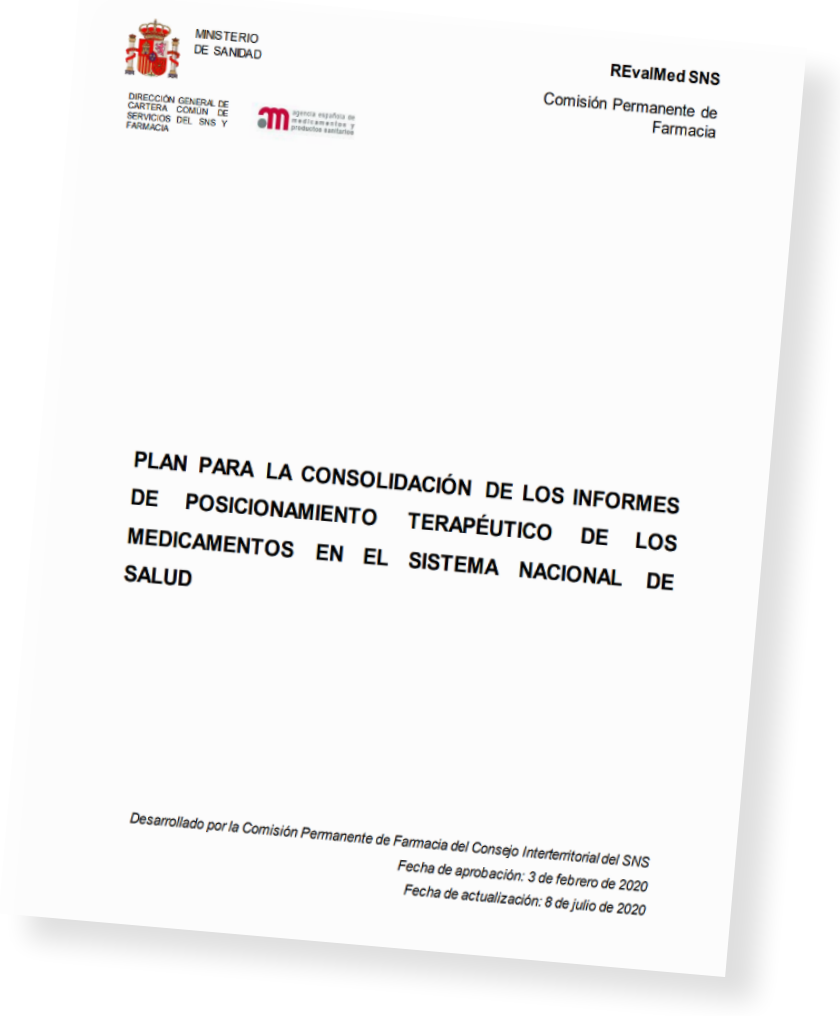
PROCESS OF ELABORATION OF AN IPT BY THE COORDINATING GROUP OF THERAPEUTIC POSITIONING (GCPT)



Source: Spanish Agency for Medicines and Health Products. General Directorate for the Common Portfolio of the National Health System and Pharmacy Services. Proposal of collaboration for the elaboration of the Reports of Therapeutic Positioning of the medicines. May 21, 2013. Available in aemps.gob.es.

REvalMed

- In 2020, after 7 years performing IPT following the mentioned process and a total of 337 reports made*, the CPF considered necessary to update it based on the learning acquired over the years.
- During these years, the need for new IPT has increased considerably, mainly due to IPT of new indications. This growth has caused a delay in the elaboration of the reports, taking up to 40 months in some cases from the beginning of the IPT until the sending of the report to the DGCCSYF.
- Likewise, in the process elaborated in 2013 there were no prioritization criteria guiding the beginning of the reports. Commonly, second indications were established as non-priority causing problems in access when the drug was already in hospitals.
- The new update, published on February 3, 2020, called "Plan for the consolidation of the Therapeutic Positioning Reports of Drugs in the National Health System", includes methodological changes such as the work on nodes through a newly developed Network called REvalMed and the inclusion of economic evaluation.


MINISTERIO DE SANIDAD

DIRECCIÓN GENERAL DE CARTERA COMUN DE SERVICIOS DEL SNS Y FARMACIA

REvalMed SNS

Comisión Permanente de Farmacia

PLAN PARA LA CONSOLIDACIÓN DE LOS INFORMES DE POSICIONAMIENTO TERAPÉUTICO DE LOS MEDICAMENTOS EN EL SISTEMA NACIONAL DE SALUD

Desarrollado por la Comisión Permanente de Farmacia del Consejo Interterritorial del SNS
Fecha de aprobación: 3 de febrero de 2020
Fecha de actualización: 8 de julio de 2020

*Taking into account IPT for new products and for new indications.

Source: Permanent Commission of Pharmacy. Ministry of Health. Plan for the consolidation of the Reports of Therapeutic Positioning of Medicines in the National Health System. February 3, 2020 (Updated: July 8, 2020). Available in mscbs.gob.es

The goal of the REvalMed evaluation network, which replaces the GCPT described in the 2013 Plan, is to draft the IPT. Thus, it is divided into a Coordinating Group and three different teams with specific functions.

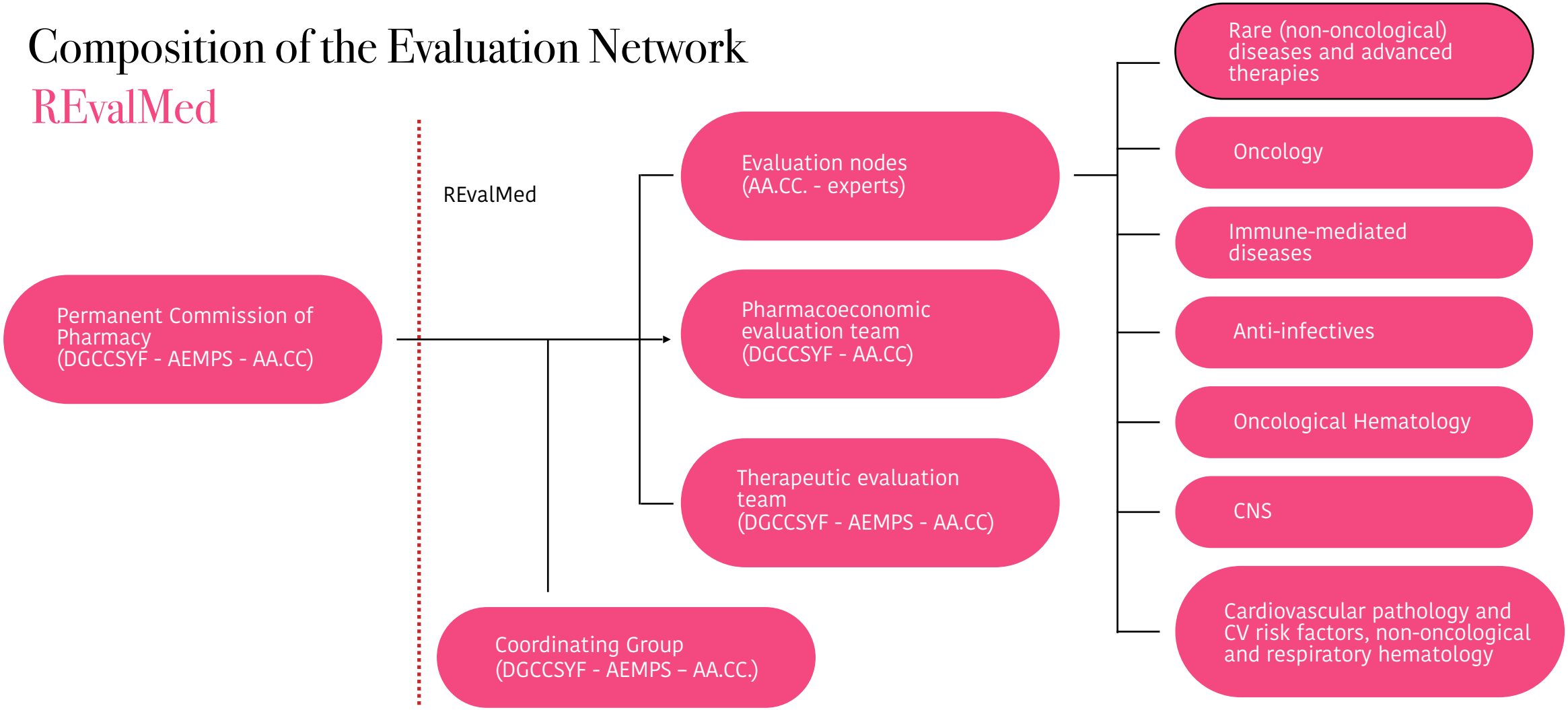
TEAMS:

- **"Therapeutic evaluation team", which elaborates the IPT therapeutic sections. It includes members of the AEMPS and the DGCCSYF, and it can be supported by the AA.CC. This team starts and develops the first draft of the IPT, with a maximum time of 20 working days per report.**
- Once the draft of the therapeutic evaluation has been finalized, the "**Pharmacoeconomic Evaluation Team**", which includes members of the DGCCSYF and can be also supported by the AA.CC, carries out the economic evaluation, with a maximum time of 10 working days per report.
- Subsequently, the different "**Evaluation Nodes**" created, review the draft of the IPT prepared by the previous teams and make their comments and contributions in 30 calendar days. The nodes include expert managers and clinicians appointed by some AA.CC., which will coordinate the node for 2 years.
- Finally, the **Coordinating Group** approves the elaborated report. The Group members are the Quality and Drugs Head of the DGCCSYF, the Head of the Drugs for Human Use Department of the AEMPS, the Coordinators of the evaluation nodes and Representatives of the AA.CC. that are not coordinating nodes. Other responsibilities of the Coordinating Group are identifying, prioritizing and approving the IPT to be developed.

