Comparison of the EU and US paediatric legislations and critical analysis of the expected impact of the FDA's "*RACE for Children Act*" on the development of paediatric cancer medicines

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List of abbreviations

BLA	Biologics License Application
BPCA	Best Pharmaceuticals for Children Act
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
EC	European Commission
EMA	European Medicines Agency
EPAR	European Public Assessment Report
EU	European Union
FDA	US Food and Drug Administration
FDAMA	Food and Drug Modernization Act
FDARA	Food and Drug Administration Reauthorization Act
FD&C Act	Federal Food, Drug, and Cosmetic Act
HLGT	High Level Group Term
HLT	High Level Term
ICH	International Council for Harmonisation
IND	Investigational New Drug Application
INN	International Nonproprietary Name
MAA	Marketing Authorisation Application
MedDRA	Medical Dictionary for Regulatory Activities
NCI	National Cancer Institute
NDA	New Drug Application
ODAC	Oncologic Drugs Advisory Committee
PD	Pharmacodynamics
PDCO	Paediatric Committee
PeRC	Pediatric Review Committee
PIP	Paediatric Investigation Plan
PK	Pharmacokinetics
PREA	Pediatric Research Equity Act
PSP	Pediatric Study Plan

PT	Preferred Term
PUMA	Paediatric Use Marketing Authorisation
RACE	Research to Accelerate Cures and Equity
RCT	Randomised Controlled Trial
RWD	Real World Data
RWE	Real World Evidence
SA	Scientific Advice
SmPC	Summary of Product Characteristics
SPC	Supplementary Protection Certificate
VFA	Verband forschender Arzneimittelhersteller

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1 Introduction

Medicinal products are generally studied extensively in adults with numerous nonclinical and clinical studies ensuring safe and efficacious treatments, while children have long been, and to a certain extent still are, neglected by the pharmaceutical industry. Even though children comprise more than 20% of the population in both Europe and the United States (US) (US Census Bureau, 2019; Eurostat, 2021), less than 30% of marketed products include paediatric patients in their labelling (Knopf et al., 2013). Traditionally, paediatric clinical studies have only been conducted rarely owing to a number of reasons, including: lack of post-marketing financial incentives (as adults generally make up the larger fraction of the market), ethical concerns, differences in disease manifestation, higher costs, more challenging recruitment or difficulties in trial design.

Inevitably, the absence of data regarding safety, efficacy and dosing of medicinal products obtained through well-controlled trials in the paediatric population has resulted in a lack of appropriate medicines for children and extensive off-label administration of medicinal products in every day paediatric practice. However, children are not just smaller adults – it must be taken into account that there are well-established physiological and developmental differences between adults and children, as well as differences in the metabolism of medicinal products. Furthermore, pharmaceutical form, formulation or route of administration developed for adults may be inadequate for children.

As such, off-label use of medicinal products in this population bears a major risk for serious harm, for example, due to inadequate dosage information and resulting adverse reactions. In 2004, the European Medicine Agency (EMA) performed an investigation into the harm from off-label use in children, highlighting that adverse reactions are not just more frequent in paediatric off-label use, but they are also more severe compared to adults (EMEA, 2004). It was estimated at that time, that 50-75% of authorised medicines had not been studied appropriately in paediatric patients, if at all (Campbell et al., 1998; Conroy et al., 2000; Hoppu, 2008; Pandolfini & Bonati, 2005; Roberts et al., 2003).

1.1 Brief history of the paediatric legislations in the US and Europe

This issue was already recognised by regulators and the legislative bodies in both Europe and the US in the 1990s. The US Food and Drug Administration (FDA) published a rule in 1994 which updated the requirements of the label's "pediatric[1] use" subsection to include "*more complete information about the use of a drug[2] in the pediatric population*" (FDA, 1994). Hence, marketing authorisation holders were required to determine whether data are available that could support paediatric labelling of the medicinal product. However, as this rule did not include an obligation to carry out clinical studies in paediatric patients in the absence of sufficient paediatric use data, it did not significantly improve the situation. Only the 1997 "Food and Drug Modernization Act (FDAMA)" which allowed FDA to issue a written request outlining studies needed for a specific medicinal product in return for granting 6 months marketing exclusivity for completed studies, as well as the "Pediatric Rule" published in 1998 which required manufacturers to "*provide sufficient data and information to support directions for pediatric use for the claimed indications*" (FDA, 1998) started to address the issue. These were later replaced by the Pediatric Research Equity Act (PREA) and the Best Pharmaceuticals for Children Act (BPCA) which are in place to date and are discussed in detail in Section 3.

The European Commission (EC), together with a team of experts in paediatric medicine, also agreed in 1997 that the legislation needs strengthening with regards to requirements for pharmaceutical companies to conduct paediatric clinical studies (EMEA, 1998). The EC therefore initiated and supported the discussion of this topic by the International Council for Harmonisation (ICH) and the ICH guideline "Note for guidance on clinical investigation of medicinal products in the paediatric population" (ICH E11) was subsequently agreed and came into force in July 2002 (EMEA, 2007). Unfortunately, similar to the FDA rule from

[1] Although British English spelling has generally been used throughout this thesis, American English spelling has been used for FDA/US specific expressions, names, quotations or denotations

[2] While generally the European nomenclature of "medicinal product" has been used throughout this thesis, the FDA/US specific nomenclature of "drug" has also been used occasionally, e.g. in quotations or when describing the US system

1994, these discussions did not have an effect on the unsatisfactory situation and the lack of paediatric medicines in Europe. Only through the Paediatric Regulation (EC) No 1901/2006 (see Section 2 for more details), which came into force on 26 January 2007 and which aims to improve this situation by facilitating the development and availability of medicines for paediatric patients, without impacting adult development (Regulation EC No. 1901/2006, 2006), the development of paediatric medicines is slowly picking up.

Nevertheless, the availability of appropriate medicines for paediatric patients remains a topic of discussion amongst regulators and there still is a long way to go (EMA, 2010; EMA, 2022a).

1.2 Medical need in paediatric oncology

One therapeutic area where the medical need for (new) authorised treatment options is still extremely high is paediatric oncology. Cancer is one of the leading causes of death by disease in children in the Western world and approximately 20% of children with cancer will die from their disease (The Lancet Child & Adolescent Health, 2018; Lupo et al., 2020). Those that can be cured often have to undergo long and burdensome treatment sequelae.

Indeed, the EC has identified paediatric oncology as one therapeutic area where very little progress has been made in terms of new and better treatments for childhood cancers, following the introduction of the Paediatric Regulation (EMA, 2016). Similarly, FDA also noted that although advances have been made in understanding the genetic and molecular aetiology of cancers and thus in developing treatment options for adult patients, the development of medicines to treat paediatric cancers is still very much lagging behind (FDA, 2021a).

Paediatric cancers often differ from adult cancers in terms of aetiology, genetics, organ of origin and natural history of the disease. For example, most adult cancers develop from epithelial tissue such as lung or breast cancer, whereas the majority of paediatric cancers arise from mesoderm tissues such as leukaemias or lymphomas. Further, some cancers that are common in adults rarely or never occur in children and *vice versa* (Barry, 2021; Gröbner, 2018). Therefore, medicinal products developed for the treatment of adult cancers are often exempt from the regulatory requirements to also perform a development program in paediatric patients.

However, it has been shown that the genetic drivers and molecular abnormalities underlying adult cancers are also found in many paediatric cancers. In fact, recent publications show that 45% of genes that are drivers of paediatric cancer development have also been identified in adult pan-cancer studies and approximately 50% of paediatric cancers contain genetic or molecular alterations for which targeted treatment options are available or under development for the adult population (Gröber, 2018; Ma, 2018).

Therefore, while there is still a big medical need for paediatric cancer treatments, there is also great potential in many products that are being developed for the treatment of adult cancers. It is now in the hands of regulators and lawmakers to use this potential.

2 Paediatric regulatory landscape in Europe

2.1 Concept of obligations and rewards

In the European Union (EU), the Paediatric Regulation forms the basis for the development of safe, efficacious and high-quality medicinal products for paediatric patients. It "*aims to facilitate the development and accessibility of medicinal products for use in the paediatric population, to ensure that medicinal products used to treat the paediatric population are subject to ethical research of high quality and are appropriately authorised for use in the paediatric population, and to improve the information available on the use of medicinal products in the various paediatric populations […] without subjecting the paediatric population to unnecessary clinical trials and without delaying the authorisation of medicinal products for other age populations*" (Regulation EC No. 1901/2006, 2006).

To achieve this goal, the Paediatric Regulation sets out a system of obligations and rewards:

Sponsors are **obliged** to consider the potential of their product for the paediatric population (i.e. preterm of term newborn infants [0 – 27 days], infants and toddlers [28 days - < 24 months], children [2 - < 12 years] and adolescents [12 - < 18 years]) and to discuss a potential paediatric development program (the Paediatric Investigation Plan [PIP]) with EMA's Paediatric Committee (PDCO) early during adult development. Importantly, without such an agreed PIP, validation at the marketing authorisation application (MAA) stage will not be possible.

If PDCO considers the product to have a potential benefit for one or more of the paediatric subsets, the Sponsor will be expected to carry out a development program specifically for this age group(s). Such a development program should be designed prospectively to collect information on the product's efficacy and safety profile in the respective paediatric population(s), without exposing children to unnecessary trials.

Importantly, and as further discussed in Section 2.3.2, it should be noted that the Paediatric Regulation aims to achieve development in the paediatric indication with the highest need, which may not always be identical to the intended adult indication.

In order to offset the additional costs that arise through such studies, the Paediatric Regulation also offers a number of **rewards and incentives** for Sponsors developing medicinal products for the paediatric population. These rewards depend on the regulatory nature of the concerned products, as outlined in Table 1 below. Here, an important difference to the US system (see Section 3.2) is that in the EU orphan medicinal products are not exempted from the Paediatric Regulation. However, they are nevertheless considered separately, and different incentives are offered for the paediatric development of orphan medicinal products

Table 1: System of obligations and rewards for paediatric studies

Type of medicinal product	**Obligation**	**Reward**	**Legal basis in the Paediatric Regulation**
New medicinal product (authorised on the basis of Article 8(3) of Directive 2001/83/EC)	Paediatric study (or waiver)	• 6 months extension on SPC • Free SA for questions relating to paediatric development	Article 36
Authorised medicinal products covered by a patent/SPC with a new indication, pharmaceutical form or route of administration	Paediatric study (or waiver)	• 6 months extension on SPC • Free SA for questions relating to paediatric development	Article 36
Orphan medicinal product	Paediatric study (or waiver)	• 2 additional years of market exclusivity (on top of 10 years from orphan designation) • Free protocol assistance for questions relating to paediatric development	Article 37
Off-patent medicines	None (voluntary PIP possible for PUMA)	• 10 years of market protection if PUMA is granted • Free SA for questions relating to paediatric development	Article 38

Information from Regulation EC No. 1901/2006, 2006

Abbreviations: PUMA: Paediatric use marketing authorization, SA: Scientific advice, SPC: Supplementary protection certificate

Several conditions must be fulfilled to be eligible for the rewards, as outlined in Article 36 and Article 37 of the Paediatric Regulation (Regulation EC No. 1901/2006, 2006):

1. Positive compliance check at time of MAA demonstrating that all measures agreed in the PIP have been fulfilled
2. Inclusion of results of the studies that were performed in compliance with the agreed PIP into the product's summary of product characteristics (SmPC), as well as the package leaflet (as appropriate). Importantly, the outcome of the studies (i.e. positive or negative) does not affect the eligibility for the rewards.
3. Authorisation of the product in all EU Member States

2.2 Product-specific waivers and class waivers

For certain medicinal products or in certain conditions and indications, paediatric development is not required and can thus be waived by the PDCO as outlined in Article 11 of the Paediatric Regulation to avoid unnecessary studies in the paediatric population. This is the case for products that:

a) are likely to be ineffective or unsafe in part or all of the paediatric population
b) are intended for conditions that do not occur in the paediatric population
c) do not represent a significant therapeutic benefit over existing treatments for paediatric patients.

There are two types of waivers: product-specific waivers and class waivers.

2.2.1 Product-specific waivers

Product-specific waivers may be issued for some or all of the paediatric subsets and must be supported by an appropriate and detailed justification.

In case of a) the justification should focus on the pharmacological properties of the product or the product class, taking into account results of non-clinical studies, clinical trials, post-marketing data (where available), or a review of the scientific literature. The absence of sufficient data that are relevant to determine safety and/or efficacy in the paediatric population are typically not considered an acceptable justification.

Some conditions do not occur in the paediatric population, or subsets thereof (b)). In those cases, the Sponsor can be exempted from performing a study in the paediatric population based on a detailed description of the incidence and/or prevalence of the condition in the different populations as well as on confirmed earliest age of onset of the condition.

For other products, a significant therapeutic benefit for the paediatric population may not be assumed (c)), in which case a paediatric development program would not be ethically justifiable. This may be the case if existing medicinal products are authorised for use in the paediatric population and the concerned medicinal product would not be expected to be superior in terms of efficacy or safety. Additionally, if a disease is so rare that it would not be feasible to recruit enough patients to run a study that would give clinically meaningful results, this may also be a reason to justify a waiver on the grounds of no significant therapeutic benefit for the paediatric population.

