Paediatric Medicines Facts and Figures

EPMD-Special Report[1]

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Responding to the Paediatric Regulation all new products independently from the future Marketing Authorisation procedure (i.e., centralised or decentralised) should, at the time of the marketing authorisation (MA) provide the results of paediatric studies developed and completed according to a paediatric investigation plan (PIP) agreed by the PDCO unless the conduct of these studies was waived. The same obligation applies to in patent products willing to receive a MA variation even if they have been approved before the Paediatric Regulation entering into force. Voluntary PIPs application may be granted to off-patent medicinal products in case of a paediatric variation is proposed.[2]

This report analyses data on the results of the applications of the Paediatric Regulation with particular reference to PIPs and waivers granted, completed PIPs and their positive or negative outcomes, new paediatric medicine indications introduced on the market, and rewards granted. The main results acquired in the last three years are specifically underlined.

1. PIPs and waivers

Based on EMA dataset publicly available on the EMA website[3], a total of agreed paediatric investigation plans (including PIPs and PIPs modifications and excluding PIPs refusals), stood at 1,213 at the end of 2020. In the same period the total number of **waivers** was 863. The distribution of PIPs and waivers by year is shown in the table below. The highest number of both the procedures refer to the last three years with a total of 562 PIPs and 315 waivers agreed in 2018-2020.

TABLE 1. NUMBER OF AGREED PIPS, COMPLETED PIPS AND GRANTED WAIVERS, BY YEAR

	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	TOTAL
FULL WAIVER GRANTED	3	43	70	53	45	45	54	48	51	54	81	91	97	128	**863**
PIPS AGREED	0	22	41	121	47	51	54	63	73	92	87	103	145	314	**1213**

Table 1 also shows that the number of agreed PIPs is increased in comparison to the number of waivers.

Agreed PIPs and waivers in the EMA database are associated to a product name (i.e., **461** PIPs and **209** waivers) or to a new or already existing active substance (i.e., *752 PIPs and 759 Waivers*). In particular there are:

[1] This report was closed March 30,2022

[2] These applications may be both considered under art. 7 or art. 30 of the paediatric Regulation

[3] "Medicines_output_paediatric_investigation_plans" at: https://www.ema.europa.eu/en/medicines/download-medicine-data; downloaded on 22 March 2022.

- **PIPs and waivers associated to centrally authorised products (CAPs) in the period 2007-2020**. According to the Union Register of medicinal products, the 'EMA database including centralised approved human medicines', **670** products not withdrawn at the time of analysis, were centrally approved in the period 2007-2020, for which an obligation exists to be granted of a PIP or a waiver. With reference to these products, a total of **376 PIPs and 187 full waivers** have been granted. In some cases, more than one PIP/waiver has been granted for the same product. 294 products have been granted both a PIP and partial waivers. The remaining centrally approved products (i.e., 107 products) resulted non covered neither by a PIP or a waiver for effects of applicable derogations to the paediatric requirements. The reasons for derogations are shown in table 2.

TABLE 2. CENTRALISED AUTHORISED PRODUCTS (2007-2020) WITH NO PIP OR WAIVER

	PRODUCTS APPROVED IN 2007-2020
MAA SUBMITTED ACCORDING TO ART. 10A OF THE DIR. 2001/83 (KNOWN ACTIVE SUBSTANCE)	14
MAA SUBMITTED ACCORDING TO ART. 10C OF THE DIR. 2001/83 (INFORMED CONSENT)	31
MAA SUBMITTED ACCORDING TO ART. 10.3 OF THE DIR. 2001/83 (HYBRID APPLICATION)	29
MAA SUBMITTED BEFORE JULY 2008	33
TOTAL	107

- **PIPs and waivers associated to products centrally authorised before the year 2007**. For these products (i.e., 243 products) there is an obligation to apply for PIP or waiver only if a new product development or a variation is proposed. We have identified a total of **68** products responding to these criteria that have been granted of a PIP (47 products) or a waiver (21 products). Most of these procedures have been submitted in the period 2008-2011.
- **PIPs and waivers associated to non-centrally authorised products**. The obligations derived from the Paediatric Regulation, also apply to products that received a MA following a decentralised/mutual recognition procedure. A total of 40 PIPs and 37 non centrally approved products has been identified[4]. However, the number of decentralised products granted with PIPs or waivers may be significantly higher but impossible to be calculated due to the lack of an associated name in the EMA database and/or the lack of a non-centralised medicinal products reliable source of information.
- **PIPs and waivers associated to an active substance**. The remaining PIPs and waivers (i.e., 752 PIPs and 759 waivers) do not have an associated name in the EMA database. It is expected that for the most recently submitted procedures, the development of a new product or a product variation, based on these active substances, is ongoing while in case of very old submissions (i.e., 277 PIPs, still uncompleted, submitted from 2008 to 2014) it's unlikely that these PIPs will end with a products marketing authorisation.