Source: Permanent Commission of Pharmacy. Ministry of Health. Plan for the consolidation of the Reports of Therapeutic Positioning of Medicines in the National Health System. February 3, 2020 (Updated: July 8, 2020). Available in mscbs.gob.es

Composition of the Evaluation Network

REvalMed



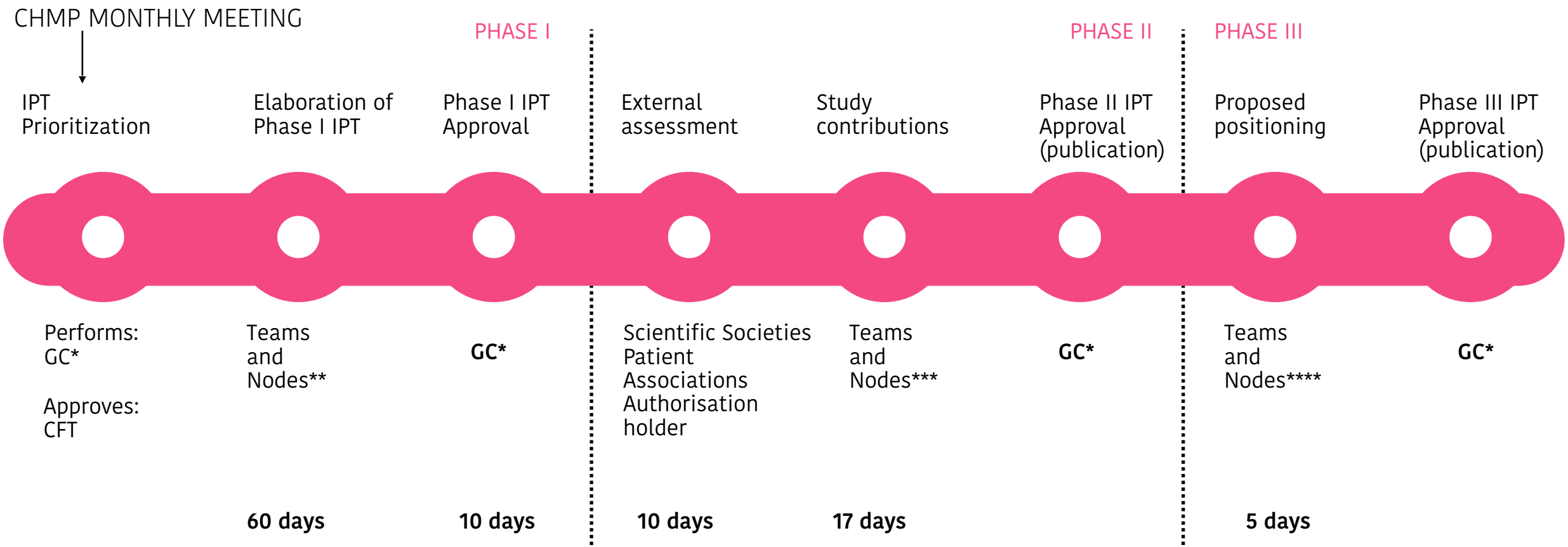
Source: Permanent Commission of Pharmacy. Ministry of Health. Plan for the consolidation of the Reports of Therapeutic Positioning of Medicines in the National Health System. February 3, 2020 (Updated: July 8, 2020). Available in mscbs.gob.es

Methodology

- **Prioritization of IPT: The new methodology includes the prioritization of IPT by the Coordinating Group.**
  - After the monthly meeting of the CHMP, the Coordinating Group will propose to the CPF the prioritization of the IPT according to the prioritization matrix described in the Plan. This matrix includes criteria such as covering an unmet need, having a clinical benefit or an incremental safety profile with respect to therapeutic alternatives, if it is a new indication or the general interest for the NHS regarding the drug.
- **Preparation of the first draft of the IPT through the three teams discussed above. The IPT is discussed and approved at the meeting of the Coordinating Group obtaining the IPT in Phase I.**
- Sending IPT in Phase I to external agents (scientific societies, patient associations and laboratories whose active substances are mentioned in the IPT) so that they can issue their contributions in a maximum of 10 working days.
  - The Therapeutic and Pharmacoeconomic Evaluation Teams review and update the IPT draft in a maximum of 10 working days.
- **The corresponding evaluation node reviews the document in 7 working days, and, once reviewed, the Coordinating Group discusses for the approval of the IPT, which will be renamed "Phase II IPT" and will be public. Phase II IPT is the basis to develop a reimbursement resolution for the product by the DGCCSYF.**
- Once the reimbursement resolution is determined by the DGCCSYF, the drug positioning is incorporated in the report. This is carried out jointly between the 3 teams, within a period of 5 working days. Finally, the Coordinating Group approves the document that is renamed "Phase III IPT".

Source: Permanent Commission of Pharmacy. Ministry of Health. Plan for the consolidation of the Reports of Therapeutic Positioning of Medicines in the National Health System. February 3, 2020 (Updated: July 8, 2020). Available in mscbs.gob.es

Process of elaboration of an IPT by REvalMed



Source: Permanent Commission of Pharmacy. Ministry of Health. Plan for the consolidation of the Reports of Therapeutic Positioning of Medicines in the National Health System. February 3, 2020 (Updated: July 8, 2020). Available in mscbs.gob.es

***GC**: Coordinating Group (because of its Spanish acronym)

****Temas and Nodes:** Therapeutic evaluation team (20 days) and Pharmacoeconomic evaluation team (10 days). Assessment by the corresponding Evaluation Nodes (30 days). The Evaluation Nodes are chosen by the Head of Quality and Drugs and the Head of Drugs of UH.

***** Temas and Nodes:** Therapeutic evaluation team and Pharmacoeconomic evaluation team (10 days). Assessment by the corresponding Evaluation Nodes (7 days).

****** Temas and Nodes:** Therapeutic evaluation team, pharmacoeconomic evaluation team and coordinator and co-coordinator of the corresponding Nodes.

REvalMed Highlights

- **New criteria to improve the performance** of this tool, a key factor in the rational use of drugs and the incorporation of innovations in the National Health System.
- Incorporation of **networking**.
- Incorporation of **pharmacoeconomic evaluation**.
- Incorporation of items for the **prioritization of IPTs**.
- **Limitation of the time required for each phase** in order to achieve a quality pharmaceutical service tailored to the needs of Spanish patients.

METHODOLOGY
Aelmhu report

Report Methodology (2013-2022)

Analysis of the Briefing Notes of the Therapeutic Positioning Coordination Group and REvalMed Coordinating Group meetings from June 2013 (first published meeting) to March 2022 (meeting held March 31, 2022) was performed following the following methodology:

01 Review the Briefing Notes by compiling the information present for all drugs in the above-mentioned period.

02 Check with official sources which of these drugs have orphan designation and gather information on the most relevant dates:

- **A** Date on which the drug obtained a positive opinion from the CHMP.
- **B** Date on which the drug obtained EMA marketing authorization (MA).
- **C** Date on which AEMPS announces that it starts working on the IPT.
- **D** Date on which the AEMPS announces the agreement to send the IPT to the General Directorate for the Common Portfolio of Pharmacy
- **E** Date on which the IPT is published on AEMPS website
- **F** Funding status and date on which the drug is funded by the SNS.

03 With the above information collected, the following KPIs have been calculated:

- **A** Months from the start of the IPT to obtaining the MA from the EMA.
- **B** Months from IPT start to agreement on its submission to the General Directorate for the Common Portfolio of the National Health System and Pharmacy Services
- **C** Months from its submission to the General Directorate for the Common Portfolio of the National Health System and Pharmacy Services until its publication*.
- **D** Months from IPT start to its final publication.
- **E** Months from IPT publication to its funding by the NHS (OD).

04 KPIs calculated have been reflected in this report. The graphs of the timings correspond to the average time of IPTs started in a specific year, in order to be able to see their annual evolution.

*Contemplated all IPTs published with publication date prior to May 13, 2022.

Note: Only IPTs for NEW PRODUCTS have been analyzed (IPTs for new indications have not been taken into account).

RESULTS

IPT initiated during the period 2013-2022*

415

IPTs initiated for new products between 2013 and March 2022

122

Orphan drugs IPTs (29%)

112

IPTs pending to be sent to General Directorate for the Common Portfolio of Pharmacy and to be published

36

Orphan drugs IPTs

36

IPTs sent to General Directorate for the Common Portfolio of Pharmacy and pending publication

13

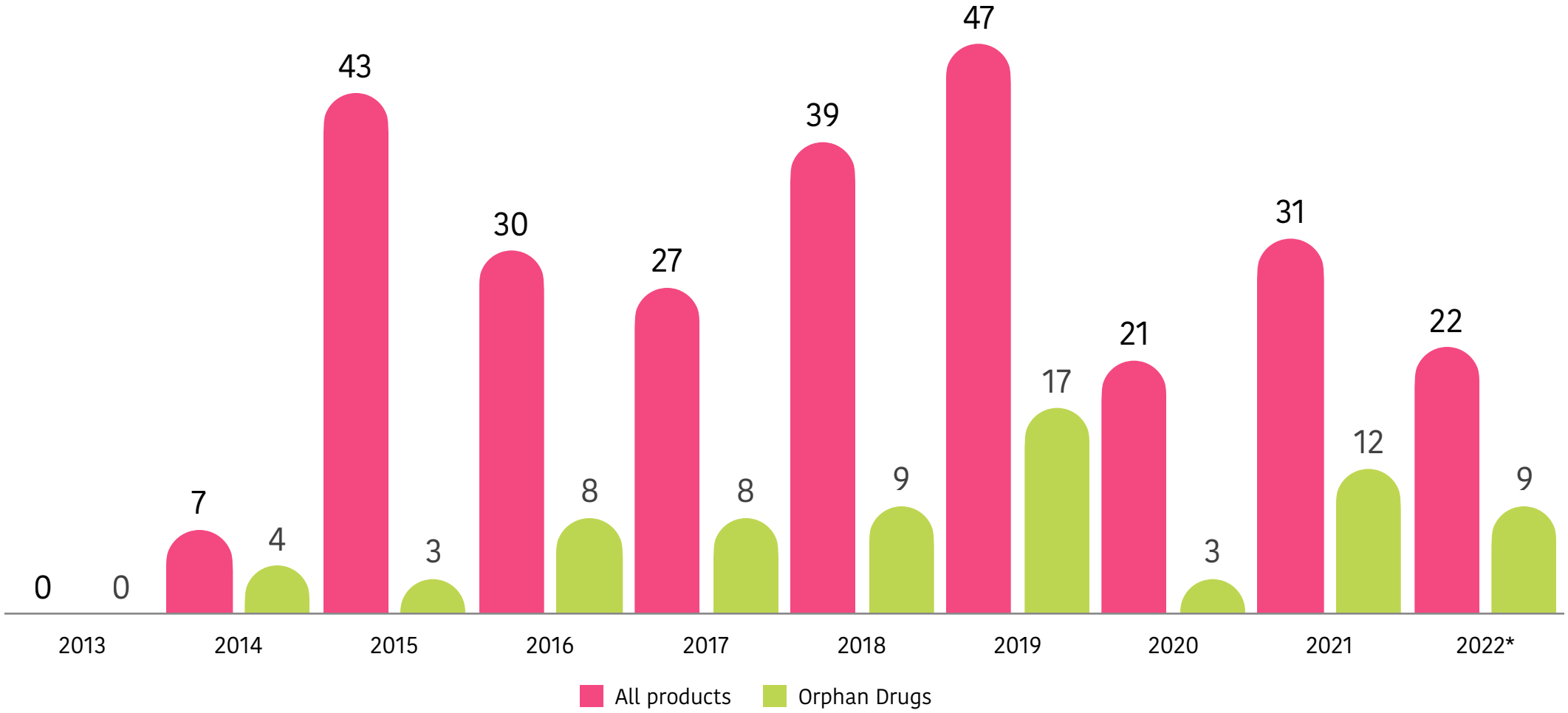
Orphan drugs IPTs

40%

Of the IPTs initiated during the 2013 - March 2022 period on orphan drugs have not yet been published.