2.2.2 Class waivers

Unlike product-specific waivers which can be requested by the Sponsor within the scope of a PIP submission, class waivers are adopted on the PDCO's own motion (Article 12 of the Paediatric Regulation). Class waivers can either refer to a medical disease (condition), to a class of medicinal products or (typically) a combination of the two, and they are based on the same grounds as product specific waivers.

A list of these class waivers is published on the EMA website (EMA, 2022b) and confirmation of the applicability of a class waiver for a specific medicinal product can be requested by the Sponsor.

2.2.3 2015 update of the class waivers list

In line with Article 14 of the Paediatric Regulation, the PDCO may review and update the list of class waivers at any time. The list was last reviewed and updated in July 2015 (EMA, 2015). Until then, most class waivers were referring to specific medical diseases, most of them in the field of oncology, based on the grounds that they do not occur in the paediatric population. Therefore, Sponsors developing products for adult patients in those conditions could easily receive a class waiver without considering the potential benefit of their products for the paediatric population in a broader context.

However, as discussed in Section 1.2 in more detail, medicinal products developed to treat adult cancers also have a huge potential for the treatment of paediatric malignancies. One example is Xalkori (crizotinib), which was authorised for the treatment of anaplastic lymphoma kinase (ALK) positive advanced non-small cell lung cancer (NSCLC) in 2012 (EMA, 2012a). At that time, "lung carcinoma (small cell and non-small cell carcinoma)" was on the class waiver list and Xalkori was thus granted a class waiver. However, ALK has also been shown to be implicated in a number of paediatric cancers such as anaplastic large cell lymphoma or neuroblastoma. Nevertheless, due to the class waiver, the Sponsor did not need to investigate the potential of Xalkori for paediatric malignancies.

The PDCO noted that the current class waivers list was opposing the primary aim of the Paediatric Regulation, which is to consider the potential benefit and support the development of medicinal products for paediatric patients. The PDCO, as well as paediatric patient representatives and academic stakeholders thus considered that many pharmacological properties or mechanisms of action and their medical plausibility for the paediatric population should be reviewed as they may be of relevance (Adamson, 2013; Institute of Cancer Research, 2014; Vassal et al., 2013).

Therefore, the class waivers list was updated by the PDCO in 2015. Some class waivers have been revoked completely, including the following two for oncology conditions:

- all medicines for treatment of liver and intrahepatic bile duct carcinoma
- all medicines for treatment of kidney and renal pelvis carcinoma

All other class waivers for oncology conditions have been revised and now only apply for certain classes of medicinal products on the basis that these products are likely going to be ineffective in the paediatric population or that they lack significant therapeutic benefit over existing treatments for the paediatric population. This applies in particular to product classes which have been studied in paediatric cancer patients and/or disease models (EMA, 2015).

The analysis of the effect of this change on the landscape of paediatric medicines, in particular for the treatment of paediatric cancers, is part of this work and results are described and discussed in more detail in Sections 6.2 and 7, respectively.

2.3 The Paediatric Investigation Plan (PIP)

2.3.1 Timing

Irrespective of whether a (class) waiver is being applied for, the paediatric development program must be discussed with PDCO early on during adult development. According to the Paediatric Regulation this should be done *„not later than upon completion of the human pharmaco-kinetic studies in adults*“ (Regulation EC No. 1901/2006, 2006). At that time, the Sponsor shall submit a PIP, an application for a product specific waiver (or a combination thereof) or request the confirmation of applicability of a class waiver.

However, it is not intended that paediatric studies must be started at that time. In fact, paediatric studies are often deferred, meaning that they are started and/or completed after the adult MAA submission. The reasons for this may include the need for further data from adults to determine a save starting dose, or the need to first develop a paediatric-specific formulation. Similarly, for medicines that are unlikely to benefit the paediatric population, a waiver system is in place, giving Sponsors a permit not to conduct paediatric studies in some or all paediatric subsets as described in Section 2.2.

2.3.2 Choice of PIP condition and content of the PIP

In the PIP/waiver application, the Sponsor details their plans for the paediatric development, including background information on the product and the disease to be treated. Importantly, when considering the scope of a PIP/waiver, the MedDRA (Medical Dictionary for Regulatory Activities) hierarchy of disease classification (Figure 1) and the product‘s mechanism of action should be taken into account in accordance with the EMA „Policy on the determination of the condition(s) for a Paediatric Investigation Plan / Waiver“ (EMA, 2012b), as the most suitable paediatric indication or the paediatric indication with the highest medical need may not always be identical to the intended adult indication.

Typically, the High Level Term (HLT) relating to the proposed adult indication would be considered as the PIP condition and all Preferred Terms (PTs) falling under this HLT could be considered for potential paediatric use (i.e. the paediatric indication). However, due to the varying granularity of the MedDRA hierarchy, and depending on the therapeutic area,

a higher (High Level Group Term; HLGT) or lower (PT) level could also be identified as the most appropriate PIP condition. In particular for PIPs in the therapeutic area of oncology, the HLGT is often chosen as the PIP condition based on the product's mechanism of action (EMA, 2012b).

Importantly, the guidance states that "*PDCO may request development in a single PIP indication under a single condition*" (EMA, 2012b). Therefore, justifications for full waiver applications must similarly cover the whole PIP condition.

Figure 1: Structural hierarchy of the MedDRA and relationship between HLT and PTs

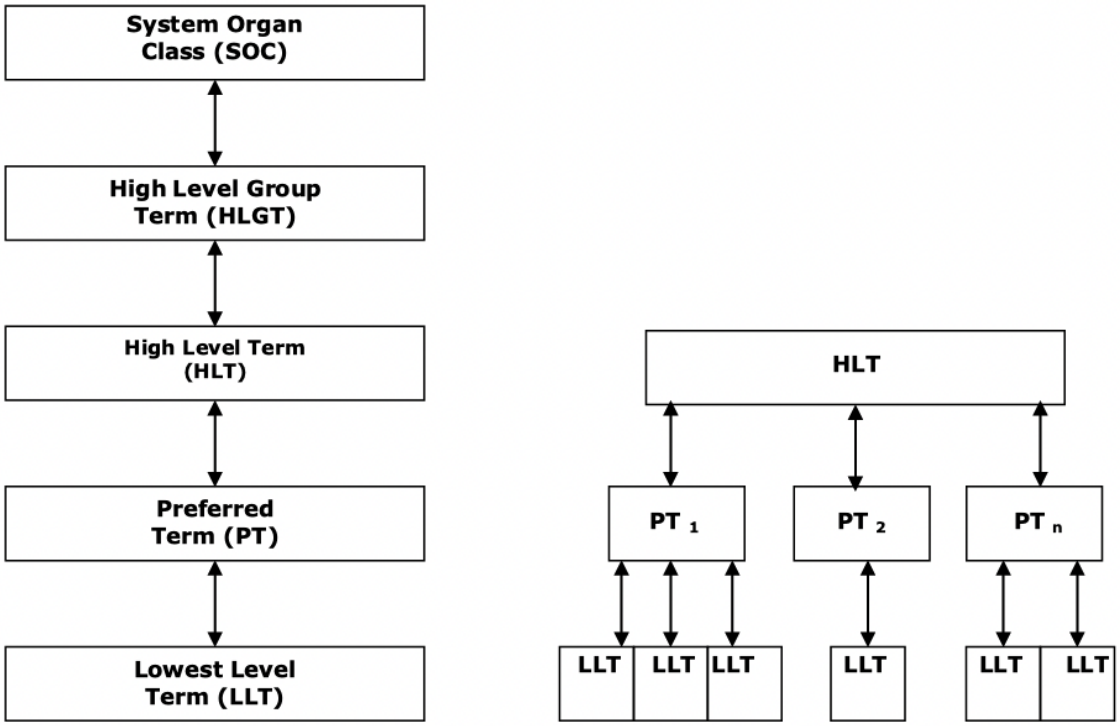


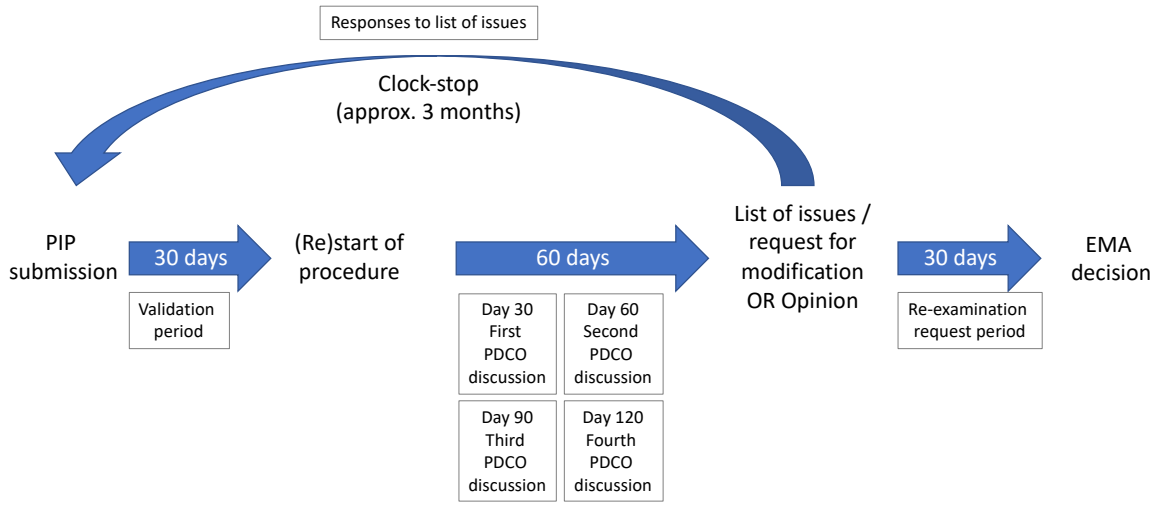
Figure taken from: Policy on the determination of the condition(s) for a Paediatric Investigation Plan / Waiver (EMA, 2012b)

In addition to background information on the condition, a justification of why the product is (or is not) considered to have a potential benefit for one or more of the paediatric subsets should be included as well as details of the planned paediatric development program designed to collect data on efficacy and safety in the respective paediatric population(s). This can include measures such as paediatric clinical studies, modelling and extrapolation studies, further paediatric-specific formulation development or additional nonclinical juvenile toxicity studies.

2.3.3 Assessment by PDCO

Upon submission, the details of this PIP/waiver application, as well as the proposed timing of any measures will be discussed up-front with the PDCO in a clearly defined procedure (as outlined by Articles 16ff of the Paediatric Regulation; Figure 2).

Figure 2: Timelines of PIP assessment by PDCO



Abbreviations: EMA: European Medicines Agency, PDCO: Paediatric Committee, PIP: Paediatric investigation plan

The PIP decision which is issued by EMA upon completion of the PIP assessment outlines the key elements of the paediatric development program (clinical, modelling/extrapolation, nonclinical and quality aspects) which will be binding for the Sponsor. It also forms the basis of the compliance check which is performed at or before MAA validation.

In case the Sponsor encounters difficulties with the implementation of any of the agreed measures, an application for a PIP modification should be submitted in due time as outlined in Article 22 of the Paediatric Regulation (Regulation EC No. 1901/2006, 2006).

3 Paediatric regulatory landscape in the US

3.1 BPCA versus PREA – "the carrot and the stick"

The US legislation framework which aims to foster the development and availability of safe and efficacious medicinal products for paediatric patients, is often described as a "the carrot and the stick" system. BPCA is the carrot, offering incentives for Sponsors performing paediatric studies voluntarily, whereas PREA is the stick, requiring Sponsors to submit paediatric data together with any marketing applications for new active ingredients, indication, dosage form, dosing regimen or route of administration.

BPCA and PREA are laid down in section 505A and 505B(a)(1)(B) of the Federal Food, Drug and Cosmetic Act (FD&C Act), respectively.

3.1.1 BPCA

BPCA has been enacted by Congress in 2002 as the successor of the 1997 FDAMA which first introduced the concept of paediatric exclusivity. With BPCA, a voluntary incentive program was established through which Sponsors who perform FDA-requested paediatric studies may receive an additional 6 months of exclusivity in addition to any existing patent or statutory market protections. It thus offers a regulatory tool to increase development in medicinal products that may have health benefits for children.

To be eligible for BPCA, FDA must issue a written request for paediatric studies. Written requests can be issued at any time, and both for products that are already marketed and for products that are still under development. If FDA determines that a certain product may provide a significant therapeutic benefit for the paediatric population (or subsets thereof), they may request paediatric studies. Studies can be requested in indications that are also the focus of adult development, as well as in indications that are different from the adult development program. The Sponsor is, however, not obliged to conduct these studies, but can chose to do so in order to receive the reward of 6 months paediatric exclusivity. Importantly, to be eligible for this reward, the study(ies) only have to be completed within the specified and agreed timeframe. They do not need to yield positive results leading to a paediatric indication in the label.

Furthermore, BPCA can also be initiated at the request of a Sponsor. For this, the Sponsor needs to submit a proposed paediatric study request to FDA in order to receive a formal written request.

3.1.2 PREA

PREA, which was signed into law by Congress in 2003 following the invalidation of the 1998 “Pediatric Rule”, constitutes a requirement (rather than a voluntary action like BPCA) for Sponsors to submit a Pediatric Study Plan (PSP) and perform studies in paediatric patients. It applies to all New Drug Applications (NDAs) and Biologics License Applications (BLAs), as well as to all supplemental applications for a new indication, dosage form, dosing regimen or route of administration, unless a waiver has been issued which exempts the Sponsor from this obligation.