TABLE 3. NUMBER OF AGREED PIPS AND WAIVERS

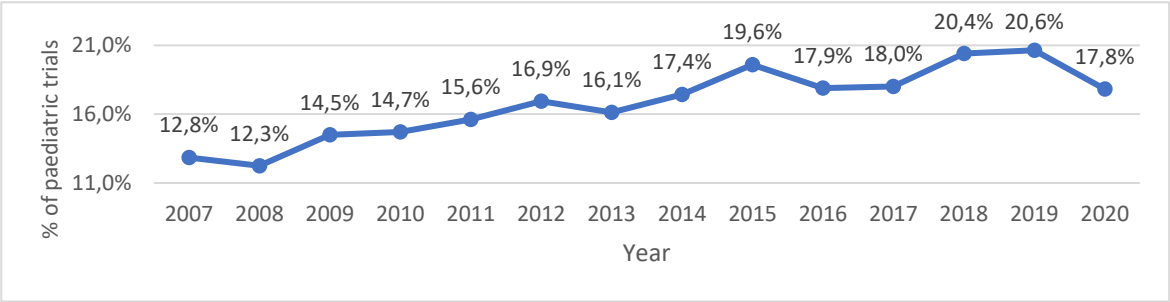
ASSOCIATED TO:	CAPS < 2007	CAPS 2007-2020	NON-CAPS 2007-2020	NO PRODUCT ASSOCIATED NAME
PIPs	**47**	**375**	**40**	**753**
WAIVERS	**21**	**188**	**n.a.**	**550**

2. Paediatric clinical studies

[4] The search has been done by the study team on the basis of the associated active substance/associated name corresponding to products present in one or more National Markets and/or products that have received a pediatric reward (i.e., SPC extension as included in MPA Service database).

The obligation for the companies to submit and agree a PIP has had a direct effect on paediatric clinical research in the EU. We considered the clinical trials including children in the whole period 2007-2020 and particularly in the period 2017-2020, by consulting the EU clinical trials register[5]. Figure 1 reports the trend of rate of paediatric trials on total trials in the whole period, demonstrating a constant increase, starting from 2011 and with the maximum value in 2019. In 2020 we noted on the contrary a decrease (less 3%) that can be attributed to the COVID-19 effects (see also the discussion reported in the main report, section 2.3.1).

FIGURE 1. PERCENTAGE OF PAEDIATRIC TRIALS (OF ALL TRIALS, BY START YEAR)



Source: EU clinical trials register

3. Completed PIPs

The EMA dataset also reports that, on a total of 1213 PIPs, 233 have been completed, i.e., have received a positive compliance check (CC), with an increasing number of completed PIPs from 2013 to 2019. The number of CCs granted in 2020 has been lower, but globally 36% of completed PIPs have been completed in the period 2018-2020, thus confirming the upward trend reported in the EC Joint Evaluation on the Orphan and Paediatric Regulations.[6]

TABLE 4. NUMBER OF PIP WITH A POSITIVE CC

	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	TOTAL
NO. OF PIPS	5	8	9	9	4	15	31	16	31	20	20	37	28	233

Of a total of the **233 completed PIPs** reported in the EMA dataset:

- **10** refer to products that at the time of the analysis resulted withdrawn by the EU market;
- **40** refer to non-centralised/national approved products;
- **25** refer to active substance/products for which an EU paediatric MA procedure was not finalised up to 2020;
- **158** completed PIPs refer **to 143 centrally approved products** (of these, 11 products [7] with more than one PIP).

Of these 143 centrally approved products:

- **128** products have been granted one or more paediatric indications (positive outcomes);
- **15** products have had the negative results of the studies included in the summary of product characteristics (SmPC) (negative outcomes).

5 https://www.clinicaltrialsregister.eu/ctr-search/search

6 SEC(2020) 291 final} - {SWD(2020) 164 final}

7 Tobi Podhaler, Yervoy, Votubia, Orencia, Nucala, MabThera, Ilaris, HyQvia, Humira, Avastin and Gardasil

In the table **5** the distribution of PIPs, waivers, completed PIPs and outcomes is reported according to the therapeutic area. [8]

TABLE 5. NUMBER OF WAIVERS, AGREED PIPs, COMPLETED PIPs, and OUTCOMES BY THERAPEUTIC AREA

THERAPEUTIC AREA	WAIVERS	PIPS, INCLUDING DEFERRAL, AGREED	COMPLETED PIPS (% ON AGREED PIPS)	CENTRALLY APPROVED PRODUCTS POS./NEG OUTCOMES
Vaccines	8	57	24 (42,1%)	16/0
Uro-nephrology	13	19	6 (31,6%)	2/0
Psychiatry -Neurology	58	104	19 (18,3%)	13/3
Pneumology – Allergology	21	42*	14 (33%)	2/0
Oto-rhino- /Ophthalmology	56	30	8 (26,7%)	3/0
Oncology	**176**	**126**	**25 (19,8%)**	**11/5**
Infectious Diseases	26	148	28 (18,9%)	23/0
Immunology-Rheumatology-Transplantation	37	87	22 (25,3%)	12/0
Haematology-Hemostaseology	30	81	19 (22,2%)	18
Gastroenterology-Hepatology	21	77	12 (15,5%)	4/1
End-Gyn-Fertility-Metabolism	103	124	27 (21,8%)	17/3
Pain /Anaesthesiology	35	26	2 (4,8%)	-
Neonatology	1	14	1 (7,1%)[9]	2/0
Cardiovascular Diseases	195	52	9 (17,3%)	1/3
Dermatology	30	45	6 (13,3%)	2/0
Other (including diagnostic and -nutrition)	53	65	11 (16,9%)	2/1
TOTAL:	**863**	**1213**	**233 (19,2%)**	**128/15****

**114 PIPs granted in 2010-2011 due to a change in the German regulation have been excluded.*
*** this column refers only to CAPs*

The analysis of data in **TABLE 5** identifies differences and criticisms in specific therapeutic areas:

- Agreed and completed PIPs, as well as paediatric medicinal products are particularly lacking in some areas like neonatology, pain, cardiology already recognised as area of special paediatric need.[10] Moreover the higher number of agreed PIPs corresponds to the disease area with a more limited disease burden expressed as a percentage of total DALYs [11] even if we noted an increased number of PIPs in neurology that is the area having the higher disease burden (even if the same effect is not evident in case of neonatology) (see Figure 2).
- Oncology and cardiovascular are the two areas in which the number of waivers is prevalent respect to the number of PIPs and the rate of completed PIPs is particularly lower. However, the rate of the oncology

[8] Source: elaborated by the study team, based on EMA dataset publicly available on EMA website ("Medicines_output_paediatric_investigation_plans" spreadsheet) at: https://www.ema.europa.eu/en/medicines/download-medicine-data; downloaded on 22 March 2022.