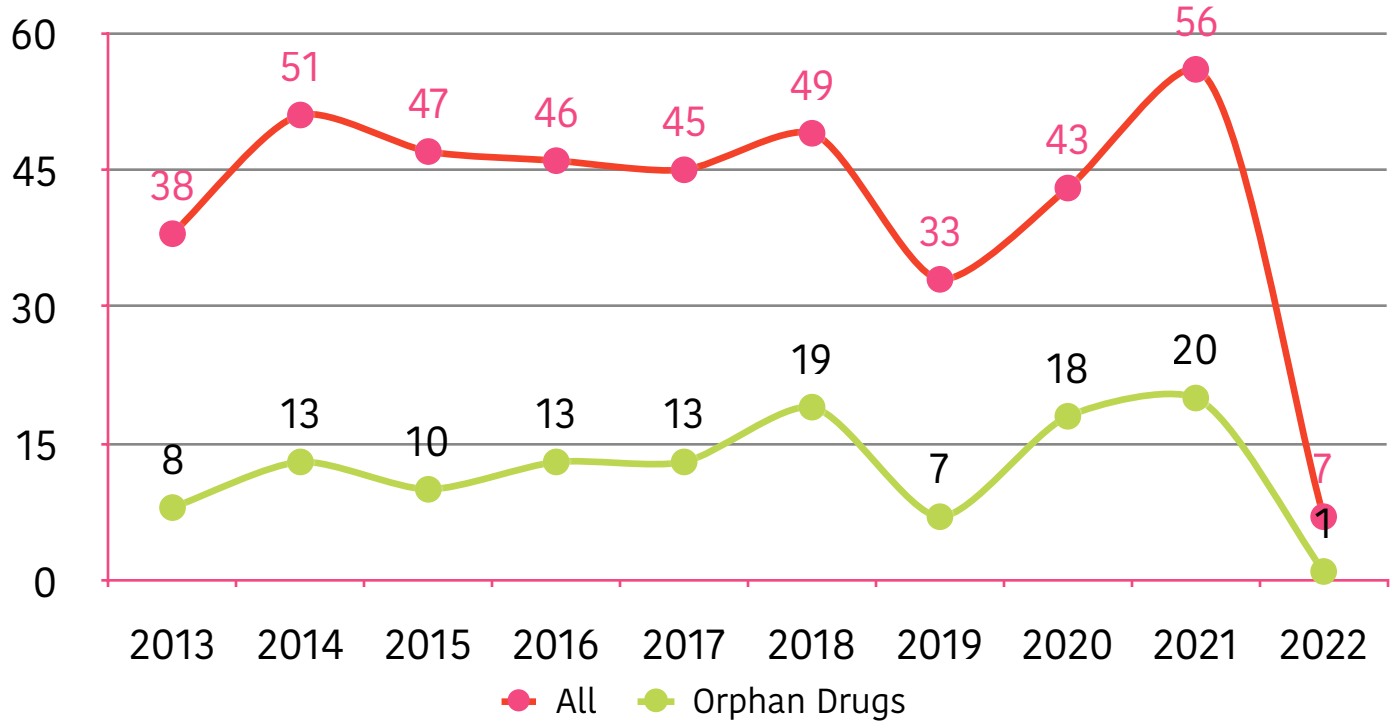
* Revised IPT started prior to March 2022 and published up to May 13, 2022.

IPT of new products published during 2013-2022*



* Revised IPT published up to May 13, 2022.

Number of new IPT started by year 2013-2022*



- In total, the IPT procedures of 415 new productos have been started during 2013 and march 2022. 29% of them were of Orphan drugs (122).
- The number of new IPT started by year increased a Little bit in 2021, especifically 30% in relation to 2020.
- The number of new IPT for Orphan Drugs increased a 90% in 2018 in relation to 2015, and since then it has remained more or les constant, except for the year 2019, when a very significant decrease was of 63 in relation to 2018.

* Revised IPT started prior to March 2022

Analysis of the average time since the start of IPT until EMA authorization

- The IPT is initiated approximately 1 or 2 months before EMAMarketing Authorization (MA), once the producto have obtained a positive answer from CHMP
- Between 2013 and 2021, the average time since the start of the IPT and EMA MA was of 1,2 months, 1,1 in case of Orphan Drugs
- Just in 4 cases, the start of an Orphan Drug IPT was delayed by more tan one year since EMA MA, and it occured with products that obtained MA between 2011 and 2012.

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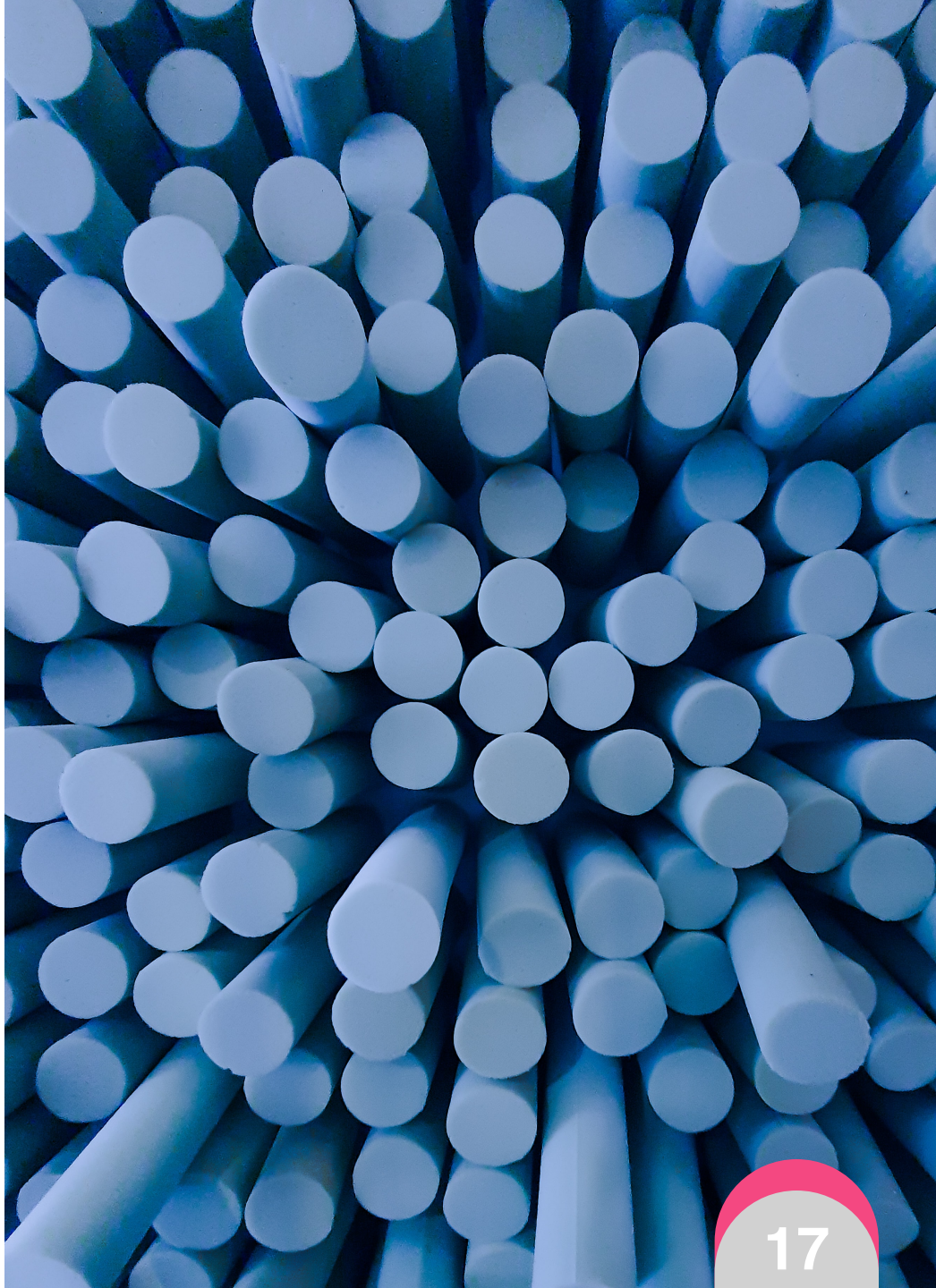
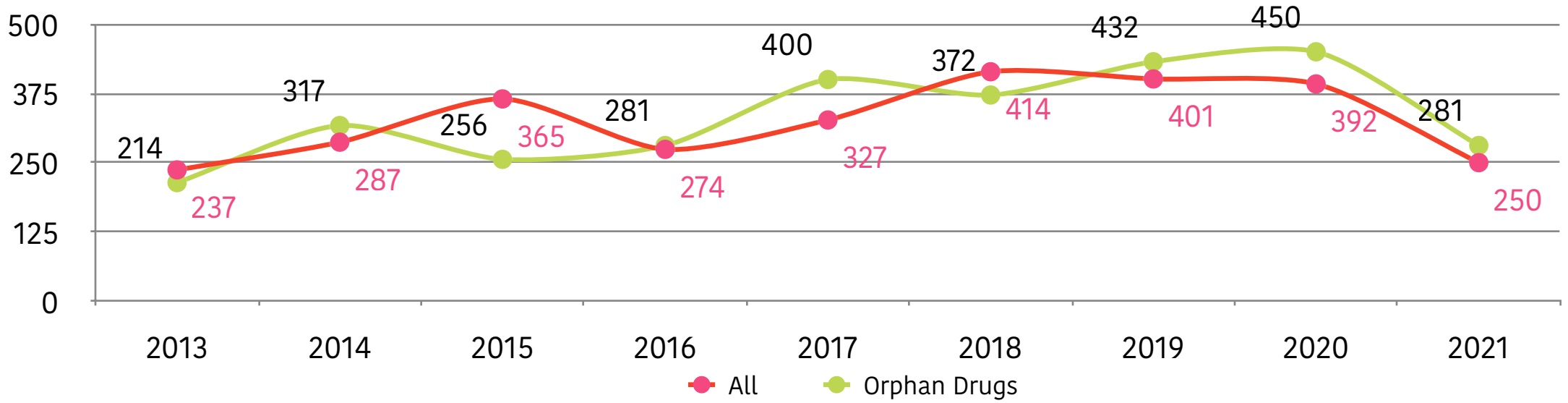