3.2 Drug-specific waivers and orphan drug exemptions

3.2.1 Drug-specific waivers

Like in the EU, paediatric development may not be required for all medicinal products and drug-specific waivers can be requested under PREA for some or all subsets of the paediatric population (FDA, 2020). This is the case if:

a) necessary studies are impossible or highly impracticable (because, for example, the number of patients is so small or the patients are geographically dispersed)
b) there is evidence strongly suggesting that the drug would be ineffective or unsafe in that age group
c) the drug does not represent a meaningful therapeutic benefit over existing therapies for paediatric patients in that age group and is not likely to be used in a substantial number of paediatric patients in that age group.

For partial waivers that are requested only for a specific age group, a fourth waiver category exists:

d) the applicant can demonstrate that reasonable attempts to produce a paediatric formulation necessary for that age group have failed.

All waiver requests need to be supported with a relevant justification, including supportive data from all available sources, similar to the EU requirements for waiver justifications as outlined in Section 2.2.1.

3.2.2 Waiving of orphan indications

PREA generally does not apply to products that have been granted an orphan designation for a rare disease or condition, due to the PREA orphan exemption. For those products, submission of a PSP is not required.

This has long been used as a loophole for Sponsors to not conduct paediatric studies under PREA as FDA used to issue orphan designations for "paediatric subpopulations" which would provide eligibility for the orphan exemption. However, in July 2018, FDA closed this loophole and announced to no longer issue any "paediatric subpopulation" orphan designations (FDA, 2018a).

Furthermore, in 2017 the US Congress passed the "*Research to Accelerate Cures and Equity (RACE) for Children Act*", which came into effect in August 2020 and further limits the PREA orphan exemptions specifically for oncology products (US Congress, 2017). This Act is described and discussed in more detail in the next section (Section 3.2.3).

3.2.3 RACE for Children Act

The RACE for Children Act was included as Title V in the 2017 *Food and Drug Administration Reauthorization Act (FDARA)*. In particular, Section 504 of FDARA makes amendments to Section 505B of the FD&C Act (PREA) for the development of drugs and biological products for paediatric cancers. It eliminates the PREA orphan exemptions from paediatric studies for drugs that are being developed for the treatment of adult cancers and that are directed at a molecular target which may be of relevance to treat paediatric cancers.

As discussed in detail in Section 1.2, even years after introduction of regulations and legislations which aim to foster development of paediatric medicines, paediatric oncology is still a therapeutic area with a huge medical need. And the potential of products developed originally for the treatment of adult cancers has not been utilised well. This is due to a combination of the nature of diseases and the way the legislations were set up.

Before the introduction of the RACE for Children Act, those submissions that would usually require a PSP, were exempted from this requirement if they were for indications for which orphan designation has been granted. However, many types of cancers (both paediatric and adult) are rare diseases, so that the majority of submissions for adult oncology indications received a waiver for the PSP based on the PREA orphan exemption. Furthermore, under PREA, the requirements to consider to what extent it would be medically plausible to perform paediatric clinical studies are directly related to the adult indication (in contrast to the EU PIP where the mechanism of action is also taken into account to a certain extent for the choice of PIP condition as outlined in Section 2.3.2). If the disease does not occur in the paediatric population a full waiver is generally accepted. This also used to be the case for non-orphan oncology indications such as lung cancer, which does not occur in the paediatric population. This of course creates a big gap in the development of paediatric cancer treatments, despite the fact that many treatments developed for adult patients bear a huge potential to also be effective for the treatment of various types of cancer in paediatric patients.

With the RACE for Children Act, the FDA now has the opportunity to demand the evaluation of new drugs or biologics in a paediatric oncology indication in case the product is intended for the treatment of an adult cancer, and the molecular target of the product is considered substantially relevant to the growth or progression of paediatric malignancies (US Congress, 2017; FDA, 2021a). As such, the RACE for Children Act has put an end to the PREA orphan exemptions and waivers based on disease not occurring in the paediatric population for products developed as cancer treatments.

As part of these legislative amendments, the FDA was also required, together with an internal committee, the National Cancer Institute (NCI) and the Pediatric Subcommittee of the Oncologic Drugs Advisory Committee (ODAC), to establish a list of molecular targets which are to be considered “substantially relevant” to the growth or progression of paediatric cancers. This list is updated regularly based on new data becoming available, and is published on the FDA website (The Relevant Molecular Target List). Similarly, a list of molecular targets that are “not substantially relevant” (The Non-Relevant Molecular Target Leading to Waiver List) is also published (FDA, 2021b). Both lists should be considered by Sponsors for the planning of their paediatric development plan.

As the RACE for Children Act only came into force relatively recently, data on its effectiveness in closing the gap of paediatric cancer treatments do not exist yet. However, an analysis of the impact that it is expected to have, is the focus of this work and will be described and discussed in detail in Sections 6.1 and 7.

3.3 The pediatric study plan (PSP)

3.3.1 Timing

Whereas PIPs in the EU are expected to be submitted as early as after completion of the adult pharmacokinetics (PK) studies (i.e. typically after Phase 1), the FDA guidance on PSPs states that "*a sponsor must submit an iPSP, if required under PREA, before the date on which the sponsor submits the required assessments or investigation and no later than either 60 calendar days after the date of the end-of-phase 2 meeting or such other time as agreed upon between FDA and the sponsor*" (FDA, 2020). However, it is recommended to initiate early dialogue with the FDA in order to identify the paediatric studies that are needed and to facilitate planning of the development program.

3.3.2 Content of the PSP

The overall content and structure of the PSP is comparable with the EU PIP. It should outline the Sponsor's detailed plans for paediatric development, including an overview of the disease to be treated, the mechanism of action and medical plausibility of the product in the condition and for the targeted paediatric subset(s), the intended paediatric formulation, as well as an outline of the planned clinical, nonclinical, modelling and extrapolation studies.

In fact, joint EMA and FDA guidance and procedural information regarding structure, content and submission of PIPs and PSPs has been published (EMA/FDA, 2020; EMA/FDA, 2021). While these are specific to products intended for the treatment of cancer and the treatment/prevention of COVID-19, some of the concepts also apply for PIPs and PSPs in other therapeutic areas.

As already described in Section 3.2.1, for some products, paediatric development may not be necessary or feasible in which case a request and justification for a waiver should be

included in the PSP. Similarly, if it is not scientifically feasible to conduct the planned studies before the submission of the NDA or BLA (or supplement), for example if further data from the adult clinical development are required before starting any studies in the paediatric population, a request for a deferral may also be included but should be justified adequately.

3.3.3 Assessment by the FDA

In the US the PSP is submitted to the drug's Investigational New Drug Application (IND). Initial assessment by the FDA typically takes no longer than 90 days and includes internal consultation with the Pediatric Review Committee (PeRC). This is followed by another 90 days for the Sponsor to resolve and respond to the FDA's comments. The FDA will then either agree or disagree with the proposed PSP.

Importantly, and in contrast to the EU procedure, FDA does not formally grant a waiver or deferral at the time of PSP submission. They may agree that the requested waiver or deferral is reasonable, but this judgement is subject to change in case new or additional information becomes available, in which case a PSP amendment will be requested by FDA. Only at the time of NDA, BLA or supplement approval they will officially grant the waiver or deferral (FDA, 2020).

4 Objective of this thesis

The objective of this master thesis was the analysis of the impact that FDA's RACE for Children Act can be expected to have on the development of medicinal products for the paediatric population.

For this, a three-step approach was taken. First, a list of all oncology drugs that were approved by FDA (original and supplement submissions) between January 2016 and August 2020, the date of coming into effect of the RACE for Children Act, was assembled and aligned with information from the "Relevant Molecular Target List" and "Non-Relevant Molecular Target Leading to Waiver List" from FDA to analyse how many products and indications would fall under the new RACE for Children Act. Based on this information, as well as information about the PIP status in the EU, the potential of this new legislation was discussed.

In a second step, the impact of PDCO's class waiver list update was evaluated by analysing its effects on the number of PIP and waiver applications in the EU in general and for oncology products specifically. The aim of this class waiver list update was similar to that of the RACE for Children Act, as it gave the PDCO more options to request paediatric development in indications that are distinct to the adult indication but have the same or similar underlying disease mechanism. As such, this analysis was used as an indicator of the potential impact of the FDA's RACE for Children Act.

Finally, oncology products approved by FDA between August 2020 and December 2021 and falling under the RACE for Children Act were assessed to examine whether the assessments and predictions of the first two steps hold true for this preliminary dataset.

5 Methods

5.1 Step 1: Analysis of FDA approved oncology medicinal products between January 2016 and August 2020

5.1.1 Assembly of the data set

Collection of oncology approvals

First, a list of all oncology medicinal products that were approved by FDA between January 2016 and August 2020, the date of the RACE for Children Act coming into effect, was assembled. The data was collected from the FDA "*Oncology (Cancer) / Hematologic Malignancies Approval Notifications*" website https://www.fda.gov/drugs/resources-information-approved-drugs/oncology-cancer-hematologic-malignancies-approval-notifications), considering both new submissions and indication extension supplement submissions for previously approved medicinal products.

The following information was collected:

- Approval date
- International nonproprietary name (INN)
- Active substance
- Submission category (original submission / new application vs supplemental submission / indication extension)
- Approved indication(s)
- Condition(s) relating to the approved indication(s)
- Paediatric age groups included in the label (if any)

Identification of molecular target and orphan status

For each active substance, the molecular target was then identified either from the product's label (Section 12.1 – Mechanism of action) or found out by performing a literature search in databases such as PubMed (https://pubmed.ncbi.nlm.nih.gov/) or DrugBank online (https://go.drugbank.com/). This information was then compared with the "*Relevant Molecular Target List*" and the "*Non-Relevant Molecular Target Leading to Waiver List*" published by the FDA (https://www.fda.gov/about-fda/oncology-center-

excellence/pediatric-oncology; accessed on 6th November 2021), as well as the FDA's "*Orphan Drug Designations and Approvals*" database (https://www.accessdata.fda.gov/scripts/opdlisting/oopd/).

Collection of data regarding EU PIP status

For each combination of product and indication on the list, it was then checked whether an EU PIP exists by using the search function on the EMA website, (https://www.ema.europa.eu/en/medicines/ema_group_types/ema_pip) selecting the category "*Paediatric investigation plans*". The following information was collected:

- PIP condition
- Paediatric age groups (if applicable)
- Granting of full waiver
- PIP decision number

For those products and/or indications which are already authorised in the EU and for which no PIP decision could be found, an additional search of the respective European Public Assessment Report (EPAR) was performed to analyse whether a class waiver had been granted.

5.1.2 Data analysis

The data set was analysed using Excel data processing tools and functions. In addition, integrated Excel data visualisation tools were used to create graphical representations of these data.

5.2 Step 2: Comparison with effect of EU class waiver list revision

5.2.1 Assembly of the data set

In the second step, an overview table of EU PIP opinions between the years 2008 and 2020 was created based on data collected from the EMA annual reports (https://www.ema.europa.eu/en/about-us/annual-reports-work-programmes). The "*PDCO opinions and EMEA decisions on paediatric investigation plans and waivers*" annex for each annual report was manually analysed concerning the following information:

- Total number of opinions on PIPs (both positive and negative opinions)
- Total number of positive opinions on new applications
    - Further divided into applications for a study (with or without deferral and partial waiver) or full waiver
- Total number of positive opinions on PIP modifications
- Each of the above was further delineated into total number of opinions and opinions in the field of oncology based on the therapeutic area classifications by PDCO

5.2.2 Data analysis

The data set was analysed using Excel data processing tools and functions. In addition, integrated Excel data visualisation tools were used to create graphical representations of these data.

5.3 Step 3: Review of FDA approved oncology medicinal products between August 2020 and December 2021 falling under the RACE for Children Act

5.3.1 Assembly of the data set

Collection of original oncology approvals

First, a list of all oncology medicinal products that were approved by FDA between August 2020 and December 2021, the cutoff date for this thesis, was assembled, taking into account only original (new) submissions. The data was collected from the FDA "*Oncology (Cancer) / Hematologic Malignancies Approval Notifications*" website https://www.fda.gov/drugs/resources-information-approved-drugs/oncology-cancer-hematologic-malignancies-approval-notifications), as well as FDA's Center for Drug Evaluation and Research (CDER) and Center for Biologics Evaluation and Research (CBER) "*Novel Drug Approvals*" websites (https://www.fda.gov/drugs/new-drugs-fda-cders-new-molecular-entities-and-new-therapeutic-biological-products/novel-drug-approvals-2020; https://www.fda.gov/vaccines-blood-biologics/development-approval-process-cber/biological-approvals-year).

The following information was collected:

- Approval date
- Submission date
- International nonproprietary name (INN)
- Active substance
- Approved indication(s)

Identification of molecular target

For each active substance, the molecular target was then identified either from the product's label (Section 12.1 – Mechanism of action) or found out by performing a literature search in databases such as PubMed (https://pubmed.ncbi.nlm.nih.gov/) or DrugBank online (https://go.drugbank.com/). This information was then compared with the "*Relevant Molecular Target List*" and the "*Non-Relevant Molecular Target Leading to*

Waiver List" published by the FDA (https://www.fda.gov/about-fda/oncology-center-excellence/pediatric-oncology; accessed on 10th January 2021).