[9] This refer to medicines developed for exclusive use in neonatal diseases. Some products in other area may include use in the neonatal population.

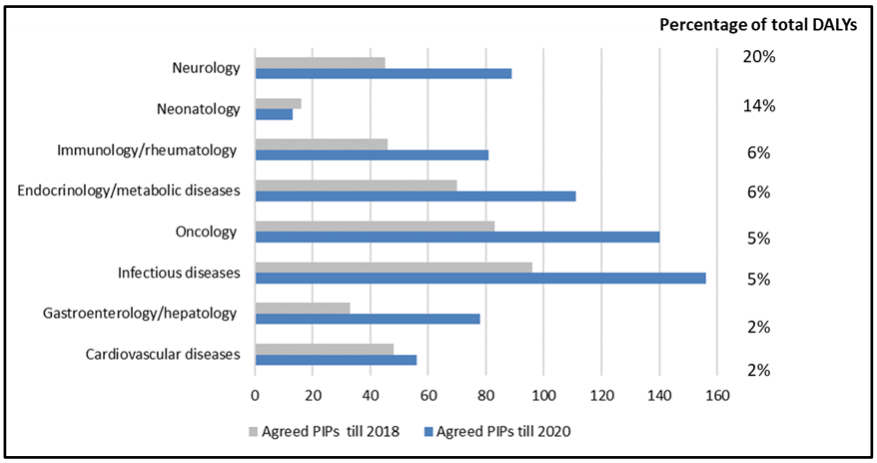
[10] Toma M, Felisi M, Bonifazi D, Bonifazi F, Giannuzzi V, Reggiardo G, de Wildt S, Ceci A; TEDDY European Network of Excellence for Paediatric Research. Paediatric Medicines in Europe: The Paediatric Regulation-Is It Time for Reform? Front Med (Lausanne). 2021 Feb 2;8:593281. doi: 10.3389/fmed.2021.593281. PMID: 33604345; PMCID: PMC7884470.

[11] Global Health Estimates (GBE) for European Union Member States, 2019; World Health Organization Department of Health Statistics and Information Systems'. Available at http://www.who.int/healthinfo/global_burden_disease/estimates/en

completed PIPs in the last 3 years has increased from the 10% to 19,8% while it's 2% less (17,3%) in the cardiovascular area (previous value: 19,2%). In the interpretation of this data, it should be considered the effect of the revision of the class waivers introduced in 2015. The revision was aimed to reduce the number of class waivers in favour of more PIPs for products of potential benefits for children especially in case of new products presenting completely novel pharmacological properties. However, despite this intention, the number of waivers granted in some areas like oncology and cardiovascular, has increased and has remained higher than the PIPs due to the increased number of voluntary product-specific waiver applications submitted by the sponsors.

- In the group of vaccines, the number of PIPs is 7 times the number of waivers. In addition, in this area the percentage of CC is higher than in all the other area and equal to 42%.
- On the contrary other areas present a very high number of PIPs and a very low number of CC but globally the rate of completed PIPs raised from 12% to 19,1% in the last 3 years.

FIGURE 2. AGREED PIP TILL 2017 AND TILL 2020, COMPARED TO DISEASE BURDEN



Source: elaborated by the study team on the agreed PIPs in two period: up to 2018 and up to 2020.

PIPs positive outcomes

- Globally the PIPs positive outcomes, i.e. paediatric MAs and Mas variation granted, are increased in the last three years. The approved paediatric indications reported in the Joint Evaluation, following a completed PIP were 71, compared to 126 in the period up to 2020 with an increase of 43,6%.
- In oncology the PIPs positive outcomes increased from 2 to 11 from June 2018 to Dec. 2020. However, for 5 out of 16 oncology the paediatric MA submission concluded with a refusal, that represents the highest percentage of negative outcomes observed.
- It should be also considered that a total of 90 paediatric MA submissions have been done using paediatric studies results from non completed PIPs. These procedures have generated paediatric MA and/or updated paediatric indication in a total of 82 centrally approved products, covering, almost partially, the indications targeted in the PIPs. In particular only some age groups and few ad hoc paediatric formulations, among what stated in the PIP, are covered by the approved indications. However, considering that these PIPs are still ongoing further paediatric variations to complete the PIPs requirements are expected in the next years. More details on these products are included in paragraph 6.

4. Deferral

The products granted with a deferral represent almost the totality of the products for which a PIP has been agreed, i.e., **86%** in the whole 2007-2020 period. The rate of deferred PIPs on total PIPs agreed was globally higher in the years 2011-2017 and a progressive decrease has been observed in the last three years (see table 6) and particularly in 2020.