Analysis of the average time between the start and its delivery to General Directorate for the Common Portfolio of the National Health System and Pharmacy Services

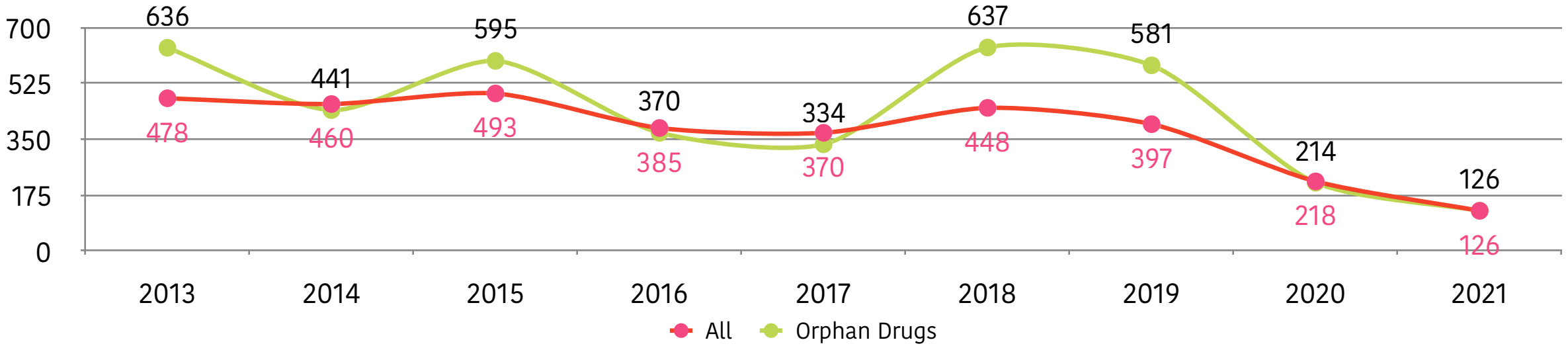


- IPT started on 2022 don't appear in the graphic, because none of the 7 IPT started on march from this year were sent General Directorate for the Common Portfolio of the National Health System and Pharmacy Services nor published
- Besides, data from 2021 are not representative because, of the 56 IPT started, just 4 (7%) have been published. In case of Orphan Drugs, of the 20 IPT started, just 3 have been published (15%).*
- The average time between the start of the IPT and its delivery to General Directorate for the Common Portfolio of the National Health System and Pharmacy Services increases during 2013-2020.
- The average of time of Orphan Drugs is mantained in the same line than all products, with a Little increased from 2019.

Note: Sampe of each year included the average between the start day and the date of its publication of the IPTs started during that year

* Revised IPT published up to May 13, 2022.

Analysis of the average time between the IPT delivery to General Directorate for the Common Portfolio of the National Health System and Pharmacy Services and its publication



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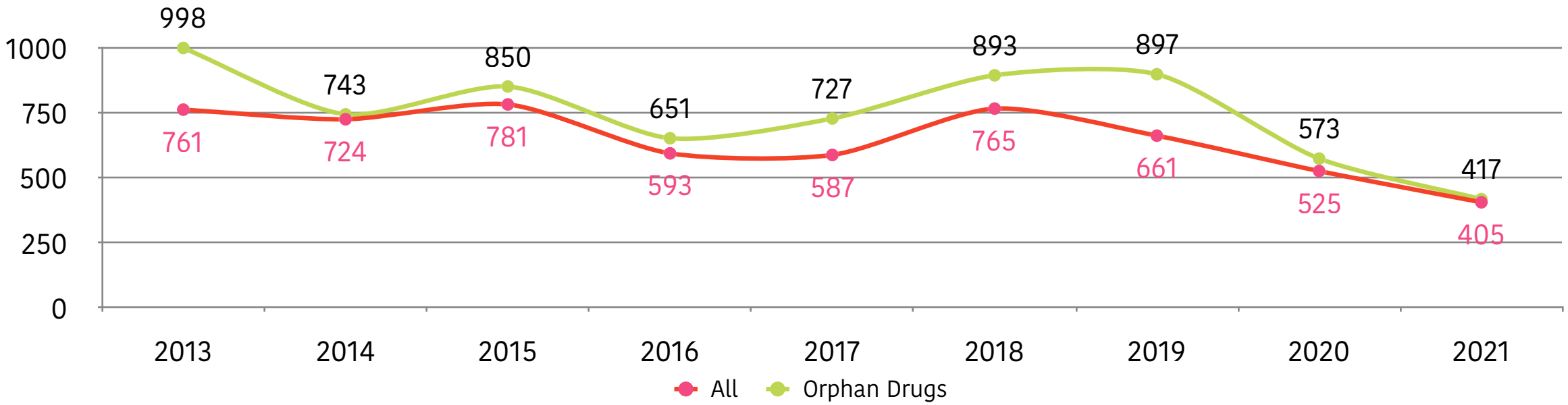
- Besides, data from 2021 are not representative because, of the 56 IPT started, just 4 (7%) have been published. In case of Orphan Drugs, of the 20 IPT started, just 3 have been published (15%).*
- In general, during 2013-2020 the average time between the IPT delivery to General Directorate for the Common Portfolio of the National Health System and Pharmacy Services and its publication is higher in the case of Orphan Drugs
- Of the 4 IPT started on 2021 that have been published, 75% of them were of Orphan Drugs, with an average of 4.2 months between their submission to the Common Portfolio and their publication.

Note: Sampe of each year included the average between the start day and the date of its publication of the IPTs started during that year

* Revised IPT published up to May 13, 2022.

Analysis of the average time between the start and publication of IPT



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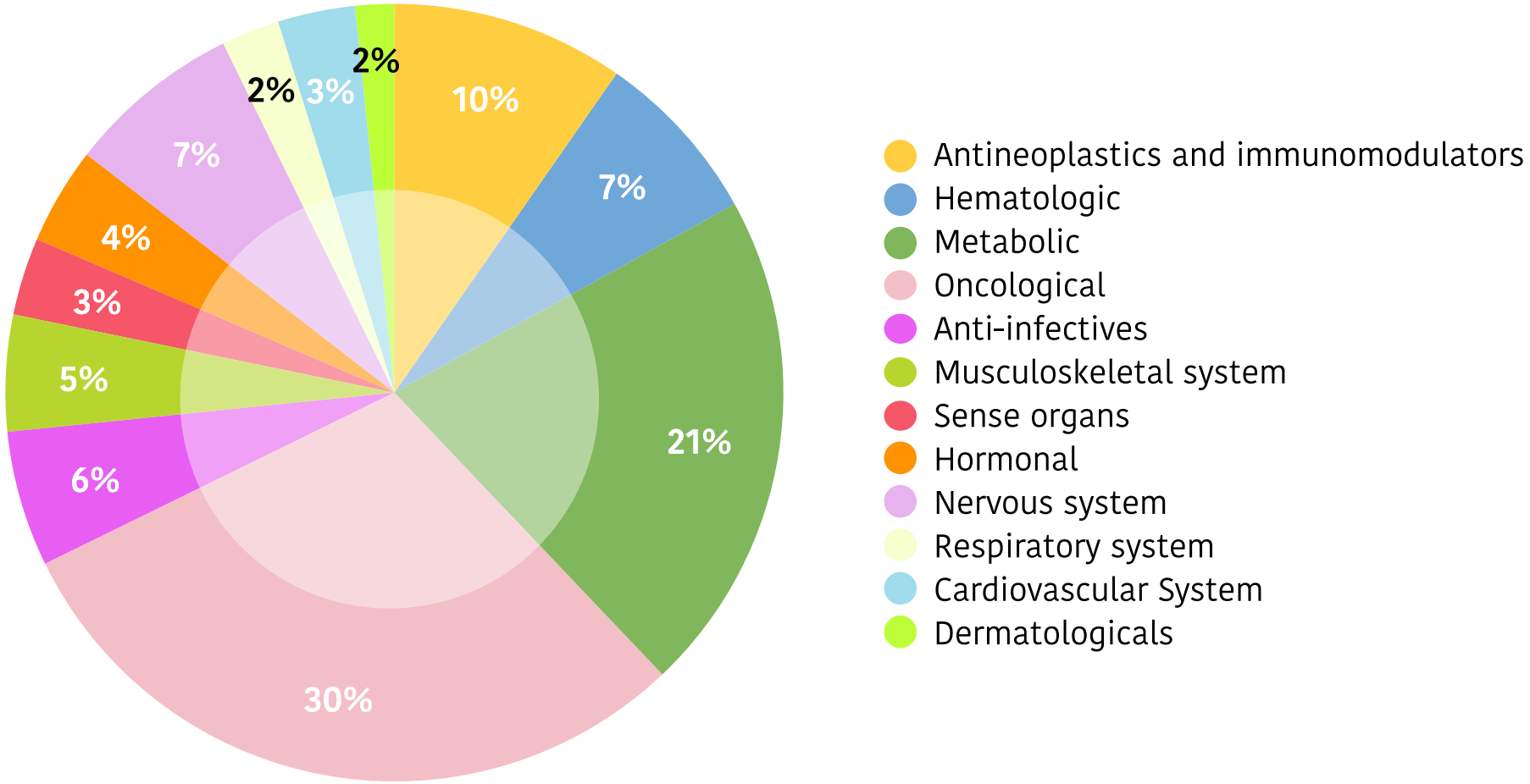
- Besides, data from 2021 are not representative because, of the 56 IPT started, just 4 (7%) have been published. In case of Orphan Drugs, of the 20 IPT started, just 3 have been published (15%).*
- As well, of the 43 IPT started on 2020, just 14 were published (32%), 3 of them were Orphan Drugs IPT, so of the 18 Orphan Drugs IPT started on 2020, just a 17% were published, with an average of time of 473 days (19 months approximately). *
- The average time since the start of IPT and its publication during 2013-2021, is higher for Orphan Drgus than the sample of all products. For example, in 2019, a difference of 236 days (8 monts) is observed between both groups.