Collection of data on PSP status

For each submission, it was then checked whether a PSP was agreed with FDA by searching the product's approval letter ("*Required Pediatric Assessments*" Section), accessed via the "*Drugs@FDA: FDA-Approved Drugs*" searchtool (https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm). The following information was collected:

- PSP
- Waiver (including the grounds for granting the waiver)

5.3.2 Data analysis

The data set was analysed using Excel data processing tools and functions.

6 Results

6.1 Step 1: Analysis of FDA approved oncology medicinal products between January 2016 and August 2020

6.1.1 Description and baseline analysis of the data set

The table with the complete data set can be found in Annex 1.

Between January 2016 and August 2020, a total of 204 submissions have been made to the FDA's Oncology Divisions, comprising 106 different products. Of those, 80 (39%) were original NDAs or BLAs and 124 (61%) were supplement applications.

The approved indication wording from the labels was classified into higher-order "associated conditions" to be able to better screen and analyse the data. This also included breaking up label indications into several individual conditions. Examples for this are provided in Table 2.

Table 2: Examples for indications in label and the associated condition(s)

Indication in label	Associated condition(s)
first-line treatment of stage III non-small cell lung cancer (NSCLC) in patients who are not candidates for surgical resection or definitive chemoradiation, or metastatic NSCLC expressing PD-L1 (TPS ≥ 1%) as determined by an FDA-approved test, with no EGFR or ALK genomic tumor aberrations	non-small cell lung cancer
previously treated follicular lymphoma (FL) and previously treated marginal zone lymphoma (MZL)	follicular lymphoma
	marginal zone lymphoma
maintenance treatment of recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer after complete or partial response to platinum-based chemotherapy	ovarian cancer
	fallopian tube cancer
	primary peritoneal cancer

Taking into account that a single submission could thus contain several conditions, a total of 233 individual conditions were included in the 204 overall submissions. However, only

182 (78%) conditions were uniquely scored for the respective product; this means that each condition would only be counted once per product like in the example in Table 3.

Table 3: Example for scoring of individual conditions

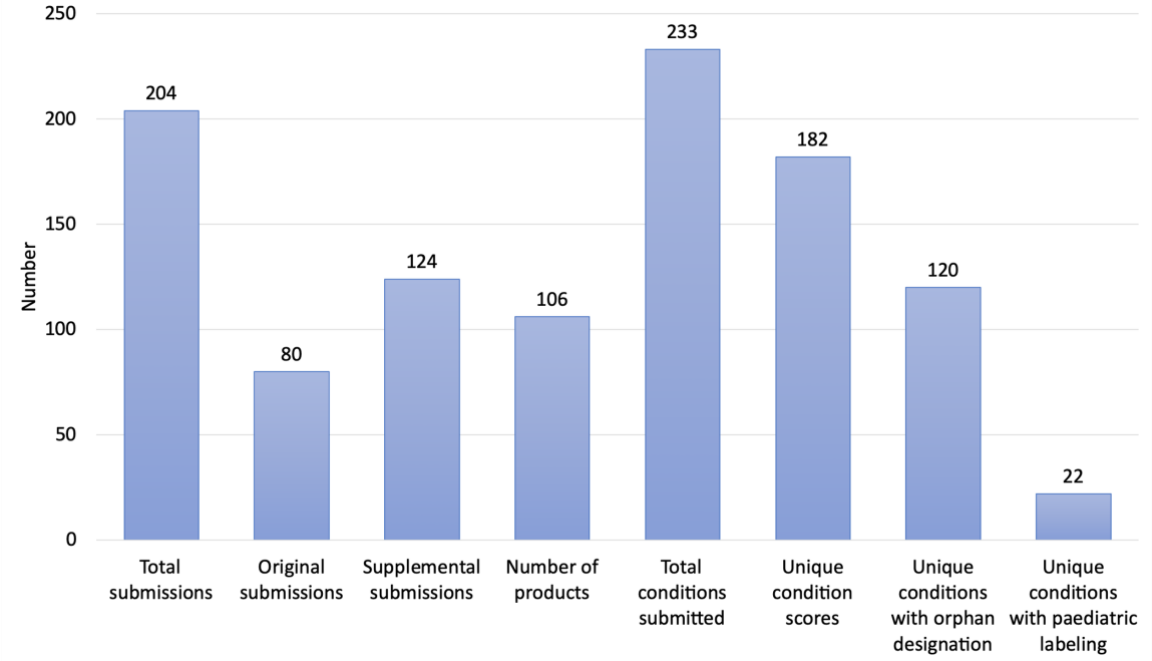
INN	Active substance	Submission	Indication in label	Associated condition
ALUNBRIG	brigatinib	ORIG-1	anaplastic lymphoma kinase (ALK)-positive metastatic non-small cell lung cancer (NSCLC) who have progressed on or are intolerant to crizotinib	non-small cell lung cancer
ALUNBRIG	brigatinib	SUPPL-8	anaplastic lymphoma kinase (ALK)-positive metastatic non-small cell lung cancer (NSCLC)	non-small cell lung cancer

For ALUNBRIG, the condition "non-small cell lung cancer" was only scored once, even though the indication in the label is not fully identical. Grey text means: not scored/counted towards number of unique conditions.

Of the 182 unique conditions, 120 (66%) have been granted orphan designation.

These baseline parameters are also summarised in Figure 3 below.

Figure 3: Summary of baseline analysis of the data set



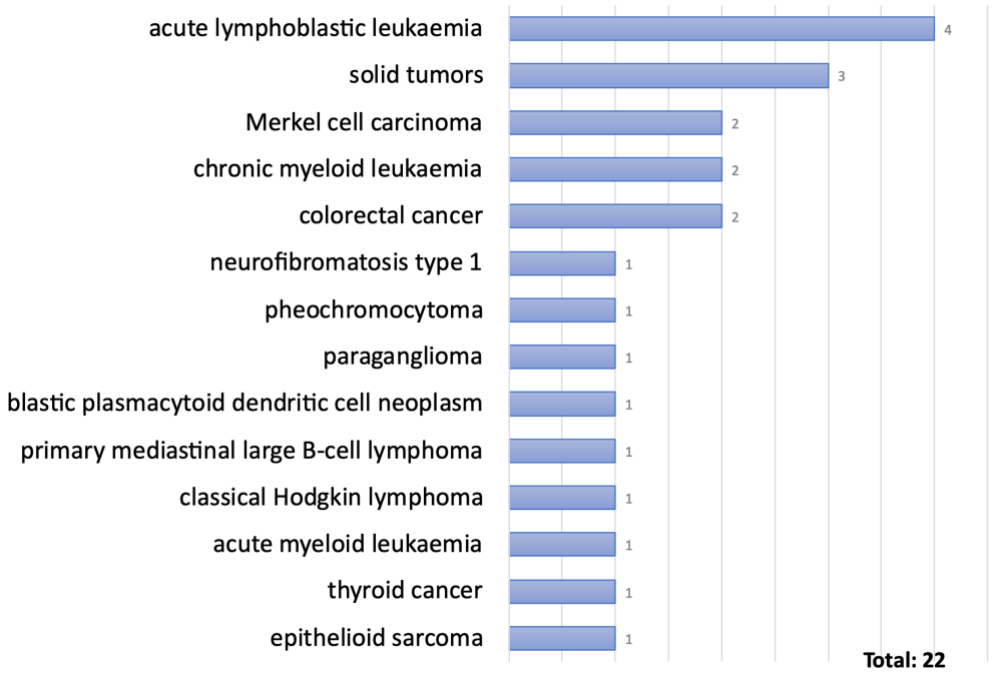
Expectedly, only very few (22 (12%) of the 182) unique condition scores were associated to an indication that includes paediatric labelling (Figure 3). All other submissions were covered by a PSP waiver. Those 22 unique condition scores covered only 14 distinct

paediatric conditions, the most common ones being acute lymphoblastic leukaemia (4 products) and solid tumours (3 products), followed by Merkel cell carcinoma, chronic myeloid leukaemia and colorectal cancer (2 products each) (Figure 4).

In contrast, the total of 182 unique scores are distributed over 61 different conditions. While almost half of them (29; 48%) have only been approved with a single product, others are included in the labels for several products, such as non-small cell lung cancer (18 products), breast cancer (15 products), urothelial carcinoma (8 products) or acute myeloid leukaemia (8 products).

The exact breakdown is shown in Figure 5.

Figure 4: Unique conditions covering indications with pediatric labeling



Number behind bar indicates the number of products with a paediatric indication within this condition

Figure 5: Breakdown of total unique condition scores

Number behind bar indicates the number of products with an indication within this condition

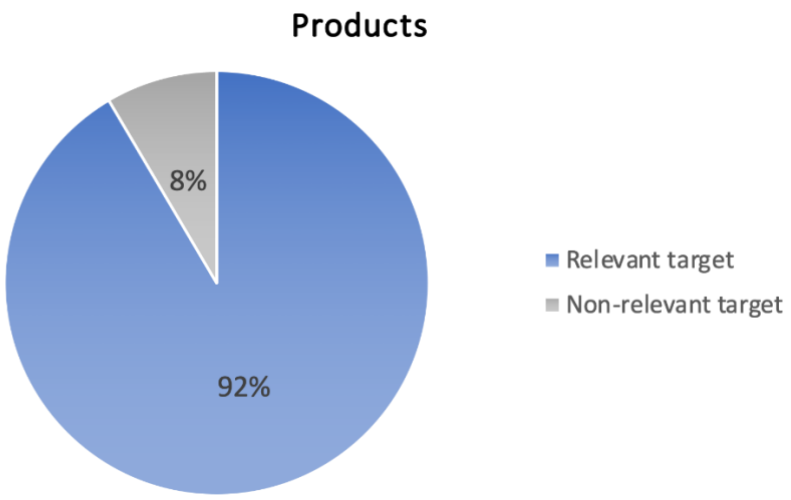
6.1.2 Assessment of molecular targets

As a next step the products' molecular targets were taken into account since only those products which are directed at a molecular target that was determined by FDA to be substantially relevant to the growth or progression of a paediatric cancer are covered by the RACE for Children Act (FDA, 2021b).

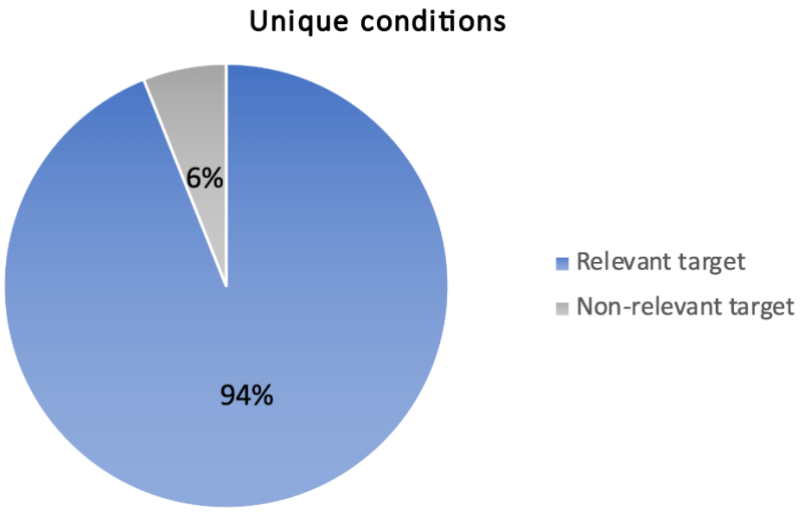
Of the 106 different products included in this data set, 97 (92%) are directed at a relevant molecular target and would thus fall under the requirements of the RACE for Children Act. Similarly, 171 (94%) of the 182 unique conditions are approved in products directed at a relevant target (Figure 6).