TABLE 6. DEFERRAL: DISTRIBUTION BY YEAR

	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	TOTAL
No. and % of PIPs including a deferral	-	22/31 69%	47/61 78%	37/43 86%	39/43 88%	37/43 88%	27/34 79%	29/31 94%	22/25 92%	24/30 89%	32/33 97%	21/23 95%	15/18 83%	8/14 69%	361/420 86%

To monitor and verify companies' compliance with the granted deferrals, they are required to submit annually the justification of any delay in the PIPs completion. Then the list of companies that have not submitted their justifications are included in the annual reports prepared from the Agency[12]. From 2007 to 2019, the EMA received 1342 reports on a total of 40% of deferred PIPs, including justifications whether the PIP was progressing as planned or not. However, these reports do not provide specific information on the effects of the deferred measures on the global performance of the PIPs, especially in term of the time to completion since the length of the deferrals is not explicitly provided in the PIP decision where on the contrary the 'expected' PIP duration is stated as the sum of the duration of the studies and of the deferrals possibly granted.[13]

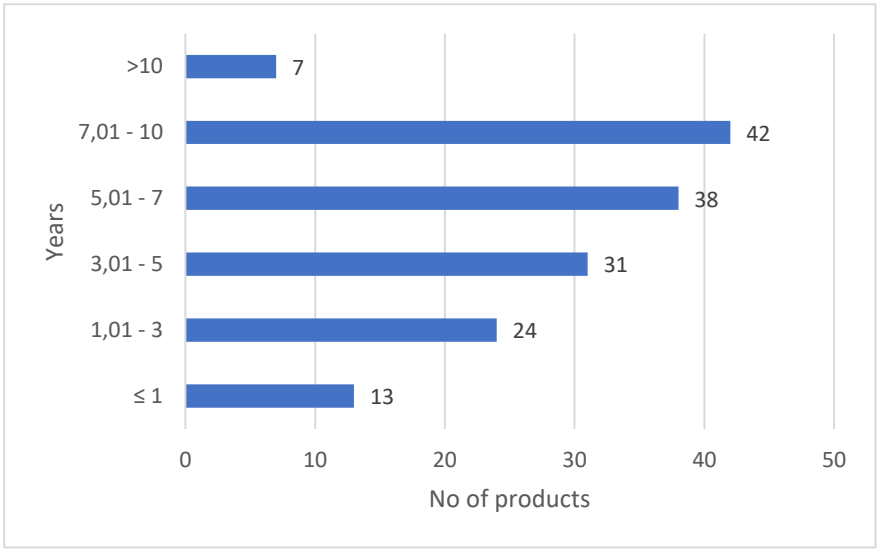
5. Time to complete a PIP

To measure the time to complete a PIP including the effects of deferrals, two measures have been adopted:

1. **The actual time measure,** corresponding to the interval between the EMA PIP decision date and the compliance check date.
2. **The expected PIP completion time** measure, corresponding to the interval between the decision PIP date and the expected PIP completion date[14], including deferrals.

Actual Time. It has been estimated on a total of 155 completed PIP[15] 112 were deferred and 43 not deferred. Results of the analysis show that the average completion time was **5.39 years** and that 56% and 32% of PIPs is developed in more than 5 and 7 years respectively with a maximum duration of a PIP equal to 11,79 years. (Fig. 3)

FIGURE 3. ACTUAL DURATION OF PIP



Source: Analysis done by the study team on EPARs Products details on completed PIPs and from the Medicine outputs of PIPs and waivers downloaded by EMA website

[12] Last annual report (2020) available at the link: https://ec.europa.eu/health/system/files/2021-12/2020_annual_report.pdf

[13] The expected completion date is provided in the PIP first approval decision and in the subsequent PIP modifications that can be downloaded by the EMA website. It is to be considered as the sum of both the estimated duration of the PIP' studies and of the deferral(s) granted.

[14] As reported in the PIPs decision

[15] For three PIPs data were not available.

The average PIP duration resulted to be 6 years in products including a deferral and 3.89 years in products that did not include a deferral. (p= < 0,01)

Expected PIP completion time. It has been calculated on a total of 262/267 not yet completed PIPs of whom 246 were deferred and 16 not deferred. It was not possible to estimate the duration in 5 cases (1 PIP discontinued, 1 case presenting discrepancies between the reported dates, 3 vaccines with length not expressed in years). The average expected duration is 9.18 years.

The expected PIP duration has also proved to be very variable and in particular it is less than 1 year in few cases (2 PIPs) while ***for more than 70% of the PIPs the expected duration is more than 7 year*** and for more than 40% it exceeds 10 years with 12 cases in which it is more than 15 year (see Figure 4). The average expected PIP duration resulted to be 6.17 for non-deferred PIPs and 9.38 for deferred PIPs (p ≤ 0,01). The longest PIPs expected durations are concentrated in the area oncology with the maximum observed value equal to 20 years and 9 months.

FIGURE 4. PIPS EXPECTED DURATION (262 PIPS, BOTH DEFERRED AND NOT DEFERRED)