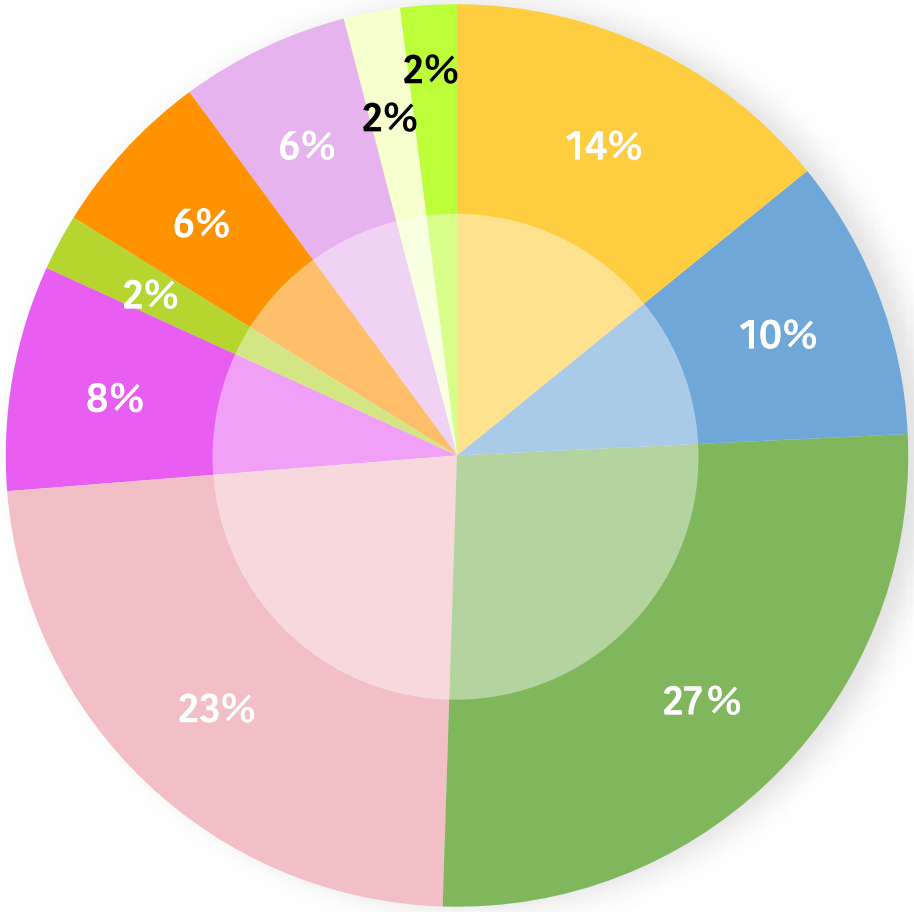
Note: Sampe of each year included the average between the start day and the date of its publication of the IPTs started during that year

* Revised IPT published up to May 13, 2022.

Analysis by therapeutic área of Orphan Drugs IPT

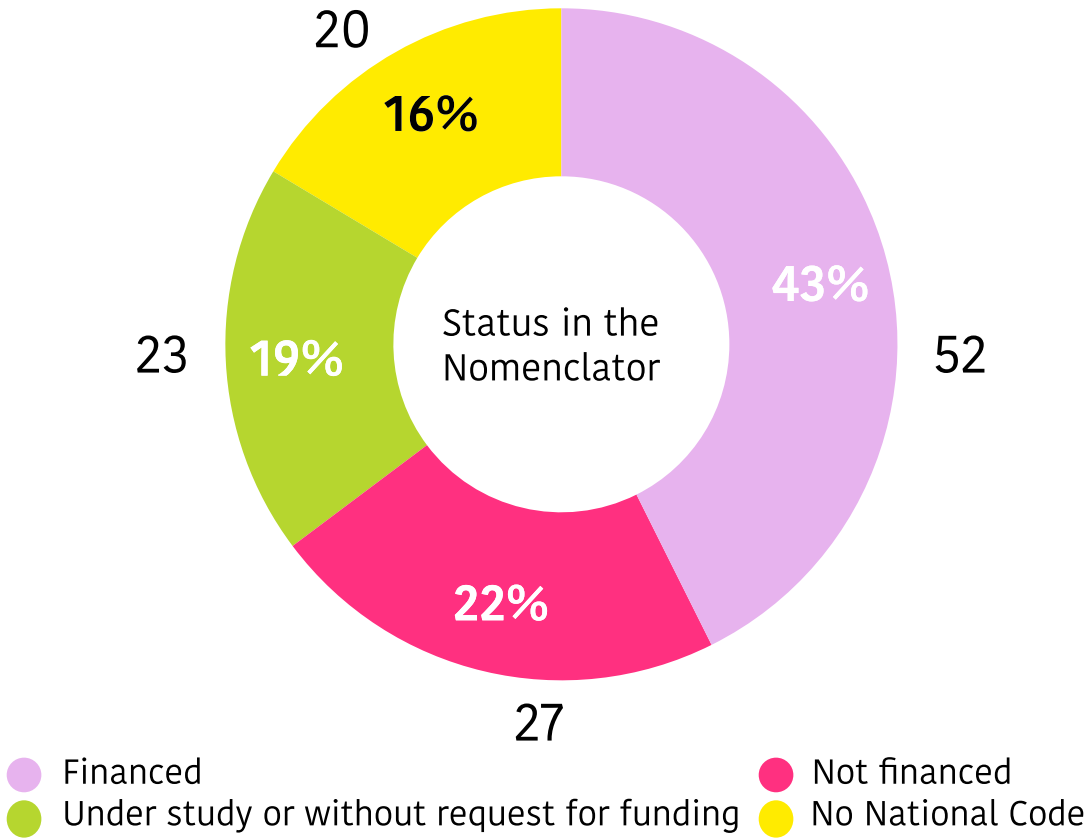


Analysis by therapeutical area of Orphan Drugs IPT that don't have IPT published *



* Revised IPT published up to May 13, 2022.

Analysis of the reimbursement state of Orphan Drugs IPT started between 2013-2022 *



- In 38 of the 52 Orphan Drug IPTs funded by National Health System (73%), the OD ones was funded before the IPT publication. In this case, the difference between funding and publication of IPT was of 78 days of average (2,6 months).
- In 9 of them (17%), the OD ones were funded later than the publication of their IPT, beeing the average of 487 days (16,2 months).
- Out of 52 Orphan Drugs with positive funding, the remining 5 don't have IPT published (4 of them haven't sent the IPT to General Direction of the Portfolio Services of the Naciontal Health System).
- Out of 27 not funded by resolution, 3 don't have the IPT published (two of them haven't sent the IPT to General Direction of the Portfolio Services of the Naciontal Health System).
- Out of 23 Orphan Drugs under study, just 1 has its IPT published.

*Revised IPT with start date until March 2022

Analysis of Orphan Drugs with GENESIS report without IPT published

Commercial name	Laboratory	Status
Defitelio	Gentium	Without National Code
Kaftrio	Vertex	Funded
Libmeldy	Orchard Therapeutics	Under study or without funding request
Pomalidomide Celgene	Celgene	Without CN

- Out of 49 Orphan Drugs without IPT published, just 4 of them has the report of GENESIS group.
- Of these 4, just one is funded (25%), two don't have National Code (50%) and the other one is under study or without funding request.

Source: Informes de Evaluación con Metodología Programa MADRE. GENESIS-SEFH

IPT in Advanced Therapies with Orphan designation (OD)

100% of advanced therapies OD with MA have their IPT started

58% (7) IPT published*

592 days (20 months) of average time between start date and their publication

4 IPT haven’t been sent to General Direction of the Portfolio Services of the Naciontal Health System, out of 5 IPT pending of publication

* Revised IPT published up to May 13, 2022.

IPT started as a pilot according to the new REvalMed procedure Plan (October 2020-2022)

13 new IPTs of new products started eith the new procedure 6 OD (46%), 2 of them are TT.AA.

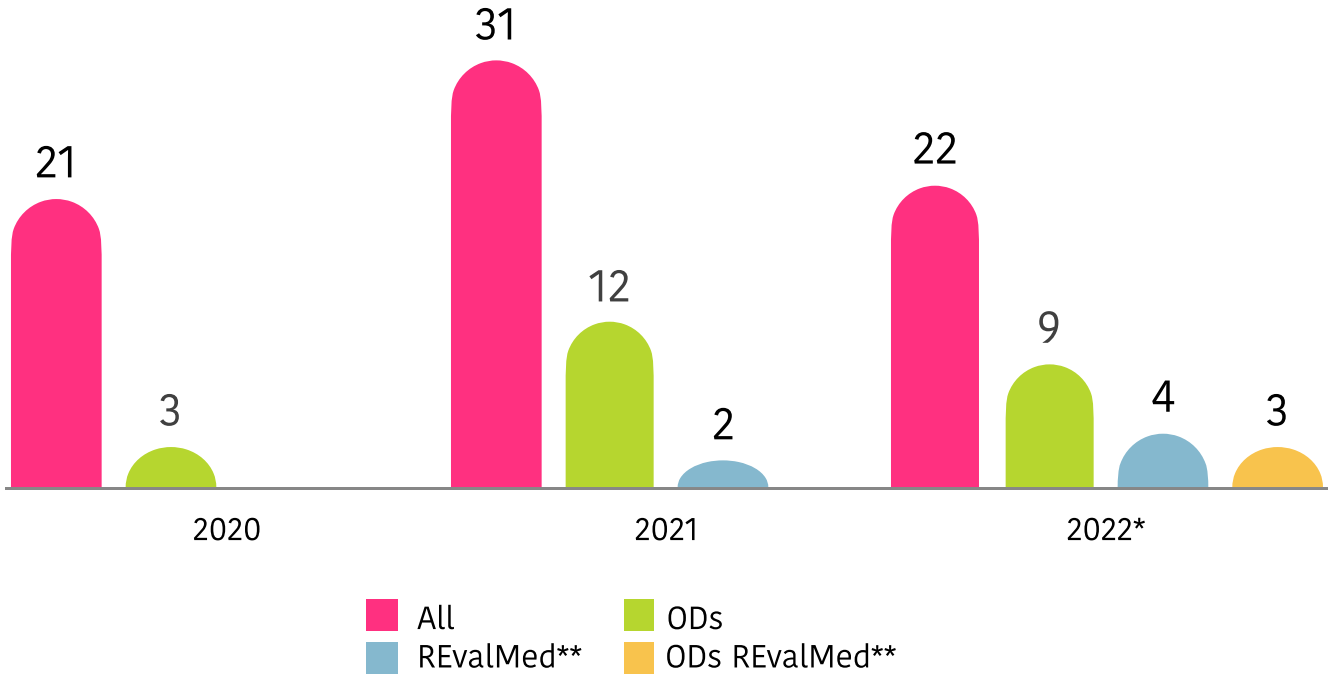
6 IPTs of new products published (46%)

3 OD (50%)

- **In total, according to the minutes, 20 IPTs have been started with the new procedure*:**
  - 7 of new indications (one of them OD)
  - 13 of new products (6 of them OD)
- **12 of then have been published*:**
  - 6 of new indications
  - 6 of new products (3 f OD)

* Revised IPT started prior to March 2022 and published up to May 13, 2022.