Figure 6: Assessment of relevant molecular targets

A)



B)



Top graph (A) shows: proportion of products directed at relevant molecular targets
Bottom graph (A) shows: proportion of unique conditions in products directed at relevant molecular targets

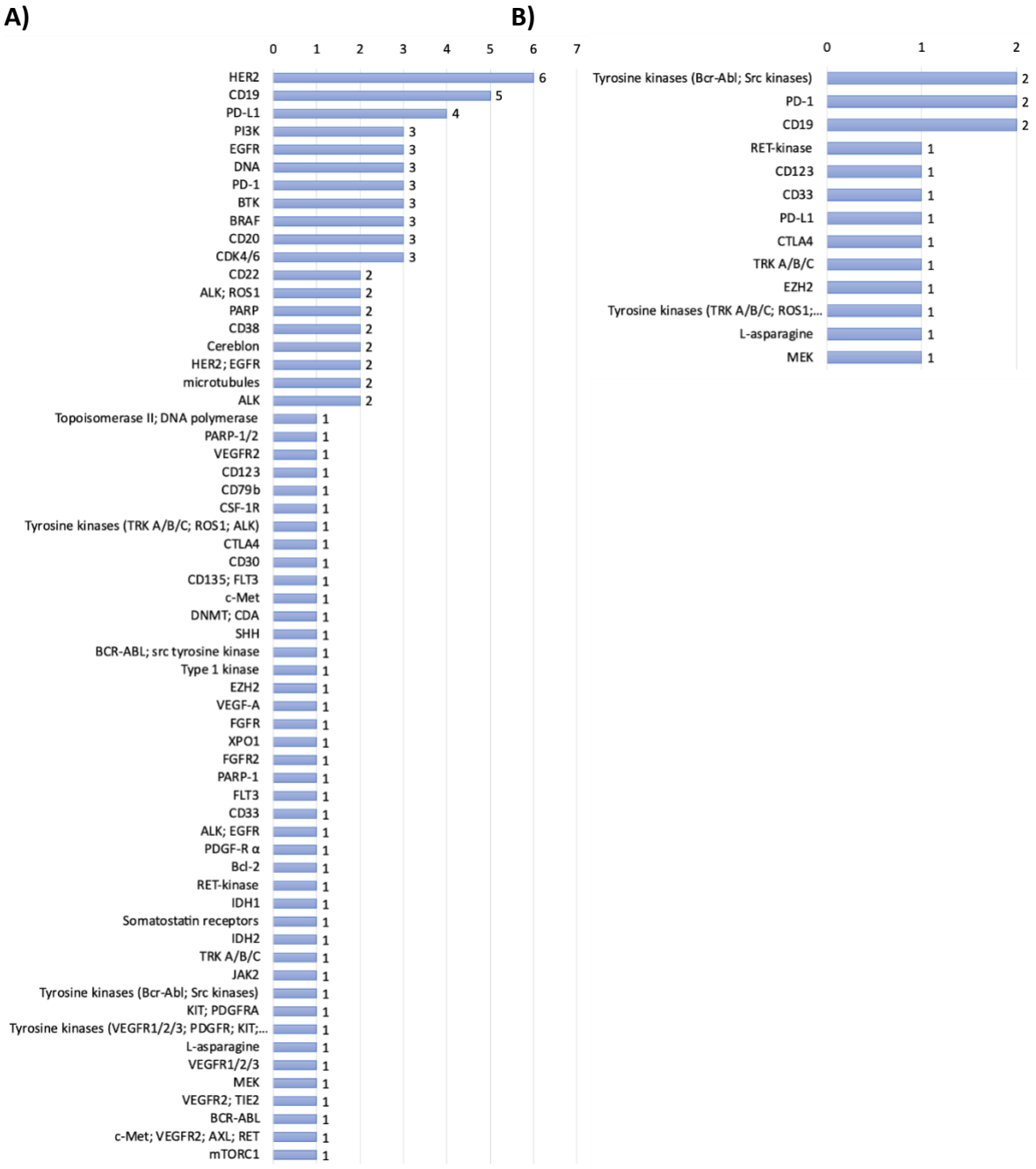
Interestingly, two conditions which are associated with a paediatric indication in the label, have been approved for a product whose molecular target has not been considered as significantly relevant by the FDA. Consequently, only 20 (12%) of the 171 conditions were associated with an indication that includes paediatric labelling.

These 20 paediatric conditions are distributed over 16 distinct products, meaning that only as few as 17% (out of 97) of products that are directed at molecular targets relevant for the treatment of paediatric cancers currently include paediatric labelling (Figure 7).

Figure 7: Number of products directed at molecular target with paediatric indication

While some of the 97 products falling under the RACE for Children Act have the same or similar molecular targets, with 6 products targeting HER2 (and another 2 products targeting HER2 as well as EGFR), 5 products targeting CD19 and 4 products targeting PD-L1, most products have a unique (set of) molecular targets that they are directed at (Figure 8A). The same is the case for the 16 products that are already authorised for the treatment of paediatric cancers (Figure 8B).

Figure 8: Molecular targets of products falling under the RACE for Children Act



A) Distribution of molecular targets for all products falling under the RACE for Children Act
B) Distribution of molecular targets for the subset of products which already have a paediatric indication included in the label

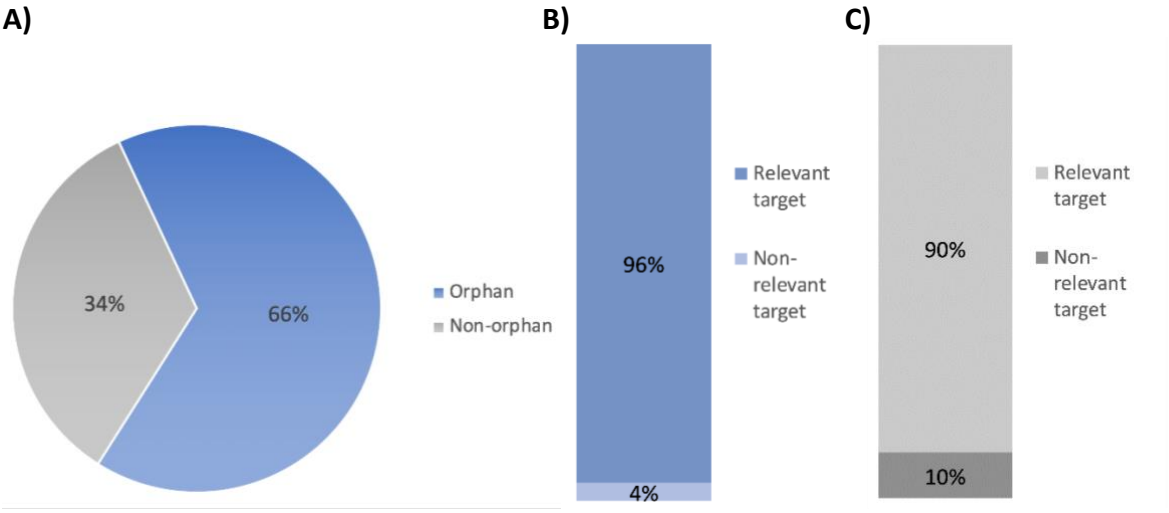
6.1.3 Analysis in orphan versus non-orphan conditions

To further distinguish the impact of the two parts of the RACE for Children Act (1. elimination of PREA orphan exemption, 2. elimination of immediate full waiver for indications not occurring in the paediatric population) the orphan status of the products for their respective conditions was also taken into account.

As some products are authorised for several indications/conditions which may not necessarily all have been granted an orphan designation, this analysis has only been done on the condition but not on the product level. As mentioned above, 120 (66% of 182 total) unique conditions with orphan designation have been identified. Of those 120, 115 (96%) also are approved in products directed at a relevant target.

Of the remaining 62 non-orphan conditions a similar proportion (56 conditions; 90%) were approved in products directed at a relevant target.

Figure 9: Assessment of orphan status



A) Proportion of unique conditions with or without orphan designation

B) Proportion of unique conditions with orphan designation for products directed at relevant or non-relevant molecular targets

C) Proportion of unique conditions without orphan designation for products directed at relevant or non-relevant molecular targets

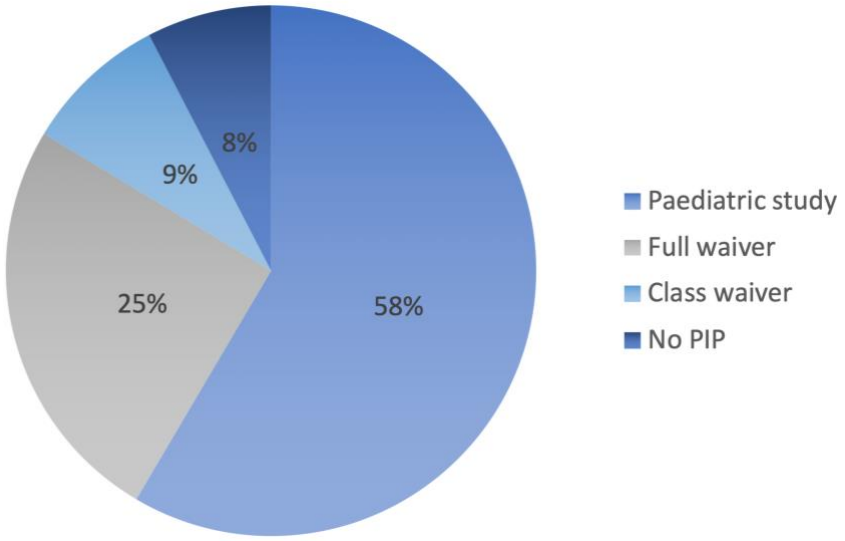
6.1.4 Comparison with EU PIP status

To further identify the potential of those products that would fall under the RACE for Children Act, it was determined whether agreed EU PIPs exist for the 171 unique conditions authorised for products directed at relevant molecular targets that have been identified above.

In the US, all products and conditions that do not already include paediatric labelling are covered by a PSP waiver. In the EU, on the other hand, for 100 (58%) of the 171 unique conditions a PIP with at least one study (with or without a deferral and with or without a partial waiver) was agreed. 43 (25%) have a full waiver, 15 (9%) are covered by a class

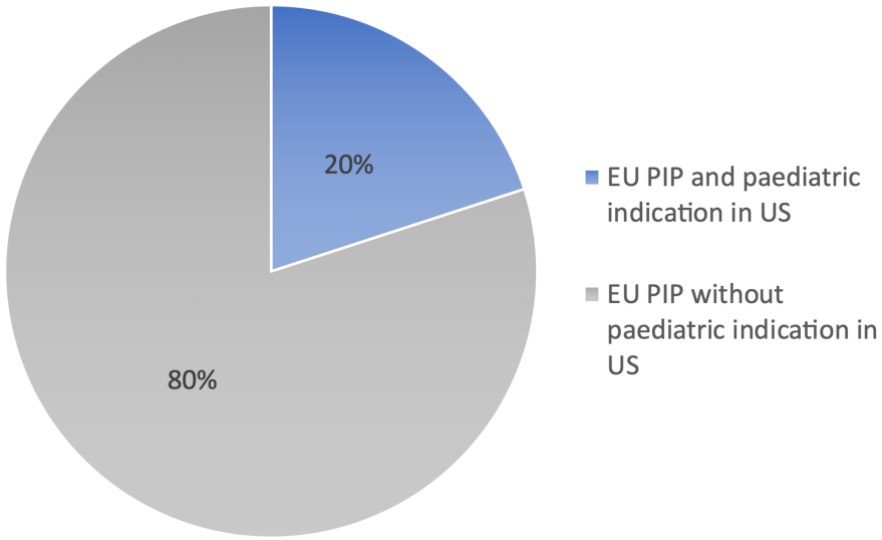
waiver, and for 13 (8%) no information was found (Figure 10). The latter may include those for which a PIP has not been agreed or for which the relevant information was not identified. These numbers are comparable for conditions with or without orphan status.

Figure 10: EU PIP status for products with conditions that would fall under the RACE for Children Act



Of the 100 conditions with a PIP (with study) in the EU and for which a medical need thus clearly exists in the paediatric population, only 20 (20%) also include a paediatric indication in the US (Figure 11). Again, there was no difference between orphan and non-orphan conditions.

Figure 11: Proportion of conditions covered by both EU PIP and paediatric indication in the US



Interestingly, almost three-quarter (73%) of the EU PIPs including at least one study are in very broad PIP conditions such as the following examples:

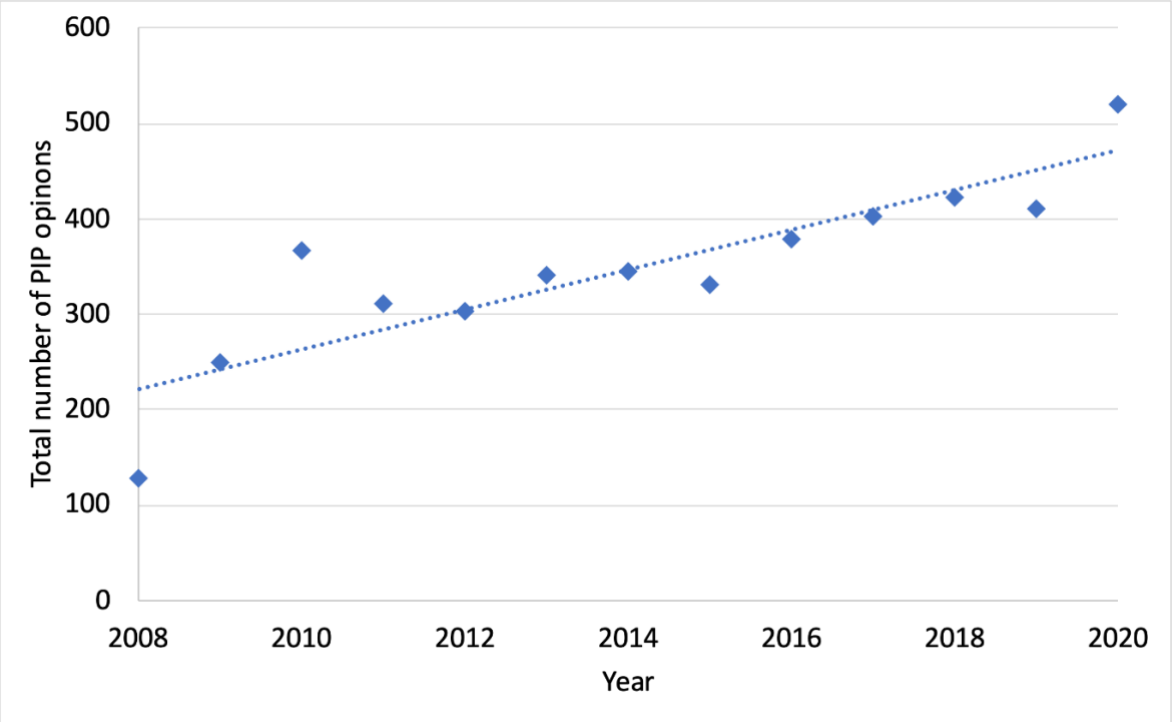
- Treatment of all conditions included in the category of malignant neoplasms (except nervous system, haematopoietic and lymphoid tissue) (6 months – 17 years)
- Treatment of solid malignant tumours (0 – 17 years)
- Treatment of mature B-cell neoplasms (1 – 17 years)
- Treatment of mature B-cell neoplasms (patients weighing at least 6 kg)
- Treatment of malignant neoplasms of the haematopoietic and lymphoid tissue (1 month – 17 years)

6.2 Step 2: Comparison with effect of EU class waiver list revision

6.2.1 Overview of PIP opinions between 2008 and 2020

Data on PDCO opinions about PIPs and waivers was extracted from the EMA annual reports between the years 2008 and 2020. The full data set is shown in Annex 2. After a steep increase in opinions from 128 in 2008 to 367 in 2010, the number of opinions went back down to 310 in 2011 but has been steadily increasing in a linear way since (Figure 12). The vast majority of all opinions issued by PDCO were positive (in total 98%)

Figure 12: Total number of PIP opinions between 2008 and 2020



Dotted line represents the trend line.