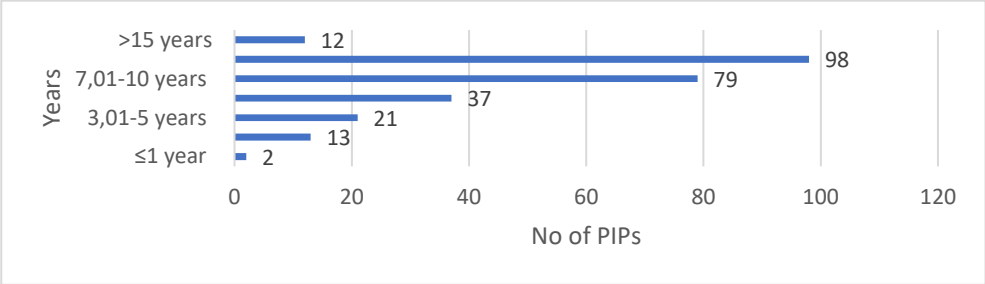
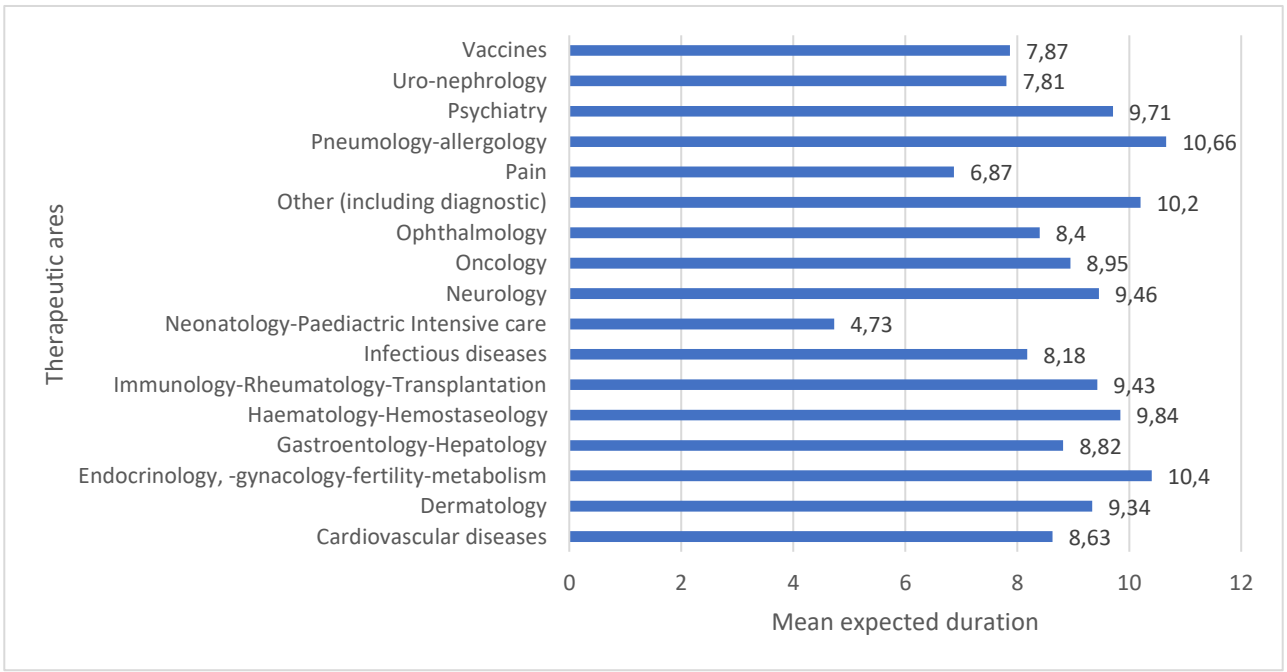


Figure 5 below, synthetises the distribution of PIP expected durations in different therapeutic areas. This figure helps to identify the therapeutic area in which the expected duration, including deferrals, is longer. Those are pneumology, endocrinology & metabolism, haematology, neurology, psychiatry and immunology.

FIGURE 5. PIPS AVERAGE DURATION (IN YEAR) PER THERAPEUTIC AREA



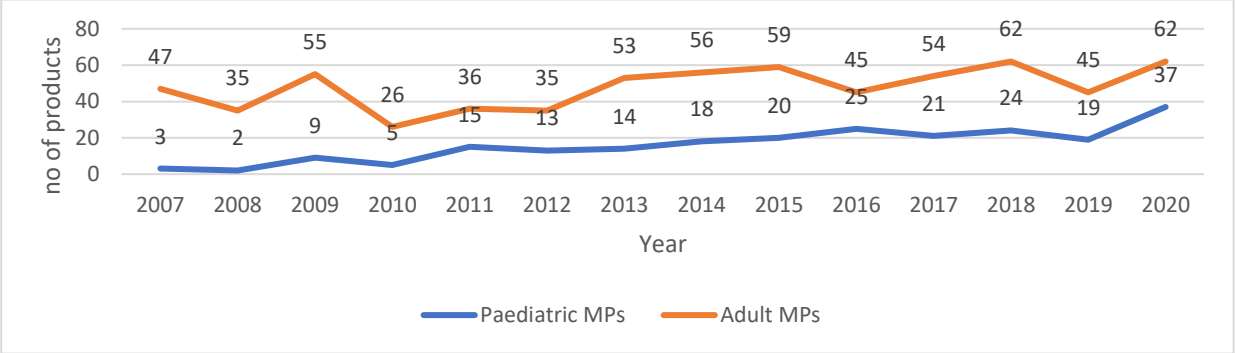
In conclusion on the basis of the documented significant difference in both *the expected and actual time* to completion among PIPs including or not a deferral, we can conclude that the deferrals represent a risk factor for delaying PIP completion and that granting too long deferrals should be avoided or appropriately limited.

Considering that the duration of the studies that are part of the PIPs cannot be reduced by EMA decision, and that the granting of deferrals should continue to be guaranteed, 'capping the duration of deferrals' might reduce in the future the completion time of PIPs. For instance, deferral duration could be capped to a maximum calculated as a percentage of the studies' total duration, e.g., 30% for PIPs with studies' duration ≤ 5 years and 20% for PIPs with studies duration > 5 years.

6. Approved Paediatric Medicines

Information on paediatric medicines approved in EU, have been derived from the analysis of the European public assessment reports (EPARs) downloaded from EMA website by checking the presence of approved paediatric indications or paediatric data included in the summary of product characteristics (SmPC) of products centrally approved in 2007-2020. A total of **225** products have been identified. Of these Paediatric MAs, **about one third has been granted between 2017 and 2020**. Fig 6 shows the number and the rate of paediatric products on the total of EMA approved products by year and demonstrates that paediatric products represent around 33% of all the EMA approved products in the whole period (670) with a significant increase in 2020.

Figure 6. Centrally authorised medicines for adults and children in the EU (2007-2020)



Source: compiled by the study team based on 'European public assessment reports (EPAR)'[16] and 'European Paediatric Medicines Database' (EPMD)[17].