IPT of new products published betwen 2020 and May 2022 IPT *



- Out un 31 IPTs published in 2021, 2 were started with the new REvalMed (6%) procedure.
- During 2021 there weren't any IPT of OD published started with the new procedure.
- Out of 22 IPTs published in 2022, 4 were started with the new procedure (18%). 3 of them were OD.

*Revised IPT published up to May 13, 2022
**IPT started as a pilot according to the new REvalMed Plan procedure and published

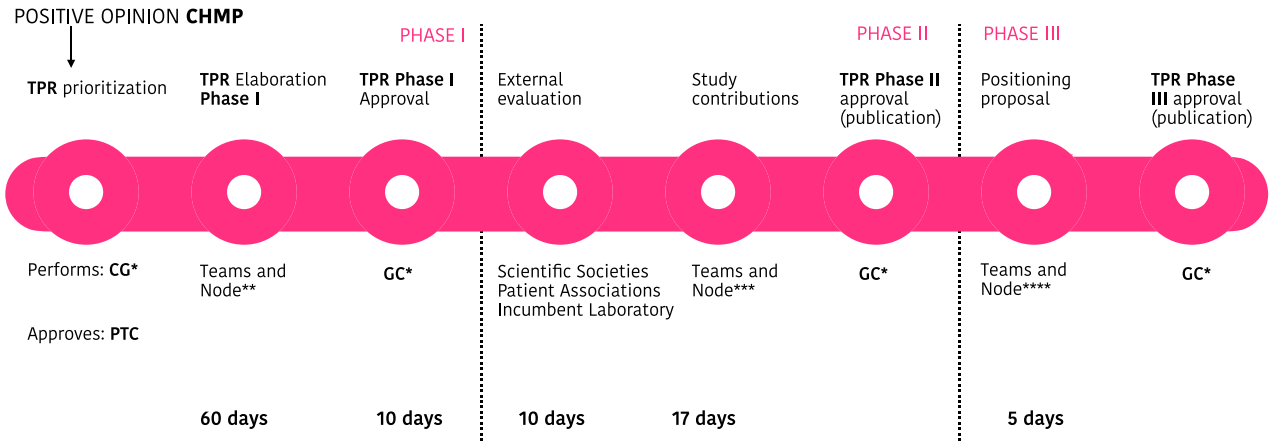
IPT started as a pilot according to the new REvalMed procedure Plan

Drug	Start date of IPT	Delivery date to DGCCSYF*	Publication date of IPT	Funding status	START IPT TO COMMON PORTFOLIO (days)	COMMON PORTFOLIO TO IPT PUBLICATION (days)	IPT START TO IPT PUBLICATION (days)
Aspaveli	21/10/2021	Not sent	IPT not sent	Under study or without funding request	-	-	-
Evrysdi	04/03/2021	02/02/2022	09/03/2022	Under study or without funding request	335,0	35,0	370,0
Kimmtrak	02/03/2022	Not sent	IPT not published	Without National Code	-	-	-
Skysona	27/05/2021	Not sent	IPT not published	Without National Code	-	-	-
Sogroya	04/02/2021	02/03/2022	28/03/2022	Without National Code	391,0	26,0	417,0
Tecartus	20/10/2020	-	18/01/2022	Not funded by resolution	-	-	455,0
Ayvakyt* New sign for Revalmed	22/09/2020 02/02/2022* (*New sign)	-	IPT not published	Without National Code	-	-	-

*DGCCSSNSF: General Direction of the Portfolio Services of the Naciontal Health System

IPT started as a pilot according to the new REvalMed procedure Plan

Drug	START IPT TO COMMON PORTFOLIO (days)	COMMON PORTFOLIO TO IPT PUBLICATION (days)	IPT START TO IPT PUBLICATION (days)
Aspaveli	-	-	-
Evrysdi	335,0	35,0	370,0 (12 monts)
Kimmtrak	-	-	-
Skysona	-	-	-
Sogroya	391,0	26,0	417,0 (14 month)
Tecartus	-	-	455,0 (15 month)
Ayvakyt* New sign for Revalmed	-	-	-



Theoretical:
Sending the IPT Phase II to the Common Portfolio: 97 DAYS

Report:
Average Start IPT – Send to Common Portfolio: 363 DAYS Media Start IPT – IPT Release: 414 DAYS

REvalMed: Oprhan Drugs economical evaluations

DRUG	INDICATION	CLINICAL BENEFICT EVALUATION	ECONOMIC EVALUATION	CONCLUSION
Evrysdi	Treatment of spinal muscular atrophy (SMA) 5q in patients with two months or older, with a clinical diagnosis of Type 1, Type 2, or Type 3 SMA, or who have between a and four copies of the SMN2 gene	Relevant clinical benefit in SMA type 1	• No cost-effectiveness evaluation. • Description of the costs of risdiplam and currently funded alternatives. For this, the total cost for 5 years of treatment with the maximum dose of risdiplam was equated with the one of nusinersén during this period of time: approximately €1,260,000 per patient. • Budget impact analysis	Therapeutic alternative for oral administration for the patients with SMA type 1 treatment. In the case of non-ambulatory patients with SMA type 2 and type 3, no beneficial effect with clinical relevance compared to placebo has been confirmed.
Sogroya	Indicated as a replacement for endogenous growth hormone in adults with growth hormone deficiency.	In adult patients with GHD, weekly injections have shown superiority over placebo, but less clinical efficacy than daily GH.	• Cost minimization analysis (AMC), to preferentially position the medicine that generates less budgetary impact. • Estimated budget impact.	Weekly administration of somapacitan is an alternative to daily administration of GH treatment in patients deficient in this hormone. The cost of treatment should be similar to that of GH administered daily, so as not to produce a budget impact, without an increase in therapeutic value compared to alternatives having been determined.
Tecartus	Indicated for adult patients treatment with relapsed or refractory mantle cell lymphoma (MCL) after two or more lines of systemic therapy, including a Bruton's tyrosine kinase inhibitor.	Although none of the alternatives have shown results in advanced lines of treatment, it is difficult to determine whether the response obtained with Tecartus will be maintained in the long term (phase II clinical results).	• Cost-effectiveness analysis performed by the pharmaceutical company is not considered appropriate. • Cost-effectiveness analysis prepared by NICE. • Comparison of academic CAR-T production costs. • Estimated budget impact	Clinical uncertainties based on the evidence available so far also translate into financial uncertainties. The cost of treatment is 3.9 times higher than the academic CAR-T, which at the moment based on the available results does not seem an acceptable cost. Budgetary impact is very high for the uncertainty it represents.

CONCLUSIONS

CONCLUSIONS

- Out of 112 IPT of OD started during the period 2013-March 2022, 40% remain unpublished, which may represent a "bottleneck" in the price and reimbursement process, causing delays in patient access to the drug.

- For the total IPT sample of new products, the average time between the start of the IPT and the delivery to the Common Portfolio increases by 65% (from 237 to 392 days) between the IPTs started in 2013 and those started in 2020, being generally higher in the sample of OD. Specifically, in the IPTs started in 2020, the time for the sample of OD is 15% higher than that of the total sample (450 days OD vs 392 days total sample).

- None of the IPTs initiated in 2022 have been sent to the Common Portfolio or published. Likewise, out of 56 IPTs started in 2021, only 7 (13%) have been sent to the Common Portfolio, and 4 (7%) have been published. In the case of OD, out of 20 IPTs started in 2021, only 4 (20%) have been sent to the Common Portfolio, and 3 (15%) have been published. Therefore, it is considered that it has not been possible to obtain representative data of times of the IPT initiated in 2022 and 2021.

- The average time between the delivery to the Common Portfolio and the publication of the IPT has been reduced by 54% during the 2013-2020 period (478 days 2013 vs. 218 days 2020), in the total sample of IPT of new products. In the case of the IPT of OD started in 2019, the time was 184 days higher than that of the total sample (46% higher - 581 OD vs. 397 total sample), a figure that has been seen reduced in the IPT started in 2020, where the two samples have a similar average number of days (218 total sample vs 214 OD).

CONCLUSIONS

- For the total sample of IPT of new products, the total time between the start of the IPT and its publication has been reduced between the IPT started in 2013 and those started in 2020 by 31% (761 days in 2013 vs 525 days in 2020).
- In the case of the OD, the time is always longer: within the IPT started in 2019, a difference of 236 days (8 months) is observed between both groups.
- 100% of the Advanced Therapies with OD designation have started their IPT but only 58% of the IPT have been published. The average time between the beginning and the publication of the IPT is 20 months.
- 13 IPT of new products have been evaluated with the new REvalMed procedure, 6 of them from OD. 3 IPT of DO initiated as a pilot according to the new REvalMed procedure Plan have been published during 2022, with the average between the start of the IPT and its publication being 414 days (14 months).