The total number of opinions includes opinions on new applications (either including a study or full waiver) or requests for modifications.

As expected, the number of PIP modifications has increased greatly in the first years from 4 opinions in 2008 to 153 in 2011. Since 2012 the average increase has been much smaller (Figure 13).

The number of opinions on new applications for PIPs including at least one study has been fluctuating slightly over the years with a peak in 2010 and another one in 2020. However, on average the numbers appear relatively stable (Figure 14). For opinions on full waivers,

the average number of opinions was consistently around 50 per year, but has been increasing since 2016 (Figure 14).

Figure 13: Number of positive PIP opinions on requests for modification

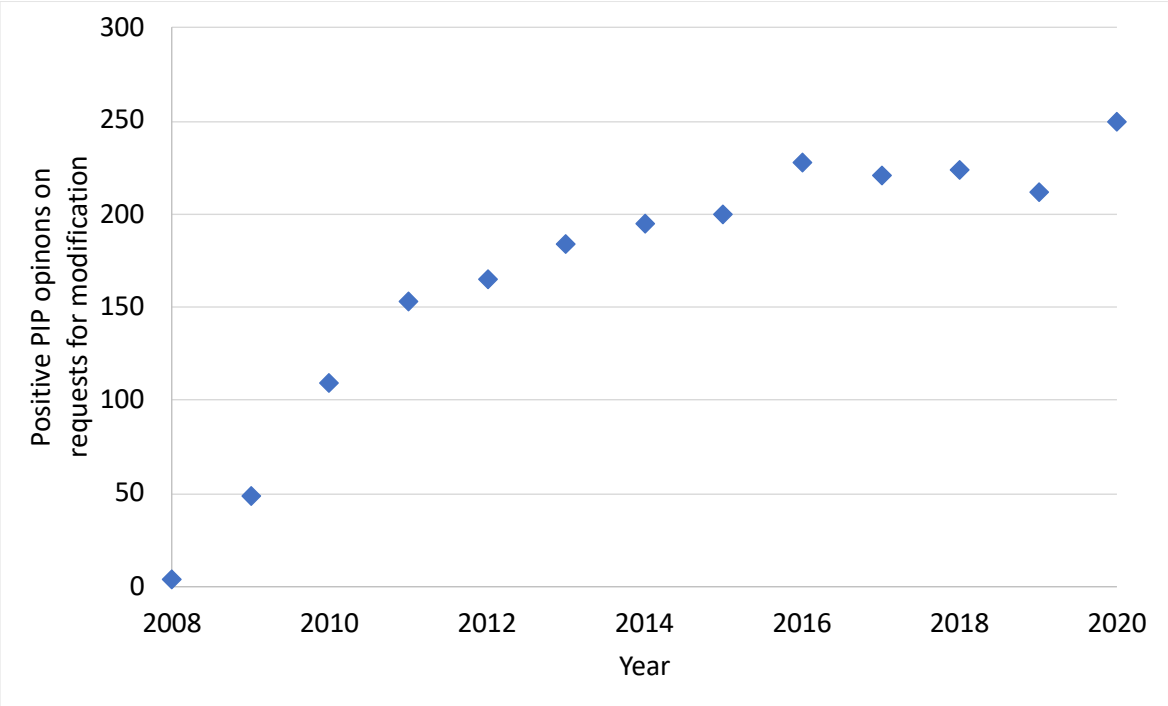
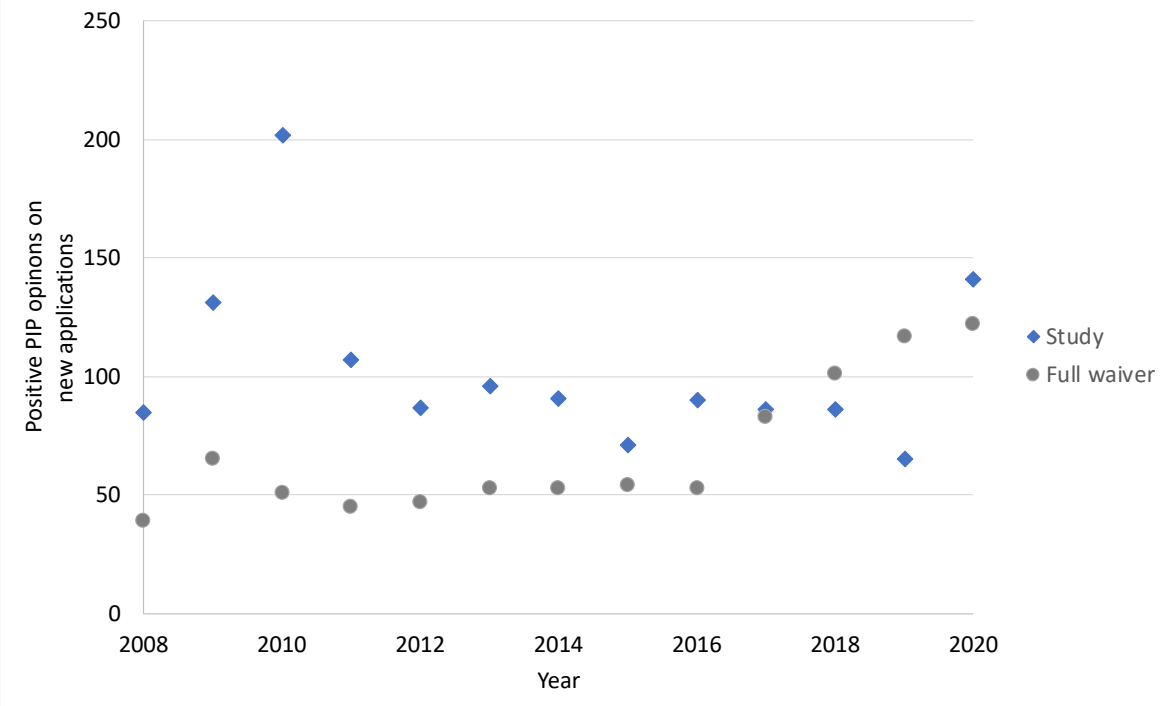


Figure 14: Number of positive PIP opinions on new applications

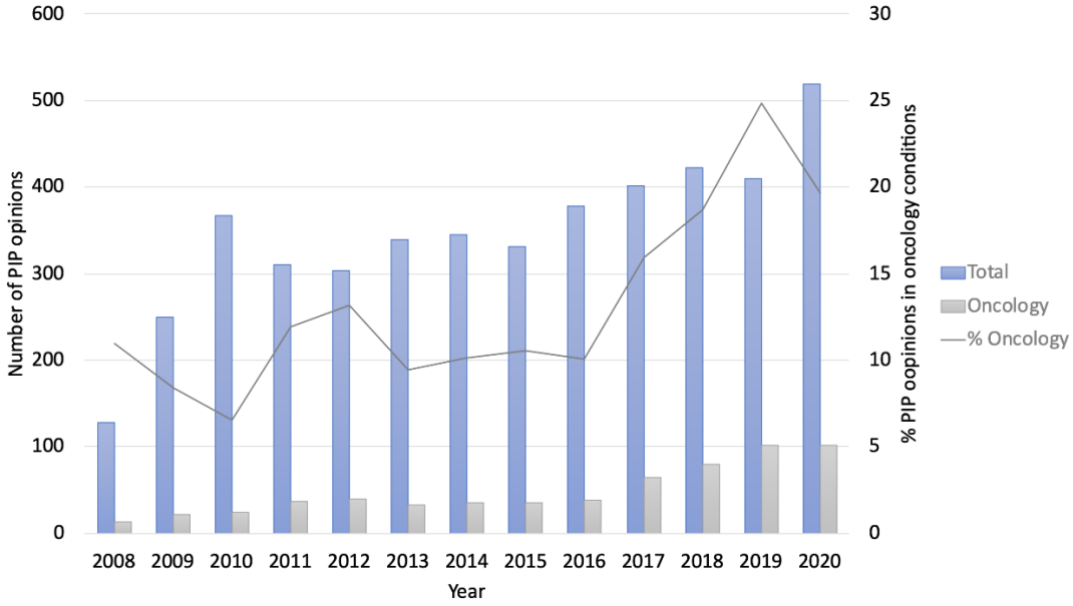


6.2.2 Effect on PIP opinions in oncology indications

In addition, the development of PDCO opinions specifically of applications in oncology conditions was analysed. This data is also summarised in Annex 2.

When looking at the number of total opinions that were given for applications in oncology conditions, this markedly increased after 2016, from 38 opinions in 2016 to 102 opinions in both 2019 and 2020. However, given that there was also a general increase in number of total opinions overall, not only the actual numbers but also the proportion of opinions in the oncology field was taken into consideration. Figure 15 shows that there is indeed an increase from around 10% up until 2016 to up to 24% in 2019.

Figure 15: Proportion of oncology conditions within total number of opinions



It was further explored whether this % increase was mainly due to more new applications or more PIP modifications. Figure 16 clearly shows that while there may also be a small increase in the proportion of oncology PIP modifications, the majority of the effect is due to more new applications in the oncology field. In addition, as presented in Figure 17, the largest increase can be seen in the proportion of opinions on full waiver requests for oncology conditions. Here the proportion of opinions on oncology applications increased from approximately 10% until 2016, to 36% in 2019 and 2020. For new applications including at least one study, the proportion increased from also approximately 10% before 2016 to 28% in 2019 and 17% in 2020.

Figure 16: Comparison of % increase of PIP opinions in oncology conditions for new applications versus requests for modifications

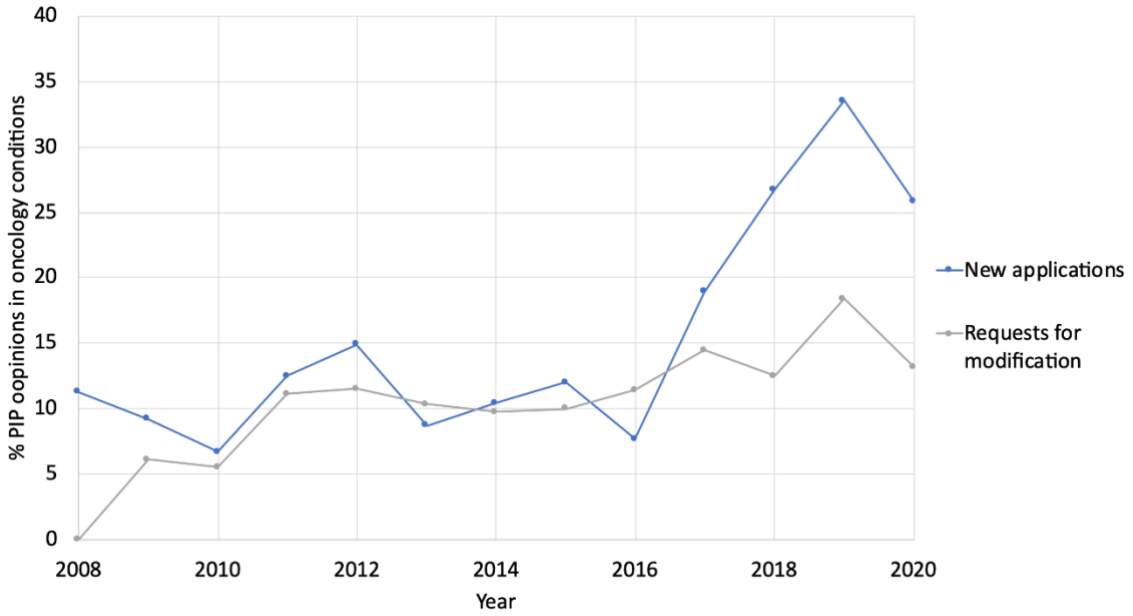
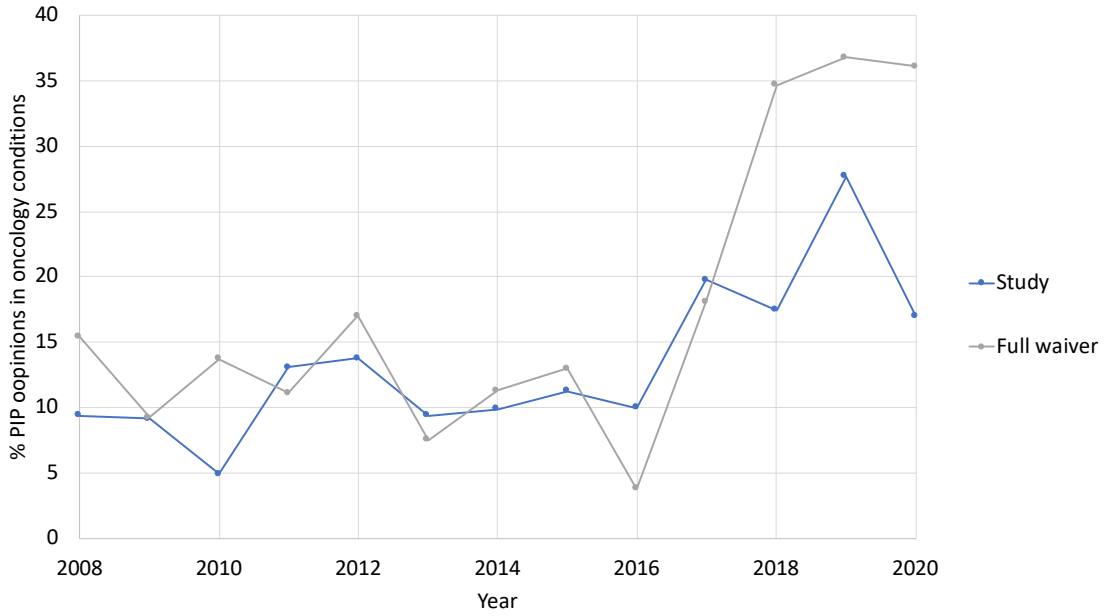