Type of products

EMA-authorised 'new medicines' include chemically based drugs as well as biologicals and vaccines. The same categories have been used to classified paediatric medicines. In details, 115 paediatric medicinal products (pMPs) are biologics (23 vaccines), 7 are advanced therapies medicinal products (ATMPs); 103 are chemical (2 vaccines). Biologics have been approved for the treatment of rheumatologic diseases (including juvenile idiopathic arthritis and Lupus Erythematosus), diabetes, hepatitis C and HIV infection and vaccines. Vaccines include a product for Covid-19 vaccination. Six out of 7 ATMPs are approved for rare diseases: beta-thalassaemia, lymphoma and large B-Cell, vision loss due to inherited retinal dystrophy, metachromatic leukodystrophy, spinal muscular atrophy and severe combined immunodeficiency due to adenosine deaminase deficiency. Six out of the 7 ATMPs and 9 vaccines have been authorised in the last three years.

Products distribution by ATC and therapeutic interest

Table 8 shows all the products with paediatric indications (210), distributed according to the ATC code and in comparison with all the EMA approved products.

[16] Available at: https://www.ema.europa.eu/en/medicines/download-medicine-data. Downloaded on 11 March 2022.

[17] Available at: http://93.63.89.65:8081/epmd2_public/. Latest update made in December 2020.

In addition, we also investigated products of special interest such as: medicines intended for paediatric only use (or products of prevalent interest in Paediatrics even if a residual use can be detected in adults), products addressing a highest paediatric unmet need (H-UMN)[18], orphan medicinal products for paediatric use, PRIME approved products:

- *ATC distribution*. The highest absolute number and rate of paediatric on adult products is found for anti-infectives, suggesting that in this area almost the totality of adult medicines have been submitted to a paediatric development. Moreover, in comparison with existing data[19], it's possible to observe an improvement in other areas such as Blood and blood forming organs, Musculoskeletal[20], Alimentary and metabolism in terms of product availability. In oncology a total of 21 paediatric MAs has been granted from 2007 to 2020 with 12 (57%) in the last three years.
- *Orphans*. Orphan medicinal products (OMPs) for paediatric use in our sample are 61, of whom 17 (28%) for metabolic diseases, 11 (18%) for tumours, 11 (18%) for blood disorders and 6 (9.8%) medicines indicated for neurological diseases (see table 8). Among the approved OMPs for paediatric use, 28 received their MA in the last three years.
- *Paediatric only use*. Products in this group are 27 pMPs and include: 6 PUMA products, 8 vaccines, 12 orphan products (one approved following the PRIME scheme). Eight out of 27 products were approved in the period 2018-2020.
- *HUMN*. Products addressing H-UMNs are 72/211 (34.1%), mainly concentrated in the following area: Oncology/immunology, Neurology, Haematology, corresponding to the 69%, 63% and 46% respectively of the total of paediatric products in the concerned area.
- *PRIME*. PRIME approved products including paediatric indications are 6 on a total of 16 products, all receiving their MA in the period 2018-2020.

TABLE 8. CENTRALLY AUTHORISED PAEDIATRIC MEDICINES BETWEEN 2007 AND 2020

THERAPEUTIC AREAS	ADULT MEDICINAL PRODUCTS	PRODUCTS WITH A PAEDIATRIC INDICATION	PAEDIATRIC ORPHAN	PAEDIATRIC ONLY	PRODUCTS ADDRESSING HUMNS	PRIME SCHEME PRODUCTS
A- Alimentary/Metabolism	95	29 (30%)	17	4	4	2
B - Blood and blood forming organs	53	28 (53%)	11	-	13	1
C- Cardiovascular	37	5 (13%)	1	2	4	-
G- Genitourinary	18	3 (16%)	1	-	1	-
H- Systemic Hormones	9	4 (44%)	-	1	1	-
J- Antiinfectives	98	68 (70%)	5	8	7	-
L- Antineoplastic and immunomodulating*	174	35 (20%)	11	2	24	2
M- Musculoskeletal	12	5 (41%)	3	2	3	-
N- Neuropsychiatric	76	16 (21%)	6	7	10	1
R- Respiratory	44	10 (23%)	3	-	4	-
Other (dermatological, sensory, antiparasitic, ophthalmology, various)	54	7 (13%)	3	1	1	-
TOTAL	**670**	**210**	**61**	**27**	**72**	**6**

**of whom 21 for paediatric oncology indications*

[18] H-UMNs products have been identified taking into account the FDA definition of 'paediatric orphan diseases' introduced in the Federal Act (FEDERAL FOOD, DRUG, AND COSMETIC ACT, Part B-Drugs for Rare Diseases or Conditions) and with the help of clinical experts. More details on H-UMN products are discussed in section. 5 of the main report

[19] Ceci a and all, Medicines for children licensed by the European Medicines Agency (EMEA): the balance after 10 years , Eur J Clin Pharmacol, 2006

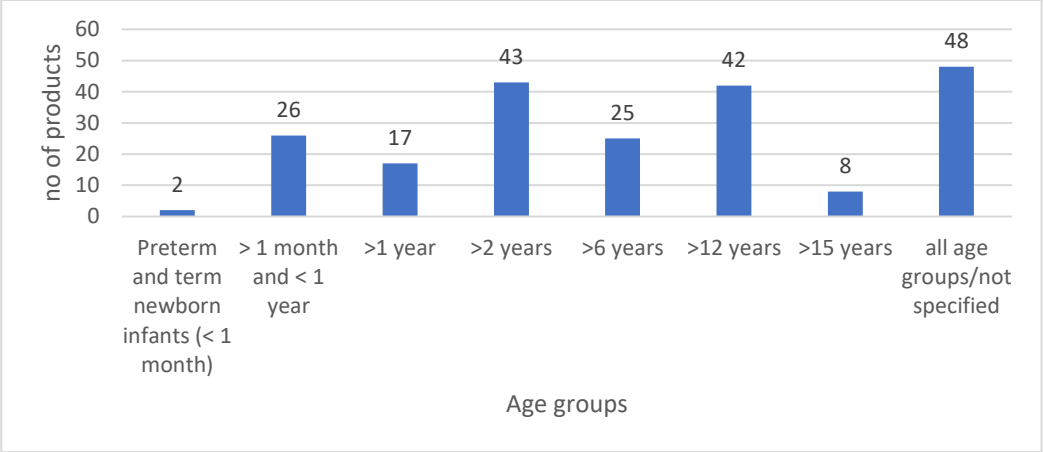
[20] It is noticeable that some orphan paediatric medicines are included in the M-ATC