ANNEXES

ANNEXES

01 Orphan Drugs IPT initiated between 2013-March 2022 (122)

02 Orphan Drugs IPT pending to be sent General Directorate for the Common Portfolio of Pharmacy and to be published (36)

03 Orphan Drugs IPT sent to General Directorate for the Common Portfolio of Pharmacy and pending to be published (13)

04 Orphan Drugs with IPT initiated between 2013-March 2022 and NHS funded (52)

05 Orphan Drugs with IPT initiated between 2013-March 2022 and not NHS funded (27)

06 Orphan Drugs with IPT initiated between 2013-March 2022 under study or without request for funding (23)

07 Orphan Drugs with IPT initiated between 2013-March 2022 without National Code (20)

08 Reasons for non-funding according to orphan drug IPT reports whose IPT has been published and which are excluded from SNS funding (24)

1. Orphan Drugs IPT initiated between 2013-March 2022 (122)

Commercial Name	Laboratory
Abecma	Celgene
Adakveo	NOvartis
Adcetris	Takeda
Adempas	Bayer
Alofisel	Tigenix, S.A.U.
Alprolix	SOBI
Amglidia	Ammtek
Artesunate Amivas	Amivas Ireland Ltd
Aspaveli	SOBI
Ayvakyt	Blueprint
Besponsa	Pfizer
Blenrep	GlaxoSmithKline
Blincyto	Amgen
Brineura	BioMarin
Bylvay	Albireo
Cablivi	Ablynx
Cerdelga	Genzyme
Chenodeoxycholic acid	Leadiant
Coagadex	Bio Products Laboratory
Cometriq	TMC Pharma
Cresemba	Basilea
Crysvita	Kyowa Kirin
Cystadrops	Orphan Europe
Dacogen	Janssen-Cilag
Darzalex	Janssen-Cilag

Commercial Name	Laboratory
Daurismo	Pfizer
Defitelio	Gentium
Deltyba	Otsuka
Dovprela	FGK
Elzonris	Stemline Therapeutics
Enspryng	Roche
Epidyolex	GW
Evrysdi	Roche
Farydak	NOvartis
Fintepla	Zogenix ROI
Galafold	Amicus Therapeutics
Gazyvaro	Roche
Givlaari	Alnylam
Hepcludex	MYR GmbH
Holoclar	ChieSI
Idefirix	Hansa Biopharma
Idelvion	CSL Behring
Imbruvica	Janssen-Cilag
Imcivree	Rhythm Pharmaceuticals
Inrebic	Celgene
Isturisa	Recordati Rare Diseases
Jorveza	Dr. Falk Pharma GmbH
Kaftrio	Vertex
Kalydeco	Vertex Pharmaceuticals
Kanuma	Synageva BioPharma
Ketoconazol HRA	Laboratoire HRA
Kimmtrak	Immunocore Ireland
Koselugo	AstraZeneca
Kymriah	NOvartis
Kyprolis	Amgen

Commercial Name	Laboratory
Lamzede	Chiesi
Ledaga	Actelion
Libmeldy	Orchard Therapeutics
Lonapegsomatropin	Ascendis Pharma
Lutathera	Advanced Accelerator Applications
Luxturna	Spark Therapeutics
Mepsevii	Ultragenyx
Minjuvi	Incyte
Myalepta	Amryt
Mylotarg	Pfizer
Namuscla	Lupin Europe
Natpar	Shire
Nexviadyme	Genzyme
Ngenla	Pfizer
Ninlaro	Takeda
Obiltoxaximab SFL	SFL
Ocaliva	Intercept Pharma
Onivyde	Baxter Innovations
Onpattro	Alnylam
Opsumit	Janssen-Cilag
Orphacol	FGK
Oxbryta	Global Blood Therapeutics
Oxervate	Dompe farmaceutici
Oxlumo	Alnylam
Palynziq	BioMarin
Pemazyre	Incyte
Polivy	Roche
Pomalidomide Celgene	Celgene
Poteligeo	Kyowa Kirin
Prevymis	Merck
Procysbi	Raptor Pharmaceuticals
Qarziba	Apeiron Biologics
Qinlock	Deciphera Pharmaceuticals
Ravicti	Horizon Therapeutics
Raxone	Santhera

Commercial Name	Laboratory
Reblozyl	Celgene
Rydapt	Novartis
Scenesse	
SIrturo	
Skysona	Bluebird Bio
Sogroya	Novo Nordisk
SomaKit-TOC	Advanced Accelerator Applications
Spinraza	Biogen
Strensiq	Alexion
Strimvelis	GlaxoSmithKline
Sylvant	
Symkevi	Vertex
Takhzyro	Shire
Tavneos	Vifor Fresenius Medical Care Renal Pharma
Tecartus	Kite Pharma
Tegsedi	Akcea
Translarna	PTC
Trecondi	Medac
Uplizna	Viela Bio
Verkazia	Santen OY
Vimizim	BioMarin
Voxzogo	BioMarin
Vyndaqel	Pfizer
Vyxeos	Jazz Pharmaceuticals
Wakix	Bioproject Pharma
Waylivra	Akcea Therapeutics
Xermelo	Ipsen Pharma
Xospata	Astellas
Yescarta	Kite Pharma
Zejula	Tesaro UK Limited
Zolgensma	AveXis
Zynteglo	Bluebird Bio

2. Orphan Drugs IPT pending to be sent to General Directorate for the Common Portfolio of Pharmacy and to be published (36)

Commercial Name	Laboratory
Abecma	Celgene
Adakveo	Novartis
Amglidia	Ammtek
Artesunate Amivas	Amivas Ireland Ltd
Aspaveli	SOBI
Brineura	BioMarin
Bylvay	Albireo
Chenodeoxycholic acid Leadiant	Leadiant
Coagadex	Bio Products Laboratory
Defitelio	Gentium
Dovprela	FGK
Elzonris	Stemline Therapeutics
Enspryng	Roche
Fintepla	Zogenix ROI
Inrebic	Celgene
Kaftrio	Vertex
Ketoconazol HRA	Laboratoire HRA
Kimmtrak	Immunocore Ireland

Commercial Name	Laboratory
Koselugo	AstraZeneca
Lonapegsomatropin Ascendis	Ascendis Pharma EndocriNOlogy DiviSIon
Minjuvi	Incyte
Nexviadyme	Genzyme
Ngenla	Pfizer
Obiltoxaximab SFL	SFL
Orphacol	FGK Representative Service
Oxbryta	Global Blood Therapeutics Netherlands
Pomalidomide Celgene	Celgene
Qinlock	Deciphera Pharmaceuticals
Ravicti	Horizon Therapeutics
Skysona	bluebird bio
Strimvelis	GlaxoSmithKline
Tavneos	Vifor Fresenius Medical Care Renal Pharma
Uplizna	Viela Bio
Voxzogo	BioMarin
Xermelo	Ipsen Pharma
Zynteglo	Bluebird Bio

3. Orphan Drugs IPT sent to General Directorate for the Common Portfolio of Pharmacy and pending to be published (13)

Commercial Name	Laboratory
Ayvakyt	Blueprint
Blenrep	GlaxoSmithKline
Daurismo	Pfizer
Hepcludex	MYR GmbH
Idefirix	Hansa Biopharma
Imcivree	Rhythm Pharmaceuticals
Isturisa	Recordati Rare Diseases
Libmeldy	Orchard Therapeutics
Oxlumo	Alnylam
Palynziq	BioMarin
Qarziba	Apeiron Biologics
Reblozyl	Celgene
Trecondi	Medac

4. Orphan Drugs with IPT initiated between 2013-March 2022 and NHS funded (52)

Commercial Name	Laboratory
Adcetris	Takeda
Adempas	Bayer
Alofisel	Tigenix, S.A.U.
Alprolix	Swedish Orphan Biovitrum
Besponsa	Pfizer
Cablivi	Ablynx
Cerdelga	Genzyme
CheNOdeoxycholic acid Leadiant	Leadiant
Cresemba	Basilea Pharmaceutica
Crysvita	Kyowa Kirin
Dacogen	Janssen-Cilag
Darzalex	Janssen-Cilag
Deltyba	Otsuka
Epidyolex	GW
Galafold	Amicus Therapeutics
Gazyvaro	Roche
Givlaari	Alnylam
Idelvion	CSL Behring
Imbruvica	Janssen-Cilag
Isturisa	Recordati Rare Diseases
Kaftrio	Vertex
Kalydeco	Vertex Pharmaceuticals
Kanuma	Synageva BioPharma
Kymriah	Novartis
Kyprolis	Amgen
Lutathera	Advanced Accelerator Applications
Luxturna	Spark Therapeutics
Mepsevii	Ultragenyx

Commercial Name	Laboratory
Mylotarg	Pfizer
Ocaliva	Intercept Pharma
Onivyde	Baxter InNOvations
Onpattro	Alnylam
Opsumit	Janssen-Cilag
Orphacol	FGK Representative Service
Polivy	Roche
Poteligeo	Kyowa Kirin
Prevymis	Merck Sharp And Dohme B.V.
Ravicti	Horizon Therapeutics
Rydapt	NOvartis
SomaKit-TOC	Advanced Accelerator Applications
Spinraza	Biogen
Sylvant	EUSA Pharma
Symkevi	Vertex
Takhzyro	Shire
Tegsedi	IONIS
Vyndaqel	Pfizer
Vyxeos	Jazz Pharmaceuticals
Wakix	Bioproject Pharma
Waylivra	Akcea Therapeutics
Yescarta	Kite Pharma
Zejula	Tesaro UK Limited
Zolgensma	AveXis

5. Orphan Drugs with IPT initiated between 2013-March 2022 and not NHS funded (27)

Commercial Name	Laboratory
Amglidia	Ammtek
Blincyto	Amgen
Cometriq	TMC Pharma
Cystadrops	Orphan Europe
Farydak	NOvartis
Holoclar	ChieSI
Jorveza	Dr. Falk Pharma GmbH
Lamzede	ChieSI
Ledaga	Actelion
Myalepta	Amryt
Namuscla	Lupin Europe
Natpar	Shire
Ninlaro	Takeda
Oxervate	Dompe farmaceutici

Commercial Name	Laboratory
Palynziq	BioMarin
Pemazyre	Incyte
Procysbi	Raptor Pharmaceuticals
Raxone	Santhera Pharmaceuticals
Scenesse	Clinuvel Europe
Sirturo	Janssen-Cilag
Strensiq	Alexion
Tecartus	Kite Pharma
Translarna	PTC Therapeutics
Verkazia	Santen OY
Vimizim	BioMarin
Xermelo	Ipsen Pharma
Xospata	Astellas

6. Orphan Drugs with IPT initiated between 2013-March 2022 under study or without request for funding (23)

Commercial Name	Laboratory
Abecma	Celgene
Adakveo	Novartis
Aspaveli	SOBI
Blenrep	GlaxoSmithKline
Brineura	BioMarin
Bylvay	Albireo
Daurismo	Pfizer
Enspryng	Roche
Evrysdi	Roche
Fintepla	Zogenix ROI
Hepcludex	MYR GmbH