Figure 17: Comparison of % increase of PIP opinions in oncology conditions for new applications with a study versus new full waiver applications



6.3 Step 3: Review of FDA approved oncology medicinal products between August 2020 and December 2021 falling under the RACE for Children Act

The table with the complete data set can be found in Annex 3.

Between August 2020 and December 2021, a total of 21 original submissions have been approved by the FDA's Oncology Divisions. Of those, 9 were also submitted after August 2020, and would thus fall under the RACE for Children Act.

8 (89%) of those 9 original submissions were for products directed at a relevant target and would thus require an agreed PSP, unless this requirement was waived for reasons outlined in Sections 3.2.1 and 3.2.3 above.

Indeed, 5 (63%) of those 8 submissions had an agreed PSP (including at least one study) and for one product the label already included adult as well as paediatric patients. The remaining 3 submissions (27%) included a PSP waiver for the reason that a study was considered highly impracticable.

7 Discussion

7.1 Urgent need for paediatric oncology medicinal products

Off-label use of medicinal products in paediatric patients is an important public health issue as the effects and potential health risks are often not predictable. Children differ from adults in terms of their physiology, PK and organ development and, therefore, age-appropriate dosing and safety-considerations, as well as suitable pharmaceutical form, formulation and route of administration have to be taken into account.

Despite the introduction of the Paediatric Regulation in the EU as well as BPCA and PREA legislations in the US, there still is a very high medical need for safe and efficacious medicinal products that have been developed specifically for the paediatric patient population. In fact, the EC is currently analysing the impacts of the Paediatric Regulation together with the EMA and is considering options to revise the Paediatric Regulation as the legal framework for the development of paediatric medicines (European Commission, 2020; European Commission, 2021).

The medical need is particularly high in the field of paediatric oncology. Since 2007, the "Verband forschender Arzneimittelhersteller" (VFA) in Germany lists only 25 medicinal products that have been authorised for paediatric oncology indications (VFA, 2021). In the same time frame, more than 250 products have been approved by the EMA for the treatment of adult cancer patients (EMA, 2022c). In the US the situation is similar as the research presented in this thesis has shown.

In recent decades research into genetic mutations and molecular pathways driving cancers has seen great progress. In contrast to the broad mechanism of action of chemotherapies which destroy both tumour cells and healthy "normal" cells, most of the medicinal products that have been (and are being) developed in the past years target unique molecular features of the malignant cancer cells. Although adult and paediatric cancers commonly differ in terms of their aetiology, genetics, organ of origin and natural history of the disease, the genetic drivers and molecular abnormalities underlying adult cancers are also found in many paediatric cancers. Therefore, in theory the potential of products being developed for the treatment of adult cancers is also very high for the treatment of paediatric cancers.

However, due to the way that the legislations were set up in both the EU and the US, this potential has not been fully utilised.

In the EU, this issue was partly addressed by a significant update of the class waiver list in 2015 (EMA, 2015), whereas in the US the implementation of the RACE for Children Act in 2020 has provided a prospect that the situation may improve in the future. The new focus on the mechanism of action rather than the adult development program alone when considering a product's potential paediatric development program has raised hopes for patients, parents and paediatricians alike.

7.2 Assessment of expected impact of RACE for Children Act

This thesis presents a comprehensive assessment on the expected effect that will be seen following the introduction of the RACE for Children Act and the subsequent changes to PREA.

In a first step the potential of the RACE for Children Act was evaluated by analysing all FDA approvals in the oncology therapeutic area between January 2016 and August 2020, including original and supplemental submissions. As expected only a very small proportion (12%) of the authorised indications included the paediatric population (or a subset thereof) in the label, covering only 14 different paediatric cancers. This is in line with data from the EU, where (as outlined in Section 7.1 above) around 10% of MAAs include paediatric labelling. Data from both regions thus highlight the big gap between adult and paediatric cancer drug development. In the US, the cancer type with the most products approved for treatment of paediatric patients is acute lymphoblastic leukaemia, with four treatment options (in the timespan assessed for this thesis). However, for the majority of cancer types, no treatments are approved to date for the paediatric population.

Out of the 106 different products included in this analysis the vast majority (92%) are directed at a molecular target that is considered by FDA to be substantially relevant for the growth or progression of paediatric cancers, which further highlights the numerical gap between actually available paediatric cancer treatments and potentially efficacious medicinal products.

Only 16 of those products (17%) already included at least one paediatric indication. While most of them have a unique (set of) molecular targets that they are directed at, some targets such as PD-1, CD19 and different tyrosine kinases seem to be more common in the approved paediatric medicines. Given that the list of relevant targets prepared by FDA covers 200 molecular targets involved in more than 60 cellular pathways (FDA, 2021b), and that those products approved in adult patients cover already more than 60 of those molecular targets, it is apparent that the RACE for Children Act in theory has a huge potential to change the landscape of paediatric oncology medicines.

As the RACE for Children Act has implications both for orphan and for non-orphan drugs by eliminating PREA orphan exemption and limiting immediate full waivers for indications not occurring in the paediatric population, the analysis was also stratified into orphan vs non-orphan status. Two-thirds of the oncology conditions approved in adults are designated orphan conditions. Furthermore, 96% of those conditions are authorised for products that are directed at a relevant molecular target, versus 90% in the non-orphan group. Therefore, the omission of the PREA orphan exemption is expected to have a proportionally larger impact. However, the potential of the non-orphan products should not be disregarded.

The potential of primarily looking at a product's mechanism of action and their molecular targets becomes even more apparent when looking at the EU PIP status for the products included in this analysis and the respective authorised conditions. While in the US all products and conditions that do not already include paediatric labelling are covered by a PSP waiver, as many as 58% have an agreed PIP with at least one study (with or without a deferral and with or without a partial waiver) in the EU and only 35% of the conditions are covered by waiver (25% full product specific waiver; 10% class waiver). This clearly highlights that there is at least a theoretical potential for those products for the treatment of paediatric malignancies. Nevertheless, only 20% of those with a PIP including a study also have a paediatric indication in the US label. Interestingly, almost three-quarter of the PIPs include studies in very broad paediatric indications which additionally emphasises the potential broad applicability of these products as paediatric oncology treatments.

In a second step, this analysis was then compared to the effects following the EU class waiver update in 2015. As this had the same purpose as the RACE for Children Act, i.e. to

increase the number of paediatric oncology treatments, this was considered an appropriate comparison.

These data show that there was a gradual increase of opinions on PIPs over the years, with some peaks in the years 2010 and 2020. A similar pattern can be seen when looking only at the positive opinions on initial PIP applications including at least one study. While the average number remains relatively stable over the years, there are clear peaks in 2010 and 2020. The large number of PIP opinions in 2010 can largely be explained by a change in the German medicines legislations which introduced the requirement of a marketing authorisation for allergen products in that year. Consequently, in 2010 EMA received 115 PIP applications for allergen products alone (EMA, 2011). For 2020 it can be speculated that the increase in PIP opinions may be due to a large number of potential products for the treatment or prevention of COVID-19 being developed and needing an agreed PIP in place. Interestingly the number of PIP opinions on full waiver applications has significantly increased since 2016.

When also taking into account the therapeutic field, it can be clearly seen that both the absolute number, as well as the proportion of PIP opinions for oncology products has increased after 2016. Considering that the class waiver update happened in 2015 and the process for PIP review and approval by the PDCO can often take a year (including Sponsor responses to PDCO questions and comments), there seems to be a correlation between this update and the increase in oncology PIPs. This is further confirmed by the fact that for PIP modifications, the proportion of opinions in the field of oncology has not increased, whereas there is a clear rise in oncology PIP opinions for new applications. However, it should be noted that this increase affects applications for full waivers much more than applications of PIPs including at least one study. Nevertheless, an increase of PIPs with at least one study in oncology conditions can clearly be observed following the update of the class waiver list.

These EU data are therefore a very promising indicator that the RACE for Children Act in the US will be very effective and also lead to an increase in paediatric studies in the therapeutic area of oncology. However, based on this comparison it should not be expected that every product developed for the treatment of adult cancers will also be studied in

paediatric cancers and many Sponsors will likely still try to receive a full waiver based on other grounds.

Finally, as the RACE for Children Act has been in effect for over a year at the time of submission of this thesis, oncology products falling under this Act (i.e. those original oncology applications submitted to FDA after August 2020) and approved by FDA until December 2021 (the cutoff date for this thesis) were assessed to examine whether the assessments and predictions of the first two steps hold true for this preliminary dataset. Indeed, 5 out of 8 submissions (63%) for products directed at a relevant molecular target included an agreement for a paediatric study(ies), while only 3 were granted a waiver. In contrast, between January 2016 and August 2020 all products and conditions that did not already include paediatric labelling were covered by a PSP waiver. Thus, despite the small size of this dataset, there already seems to be a trend for an increased number of PSPs agreed following the introduction of the RACE for Children Act. Interestingly, all 3 waivers were all granted based on paediatric studies being highly impracticable (due to the low number of patients).

Overall, it can be concluded from this assessment that the RACE for Children Act offers an enormous potential to improve the situation for paediatric cancer patients by increasing and advancing the development of safe and efficacious oncology medicinal products specifically for this age group. While this is in general also supported by extrapolating data from EU PIP opinions and by preliminary data from FDA approvals, it remains to be seen how many products will simply receive a full waiver based on different grounds.

7.3 Limitations of the analysis

This analysis includes some limitations which need to be pointed out.

Firstly, it should be noted that even though the RACE for Children Act is only applicable to original submissions, this assessment included both original and supplement submissions. Supplement authorisations were included to maximise the dataset and to also include products which were originally authorised outside the time-scope of this analysis, but which had recent indication extensions. The inclusion of these data does not change but rather supports the general conclusion that there is a huge medical need for paediatric cancer patients which could potentially be addressed by many products which are currently

being developed exclusively for adult patients. However, it should of course be considered that the extent of this potential in terms of absolute numbers of products and/or indications being developed specifically in paediatrics may be slightly overestimated.

There are also some limitations in the comparison of the expected outcome of the RACE for Children Act in the US and the actual effects seen after the class waiver update in the EU. Although this update has increased the number of paediatric studies that need to be conducted in the field of paediatric oncology, many products that previously would have received a class waiver, now receive a "normal" product-specific waiver. Although a product's mechanism of action is taken into account for the decision on the waiver condition, and although this is often considered in a broader sense for oncology products, the PIP is still very much tied to the adult development program. This means that many products may still qualify for a product-specific waiver based on the ground that the disease does not occur in the paediatric population or a significant benefit cannot be expected, simply because the paediatric cancer that would benefit from a certain product is too distinct from the targeted adult cancer in terms of its histology or organ involvement. Coming back to the example of Xalkori mentioned in Section 2.2.3, a product-specific waiver on the grounds that "*the disease or condition for which the specific medicinal product is intended does not occur in the specified paediatric subsets*" was indeed granted in 2018 for Xalkori in the condition "Treatment of lung malignant neoplasms" (EMA, 2018a). However, this is not going to be the case with the RACE for Children Act, as here the mechanism of action of the product will be the determining factor. Therefore, the effect seen from the RACE for Children Act may actually be larger than one would expect after comparison with the EU situation following the class waiver update, with more paediatric studies and fewer full waivers.

Further, both steps of the analysis compared the US situation with PIP status in the EU. However, one has to consider that not all paediatric studies will result in marketing authorisations for the paediatric population and many PIPs are also never completed (Hildebrand, 2021). Therefore, some of the conclusions of this analysis may be overestimations of the actual effect that will be seen in terms of paediatric approvals.