Source: compiled by the study team, based on EPARs publicly available on EMA website ("Medicines_output_european_public_assessment_reports" spreadsheet at: https://www.ema.europa.eu/en/medicines/download-medicine-data ; downloaded on 11 March 2021) and EPMD.

Products distribution by paediatric age

As detailed in the figure 7 below, the number of paediatric medicines currently on the market covering the different patients' age groups, is high variable, with the group of older children, especially adolescents covered by almost the totality of the available products while a significantly lower number of products is available for children up to 12 years (55%) and for neonates and preterm (24%). A limited number of medicines (13%) covers all the age groups of the paediatric population or the age is not specified (10%).. This result is in contrast with the high number of PIPs that include preclinical and clinical studies with neonates and infants[21] . However these studies are not completed at the time of the agreed paediatric MAs and the indication granted do no cover these age groups.

FIGURE 7. PAEDIATRIC MEDICINES AUTHORISED IN THE PERIOD 2007-2020 DISTRIBUTED BY AGE GROUPS[22]



Source: compiled by the study team

Other paediatric products

Data in this paragraph refer to Centralised approved MPs in the period 2007-2020 and do not consider other existing medicinal products for paediatric use. Among these:

a) Paediatric products approved following a decentralised procedure. Since an official source of data including all the non-centralised procedures is not existing, the number and type of decentralised paediatric medicines is not available. According to internal search based on few National Authority websites, we estimate that an additional 12-15% approved new paediatric indications products can be considered.
b) Paediatric products for which the submission of a PIP was not required. We collected a total of 42 paediatric approved products out of 107 that were no granted PIPs or waivers and documented that some interesting paediatric products, such as three medicines for neonates and premature, 14 covering all ages groups including very young children, 11 oncology-immunology and 16 orphan products are included in this sample.[23]

7. Paediatric Rewards and incentives

[21] Analysis of the measures included in the PIPs agreed in 2020, as derived from the *EMA dataset publicly available on EMA website ("Medicines_output_paediatric_investigation_plans" spreadsheet) at: https://www.ema.europa.eu/en/medicines/download-medicine-data; downloaded on 22 March 2022*

[22] ICH. Clinical Investigation of Medicinal Products in the Paediatric Population. ICH/Topic E11. Eudralex (2000).

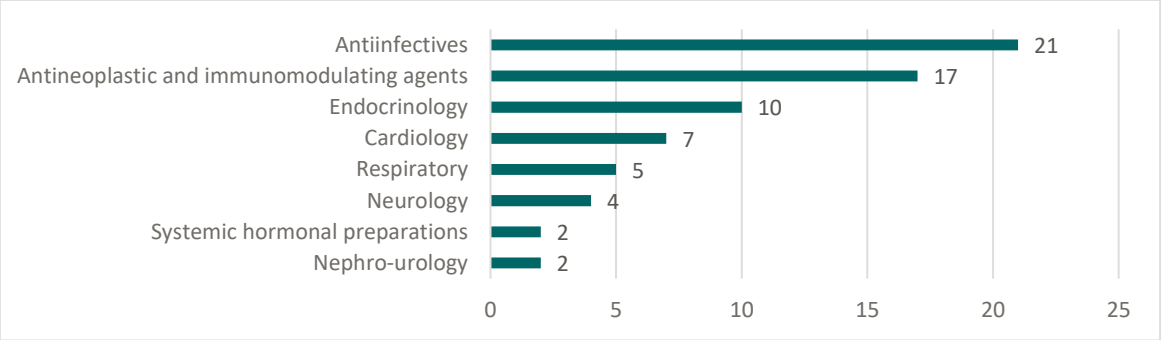
[23] Toma M, Felisi M, Bonifazi D, Bonifazi F, Giannuzzi V, Reggiardo G, de Wildt S, Ceci A; TEDDY European Network of Excellence for Paediatric Research. Paediatric Medicines in Europe: The Paediatric Regulation-Is It Time for Reform? Front Med (Lausanne). 2021 Feb 2;8:593281. doi: 10.3389/fmed.2021.593281. PMID: 33604345; PMCID: PMC7884470.

Several incentives and rewards are foreseen in the Paediatric Regulation to support the research, development and availability of medicinal products for paediatric use, including:

— ***6-month SPC extension:***

Medicines authorised across the EU with the results of studies from a PIP included in the product information are eligible for an extension of their supplementary protection certificate (SPC) by six months.[24] This is the case even when the studies' results are negative.[25] By 2020, 61 paediatric medicines in our sample have been granted the 6-month SPC extension, with more than half (56%) granted after 2017. However, most 6-month SPC extensions have been granted for products classified as anti-infectives and antineoplastic and immunomodulating agents (see figure 8).

FIGURE 8. PRODUCTS WITH AN SPC EXTENSION ACROSS KEY THERAPEUTIC AREAS



Source: compiled by the study team based on the EMA annual reports (2007-2020).