Commercial Name	Laboratory
Idefirix	Hansa Biopharma
Inrebic	Celgene
Koselugo	AstraZeneca
Libmeldy	Orchard Therapeutics
Minjuvi	Incyte
Ngenla	Pfizer
Oxlumo	Alnylam
Qarziba	Apeiron Biologics
Reblozyl	Celgene
Tavneos	Vifor Fresenius Medical Care Renal Pharma
Trecondi	Medac
Voxzogo	BioMarin

7. Orphan Drugs with IPT initiated between 2013-March 2022 without National Code (20)

Commercial Name	Laboratory
Artesunate Amivas	Amivas Ireland Ltd
Ayvakyt	Blueprint
Coagadex	Bio Products Laboratory
Defitelio	Gentium
Dovprela	FGK
Elzonris	Stemline Therapeutics
Imcivree	Rhythm Pharmaceuticals
Ketoconazol HRA	Laboratoire HRA
Kimmtrak	Immunocore Ireland
Lonapegsomatropin	Ascendis Pharma
Nexviadyme	Genzyme
Obiltoxaximab SFL	SFL
Oxbryta	Global Blood Therapeutics Netherlands
Pomalidomide Celgene	Celgene

Commercial Name	Laboratory
Qinlock	Deciphera Pharmaceuticals
Skysona	Bluebird bio
Sogroya	Novo Nordisk
Strimvelis	GlaxoSmithKline
Uplizna	Viela Bio
Zynteglo	Bluebird Bio

8. Reasons for non-funding according to Orphan Drugs IPT reports whose IPT has been published and which are excluded from SNS funding (24)

DRUG	Conclusion
Blincyto	• It lacks comparative studies and has been authorized on a conditional authorization pending more data to be provided over the next year, making it difficult to position it in relation to other options in terms of efficacy and toxicity/safety. • Significant associated toxicity, so its prevention and management is a critical aspect to be taken into account. There are subgroups of patients in which there is little information on this aspect. It should only be used in centers with logistics and trained personnel to avoid administration errors and manage toxicity adequately. • Available data suggest remission rates equal to or even better than those obtained with conventional treatments..
Cometriq	• It has shown a delay in tumor progression, however, it has not been shown to provide a clear benefit to the patient in terms of overall survival or improvement in quality of life. • It is recommended that the presence of RET mutations be studied in the tumors of patients with sporadic TNBC who are candidates for treatment with cabozantinib.
Cystadrops	• Cystadrops has shown significantly superior efficacy compared to its comparator. Despite this, it should be noted that the concentration of the chosen comparator could be considered insufficient, and it was administered with an administration schedule equal to Cystadrops. • Its long-term efficacy and safety will have to be studied in depth through post-authorization studies given the short study time of the pivotal trial (90 days).
Farydak	• The fact that panobinostat in association with bortezomib and dexamethasone has not so far demonstrated an increase in survival and added to the high toxicity of the combination, raises doubts about the relevance of the combination in clinical practice.

8. Reasons for non-funding according to Orphan Drugs IPT reports whose IPT has been published and which are excluded from SNS funding (24)

DRUG	Conclusion
Holoclar	• There are some uncertainties in comparing the results of Holoclar with existing alternatives. • For the time being data on the effect of this treatment in patients in the long term are very limited. • It should be administered in centers with extensive experience in the application of this type of technique.
Jorveza	• Data from the pivotal clinical study show a clear efficacy of the drug versus placebo, which is maintained and even increased at 12 weeks. • With the available data, the occurrence of systemic adverse effects typical of corticosteroids seems unlikely. • This new formulation is more convenient and would reduce the variability of use and therapeutic results obtained with different master formulations. • The effect of long-term treatment with budesonide bucodispersible tablets is unknown.
Lamzede	• First approved treatment for mild to moderate alpha-mannosidosis for non-neurological symptoms only. • Long-term efficacy and safety data are lacking. • The clinical and functional benefit of treatment should be carefully evaluated and recorded and, if ineffectiveness of treatment is observed, discontinuation of treatment should be considered. • At the time of writing this report, efficacy has not been evaluated in children under 6 years of age, a group that could be one of those most likely to benefit from this drug.
Ledaga	• The safety of the concomitant use of mechlorethamine with topical corticosteroids has not been established. • Patients should be monitored for possible occurrence of other types of skin cancer during and after discontinuation of treatment with mechlorethamine.

8. Reasons for non-funding according to Orphan Drugs IPT reports whose IPT has been published and which are excluded from SNS funding (24)

DRUG	Conclusion
Myalepta	• The available efficacy results are limited because they are based on a combined Phase II open-label, non-randomized study with no direct comparator. • It shows an acceptable safety profile of toxicity and tolerance. • There is uncertainty about its safety due to the small number of patients studied, the absence of a control group and the high comorbidity inherent to the disease. The efficacy and safety data should be completed with a patient registry that provides efficacy and safety data in long-term clinical practice.Translated with www.DeepL.com/Translator (free version)
Namuscla	• It provides clinically relevant benefits after a regimen of 18-22 days compared to placebo and a significant improvement in aspects of quality of life. • Its arrhythmogenic capacity is a limiting factor to be taken into account when using it, and it is essential to monitor the treatment and comply with the established risk control and minimization measures. • Considering the magnitude of the efficacy demonstrated, the absence of other authorized treatments and the chronic debilitating nature of these diseases, it is considered acceptable.Translated with www.DeepL.com/Translator (free version)
Natpar	• No data on long-term clinical benefit in relation to hypercalciuria targets, renal complications or quality of life are available from available clinical trials. • Immunogenic outcomes are limited. • It could be considered a treatment option only in adult patients with chronic hypoparathyroidism for whom calcium and vitamin therapy is insufficient.
Ninlaro	• At the time of writing, the available OS data are still immature. • There is insufficient evidence regarding the treatment sequence that achieves better OS results. • More data are needed to confirm the benefit of adding ixazomib for use with dexamethasone and lenalidomide.

8. Reasons for non-funding according to Orphan Drugs IPT reports whose IPT has been published and which are excluded from SNS funding (24)

DRUG	Conclusion
Oxervate	• Pivotal studies have shown significant improvement of 30-40% in corneal healing at 8 weeks. • A new post-authorization study will provide additional efficacy and safety data on long-term and prolonged use. • Its dosage may make patient compliance difficult. • A longer-term study will have to be awaited to adequately assess its benefits on disease deterioration.
Pemazyre	• With the uncertainties raised, it is not possible to confirm whether the response rates and their duration translate into a clinically relevant benefit for the patient. • The toxicity profiles of pemigatinib and FOLFOX are different and the administration of pemigatinib is oral, while FOLFOX involves intravenous administration every 14 days. • Taking into account the limitations of the previously used treatment (FOLFOX), as well as the uncertainties noted about the relevance of the clinical benefit, pemigatinib is considered an option for second-line treatment of cholangiocarcinoma.Translated with www.DeepL.com/Translator (free version)
Procysbi	• The new modified-release formulation does not allow conclusions to be drawn regarding improved adherence to treatment compared to the immediate-release formulation. • In the case of children, the 6-hourly administration schedule is very difficult to follow because it interrupts their sleep schedule, and in adults and adolescents there is a risk of non-adherence.
Raxone	• Evidence of efficacy is fragile. • Optimal treatment duration and long-term efficacy cannot be established as data are limited. • Some potential risks were identified, which should be monitored in further studies. • Long-term safety is limited and additional data are required.

8. Reasons for non-funding according to Orphan Drugs IPT reports whose IPT has been published and which are excluded from SNS funding (24).

DRUG	Conclusion
Scenesse	• It shows an acceptable safety and tolerance profile. • A benefit in patients' quality of life has not been conclusively demonstrated. • The data provided since authorization have failed to provide further information on the efficacy or safety of this drug and complete efficacy and safety data are hardly expected due to the rarity of the condition. • Clinical and pharmacological data are very limited, with a modest effect and of questionable clinical relevance in some respects.
Sirturo	https://www.aemps.gob.es/medicamentosUsoHumano/informesPublicos/docs/IPT-bedaquilina-Sirturo-tuberculosis-pulmonar.pdf
Strensiq	• In patients under 13 years of age, the treatment shows significant improvements in bone structure. The results are more uncertain in patients aged 13 to 18 years and in adult patients where it has not been possible to conclude a benefit of the treatment. • The available data are limited and the drug has been authorized in exceptional circumstances. • It should be prescribed by physicians experienced in the treatment of patients with metabolic or bone disorders.
Tecartus	• The clinical uncertainties based on the evidence available to date also translate into financial uncertainties. • The cost of treatment is 3.9 times higher than the academic CAR-T, which at the moment, based on the available results, does not seem to be an affordable cost. • The budgetary impact is very high for the uncertainty represented by the data available so far compared to the alternatives used.

8. Reasons for non-funding according to Orphan Drugs IPT reports whose IPT has been published and which are excluded from SNS funding (24).

DRUG	Conclusion
Translarna	• The evidence of efficacy is fragile and it has not been confirmed that the treatment increases the production of muscular dystrophin. • It may have an effect on exercise capacity, consisting of a slowing of progression rather than an improvement in gait, although so far this does not seem to translate into a significant benefit. • It has not been possible to identify any biologically plausible subgroups of patients to point to as better candidates for treatment. • There are no data on the effect of this drug in patients in more advanced stages.
Verkazia	• The evidence comes from studies carried out in a very limited number of patients, although this is justified due to the rarity of the disease. • Safety has not been studied for periods longer than 12 months. • An emulsion eye drop with the same qualitative and quantitative composition as Verkazia is already marketed in Spain. • Verkazia represents the only standardized option specifically authorized for the treatment of severe CKD in children 4 years of age or older and adolescents.
Vimizim	• The main efficacy results refer to variables related to mobility, with no data available on robust variables. • At the time of writing, efficacy has not been evaluated in patients in advanced stages of the disease or in patients under 5 years of age. • It is necessary to collect information on follow-up variables to shed more light on the existing uncertainties in order to identify those populations that could benefit the most.
Xospata	• It has shown improvement in survival compared to salvage chemotherapy used in clinical practice. • In older patients, the risks associated with treatment and the expected benefit should be carefully evaluated. • Response to gilteritinib may be delayed, so continuation of treatment for up to 6 months should be considered to allow time for clinical response to appear.

June 2022

Art & Design

Inmaculada Cagliostro

+++ 23_Monalisas