Out of the remaining products, some are no longer eligible for the incentives since the product SPC has already expired, while other products may receive the incentives for up to two years before the expiry date.[26] Data in the EMA annual reports demonstrate a high level of variability in granted SPC extensions among countries as only 8 active substances (Caspofungin acetate, Vaccine against human papillomavirus, Abatacept, Etanercept, Bevacizumab, Mepolizumab, Aprepitant, Zoledronic acid) received an SPC extension in more than 20 EU countries.

— ***PUMA***

Medicines aimed to be developed for the use in children that are already on the market but not protected by any patent are eligible for a paediatric-use marketing authorisation (PUMA). If a PUMA is granted, the product will benefit from 10 years of market protection as an incentive.[27] In *Case study 2* the study team has reported 26 PIPs applications for off-patent products potentially 'intended for future PUMA' of whom, at the date of the analysis, 3 discontinued the development and no further information has been collected on them, 6 have been granted a PUMA and are on the market, in 3 cases the PIP results were negative and in 14 cases the PIP has not been completed. All the PIP applications for these products occurred from 2006 to 2013 (further details on PUMA in Annex Case studies).

— ***Orphan reward:***

Orphan paediatric medicines receive two years of market exclusivity (ME) in addition to the 10-year ME granted to OMPs (known as 'orphan reward'). In total, 14 out of the 64 approved paediatric OMPs received the orphan reward (six of them after 2017) and six more have been granted the 6-month SPC extension instead

[24] In line with Regulation (EU) 2019/933 (working title "SPC Manufacturing Waiver") of the European Parliament and of the Council of 20 May 2019 amending Regulation (EC) No 469/2009 concerning the supplementary protection certificate for medicinal products which was approved in 2019 and introduced new exemptions to the exclusive right of SPC. The exemptions brought by the Regulation benefit EU-based manufacturers of generics and biosimilars. They apply to exporting generics and biosimilars to third countries and enable EU-based manufacturers to store medicinal products for a period of six months preceding the expiry of an SPC.

[25] EMA. Rewards and incentives for paediatric medicines. Available at: https://www.ema.europa.eu/en/human-regulatory/research-development/paediatric-medicines/rewards-incentives-paediatric-medicines

[26] Among 96 products for which information on protections expiry dates is available in our database, we have identified 2 products not more eligible for the 6-month SPC extension and 29 still eligible since the products SPC is expiring after 2019. All data have been collected by MPA business service, available at: http://mpasearch.co.uk/patent-expiry-status

[27] EMA. Paediatric-use marketing authorisations. Available at: https://www.ema.europa.eu/en/human-regulatory/marketing-authorisation/paediatric-medicines/paediatric-use-marketing-authorisations

of the orphan reward. It has been noted that the majority of products (68.75%) have not benefitted of any reward.

— ***PRIME scheme**:*

Paediatric products participated to the development of the PRIME scheme from the beginning. As reported in the document *PRIME: Analysis of the first 5 years' experience,*[28] among the 95 PRIME eligible products, 54% (51/95) include a paediatric indication while 14% (13/95) include a paediatric-only therapeutic indication.

Among the products for which a MA has been issued (21 products), 11 have received a paediatric indication (6 in the period 2018-2020). All of these products had an agreed PIP, except for a product (i.e, *Givlaari,* indicated for the treatment of acute hepatic porphyria – AHP - in adults and adolescents aged 12 years and older) for which a waiver was issued by PDCO[29] , and none of these PIPs was completed (no CC) at the time of the MA with the exception of one drug (i.e., *Skysona*, a paediatric-only medicine, subsequently withdrawn from the market).

[28] https://www.ema.europa.eu/en/documents/report/prime-analysis-first-5-years-experience_en.pdf

[29] Givlaari is authorised for usu

8. Conclusions

Two boxes summarise the main insights from the study that we consider of major interest for the 2018-2020 period. Both improvements and area of persisting concerns are listed.

Main Improvements from the Regulation in 2018-2020 period
PIPs applications increased: 562 PIPs on a total of 1,213 (46%)
Completed PIPs increased: from 28% of the 2015-2017 period to 36% (85 on a total of 233, equal to 8% increase)
Oncology completed PIP increased: from the 10 % in 2017 to 19,7%in 2020
Oncology new approved indications increased: from 2 to 11 by June 2018
All approved paediatric indication following a completed PIP increased: from 71 to 128 (44,5% increase)
Number of deferred measures start to decrease in the period 2018 - 2020
Paediatric medicines centrally approved increased: one third approved from 2018 to 2020
More Innovative paediatric medicine offering major therapeutic advantages:
6 on 7 ATMP in the last three years
27 (on a total of 61) addressing paediatric rare disease
8 (on a total of 27) medicine of exclusive or prevalent paediatric interest
32 (on a total of 72) medicine addressing highest unmet paediatric medical needs
21 oncology drugs in the period
6 paediatric indications as part of PRIME approved products (all in the last three years)

Concerns
A large number of PIPs is not completed years after the PIP approval (i.e. 277 still uncompleted, and have been agreed from 2008 to 2014). Should we consider these PIPs abandoned?
The number of waivers in oncology and cardiology areas overcome the number of PIPs.
A large number of products have been granted paediatric indication in lack of a completed PIPs. There is the need to complete these PIPs in the next years to avoid that some indications/age group remain uncovered.
The actual duration of a PIP is longer than 5 years with no reduction observed in the last three years.
The expected average duration of PIPs to be completed is up to 9.15 years
Only 13% and 42% of paediatric medicines are specifically indicated for children up to 1 years and up to 6 years of age respectively. Only two products include preterm and neonatal uses.
Several PIPs were submitted potentially leading to PUMA applications. The majority was proposed from not-for-profit research organisations but not finalised.