Lastly, the Step 3 analysis is based on very small numbers and is therefore not as robust and meaningful as the data from Step 1 and Step 2. The conclusions drawn from this

analysis should therefore not be considered as a conclusive assessment but rather as a careful initial outlook whether the results of the Step 1 and Step 2 assessments could hold true.

Despite these limitations, it can still be concluded that the RACE for Children Act is an important step in the attempt to improve the availability of safe and efficacious treatments for paediatric cancer patients.

7.4 Remaining issues in paediatric medicinal product development and potential solutions

Even though more PSPs can be expected to be agreed due to the RACE for Children Act so that Sponsors will need to conduct more studies in paediatric cancer patients, the general issues connected with development of paediatric medicinal products remain. These can be summarised into four general categories (Klingmann, 2021).

1. Recruitment of a sufficient number of patients who are eligible and consenting to the study
2. Standardised data collection using suitable and reliable methods while protecting them from unnecessary risk and burden
3. Availability of experienced investigators and clinical study sites
4. Compliance with the investigational medicinal product

In particular the first three points need to be considered in relation with the RACE for Children Act as they may be further exaggerated, especially in the first years after the implementation.

Recruitment in paediatric trials is generally considered very difficult. Many paediatric diseases are rare, especially when considering the different paediatric age-groups. This is particularly the case for paediatric cancers. In addition, many patients do not meet the inclusion criteria for recruitment (e.g. because they have already been exposed to the product off-label). With more paediatric studies recruiting from the same small pool of eligible patients, recruiting and thus trial completion will take extremely long. Similarly, as paediatric cancers are rare, so are the experts in this field and like there will be "competition" for patients, availability of experienced investigators and sites will also be a

limiting factor. Unfortunately, this means that even though more paediatric studies will investigate the use of medicinal products for the treatment of paediatric cancers, the time until they will be completed and until some of these products may be approved will still be years and may even be prolonged. In addition, it of course needs to be considered that not all studies will result in a paediatric marketing authorisation.

Furthermore, studies in paediatric patients require special considerations as there can be large differences between the age groups and these patients are particularly vulnerable. The latter is especially the case for cancer patients, and it is therefore important to protect them from unnecessary stress and risks due to study participation. On the other hand, these studies have to be designed in a way so that they yield meaningful data. However, studying a medicinal product in paediatric patients, especially very young patients, can be extremely difficult, so that it may not be possible to fully demonstrate efficacy and safety in paediatric clinical studies This is certainly a dilemma that needs to be addressed.

7.4.1 Use of extrapolation in paediatric development

One option that is gaining more and more acceptance with regulators and within industry is a modelling, simulation and extrapolation approach. This concept provides an opportunity to use existing information about the disease, as well as the product's PK and pharmacodynamics (PD), collected across target populations, to establish a relationship between dose, exposure and clinical response to estimate the treatment effect in a given target population. In cases where it is reasonable to assume that children and adults have a similar response to treatment (EMA, 2018b), it thus „*allows the quantitative use of sparse sampling, characterization and prediction of pharmacokinetics/ pharmacodynamics (PK/PD), extrapolation from adults to children, interpolation between paediatric age subsets, optimal use of scientific literature and in vitro/preclinical data*" (Manolis & Pons, 2009).

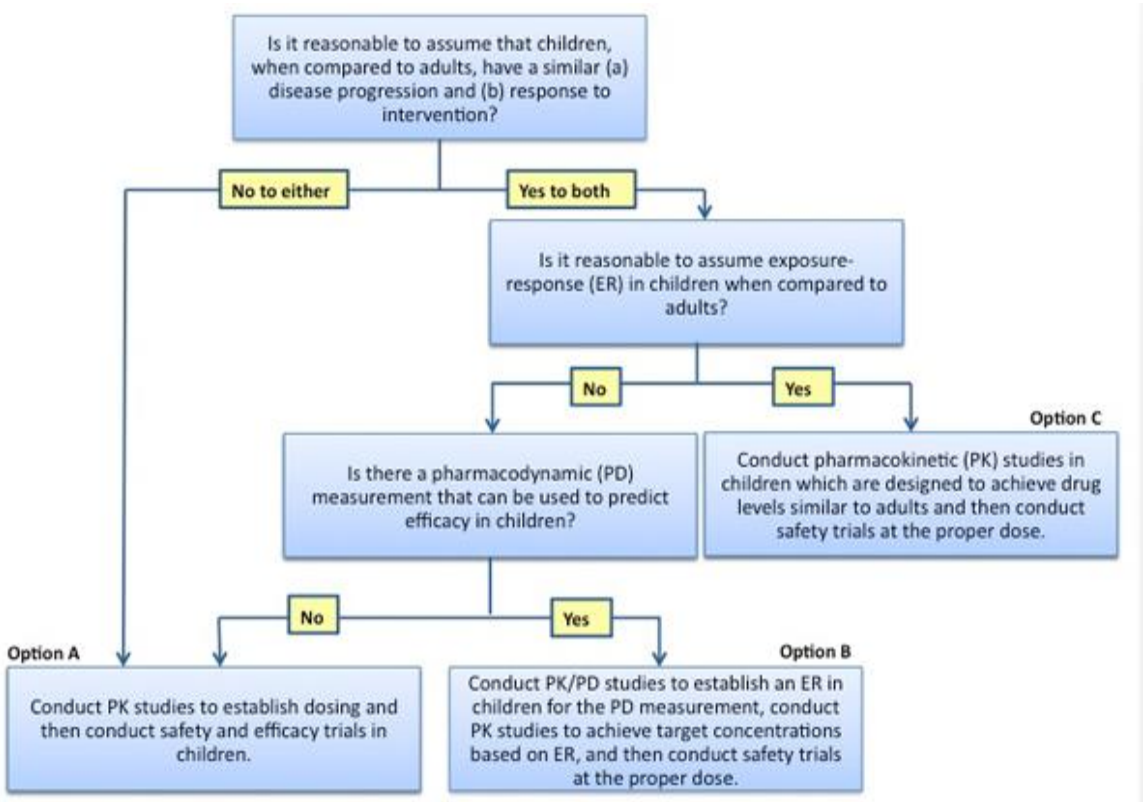
Several PIPs and PSPs already use this concept as it minimises the exposure of paediatric patients to clinical trials, while at the same time increasing speed and efficiency of paediatric medicinal product development and ensuring timely access to safe and effective medicines. Typically, extrapolation is not used as a stand-alone concept, but rather to supplement and optimise the clinical studies. Examples include the use of PK data to select

dose ranges or to extrapolate efficacy and/or safety data from adults or e.g. adolescents to younger paediatric age groups. In more rare cases, extrapolation can also be used to bridge between indications (EMA, 2018b; Manolis & Pons, 2009). This has the potential to reduce both the number of required studies as well as the number of patients included in each study and can therefore help to expedite the paediatric development program.

The FDA provides a very useful decision tree on the use of extrapolation in paediatric trials (Figure 18; FDA, 2018b) and it can be expected that the importance of these concepts will increase in the coming years with the introduction of the RACE for Children Act.

However, it must of course be noted that extrapolation will not always be an option and its use should be carefully considered on a case-by-case basis. In many cases efficacy will need to be demonstrated independently in the paediatric population using age-appropriate endpoints that have been validated for use in the respective age group(s) (EMA, 2018b; FDA, 2018b).

Figure 18: FDA paediatric study decision tree



From: FDA, 2018b

7.4.2 Use of real world evidence in paediatric development

Another concept that may be gaining importance as a data source in general, and thus potentially also for paediatric development in the future, is real world evidence (RWE). RWE is derived from the analysis of real world data (RWD), which is defined by the EMA as "*routinely collected data relating to patient health status or the delivery of health care from a variety of sources other than traditional clinical trials*" (EMA, 2020a) and can include for example patient registries, electronic health records, claims databases and prescribing records, observational studies, post-authorisation efficacy studies (PAES), post-authorisation safety studies (PASS) or health surveys (Makady et al., 2017).

As discussed above, for paediatric (oncology) trials, is it very difficult to recruit large studies. In addition, it is commonly not feasible or ethical to include (placebo) control arms, making these studies uncontrolled single-arm trials. In such situations, the use of RWE as an external historic control can be extremely useful to reduce patient numbers while at the same ensuring interpretability of the data and scientific validity of the study.

Further, paediatric patients are commonly treated off-label, especially in the oncology field. Although the ultimate aim is of course to reduce paediatric off-label use, the reality is that it is still very common. Such off-label treatment may be recorded for example in electronic health records which are used by healthcare providers more and more commonly and which contain patient characteristics, diagnoses, treatments, and clinical and laboratory data that is collected during routing practice (Ball & Hudson, 2020). This data may produce extremely useful information on effectiveness and safety of a particular medicinal product in the paediatric population. While it will most likely never replace data generated in prospectively planned clinical trials, it could help to reduce the number of patients required for paediatric trials, and support extrapolation from adults to paediatric populations as well as extrapolation across different paediatric indications (e.g. in the context of paediatric indication extensions).

In adult development the use of RWE to support and supplement clinical trial evidence is becoming more and more popular. It Is being accepted not only by Sponsors but increasingly also by regulators. However, while it has been accepted for years in the context of pharmacovigilance and risk management to generate meaningful safety data, regulators

are more reluctant when it comes to efficacy and effectiveness data. Nevertheless, both EMA and FDA agree that using RWE to support and complement well-planned clinical trials will become increasingly important in the future, in particular in areas of high unmet medical need or rare diseases (EMA, 2020a; EMA, 2020b; FDA, 2018c; FDA, 2019). Clearly, paediatric oncology indications should be considered as areas of high unmet medical need and many of them are also rare diseases. It is, therefore, in the hands of both Sponsors and regulators to collaborate and explore how to make efficient use of RWE to improve and accelerate paediatric oncology development programs.

8 Summary and outlook

Historically, studies evaluating medicinal products in the paediatric population have been rare. This has led to extensive off-label use in this population, which bears significant risks for serious harm. While paediatric legislations in both Europe and the US have improved the overall situation, there still is a long way to go. In particular, certain therapeutic areas such as paediatric oncology are lagging behind and there is an extremely high medical need to develop safe and efficacious medicines for the treatment of paediatric cancers. Although there are differences between adult and paediatric cancers, such as in the aetiology, genetics, organ of origin or natural history of the disease, the genetic drivers and molecular abnormalities underlying adult cancers are also found in many paediatric cancers. Thus, products being developed for the treatment of adult cancers may also have a very high potential for the treatment of paediatric cancers.

In the US, the RACE for Children Act was introduced and came into effect in August 2020. The FDA now has the opportunity to demand the evaluation of new drugs or biologics in a paediatric oncology indication in case the product is intended for the treatment of an adult cancer, and the molecular target of the product is considered substantially relevant to the growth or progression of paediatric malignancies.

This thesis evaluated the expected effect of the RACE for Children Act on the development of paediatric cancer medicines.

The evaluation shows that the RACE for Children Act has indeed a lot of potential to significantly improve the situation for paediatric cancer patients in the US. There is a big gap between actually available paediatric cancer treatments and potentially efficacious medicinal products which are available or being developed for adults. Until recently, the majority of these products were excluded from the PREA requirements to submit a PSP either due to the PREA orphan exemption or because the adult indication does not occur in the paediatric population, and were thus only developed for adult cancer patients. Under the RACE for Children Act, however, Sponsors now also need to consider their potential for paediatric patients in a much broader context. It can thus be expected that many more medicinal products will also be developed for the treatment of paediatric cancers in the

future. A comparison with the situation in the EU and the number of agreed PIPs in the oncology field further highlights this potential.

In addition, a comparison with the effects following the EU class waiver update in 2015 was performed, as this had the same purpose as the RACE for Children Act, i.e. to increase the number of paediatric oncology treatments. These data further indicate that the RACE for Children Act in the US will likely be very effective. In fact, it may even be more effective than the class waiver update due to the fact that the sole driver will be the product's mechanism of action so that oncology PSPs in the US are no longer restricted by their adult indication unlike EU PIPs where the adult indication is also taken into account to some extent.

Finally, oncology products approved by FDA between August 2020 and December 2021 and falling under the RACE for Children Act were examined to investigate whether the assessments and predictions of the first two steps hold true for this preliminary dataset. While conclusive assessments can certainly not be drawn from this small dataset, there is a clear trend for an increase in number of PSPs, which supports the evaluations and assessments of this thesis.

Nevertheless, several issues connected with the development of paediatric medicinal products in general will remain, such as limited availability of a sufficient number of eligible patients as well as lack of experienced investigators and clinical study sites. While these can potentially be limited by smart trial designs and use of modelling/extrapolation concepts, or the use of RWE wherever possible, it remains to be seen how open both Sponsors and regulators are and continue to be to such approaches.

Overall, however, it can be concluded that in the long-run the RACE for Children Act is expected to be a milestone for the development of safe and efficacious treatment options for paediatric cancer patients.

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Annex 1: FDA approved oncology products between January 2016 and August 2020

INN	Active substance	Submission	Approval Date (MM/DD/YY)	Target	Relevant target?	Indication in label	Associated condition	Orphan designation granted?	Paediatric indication in label	EU PIP (condition (age group); decision number)	EU Waiver
ADCETRIS	brentuximab vedotin	SUPPL-99	11/16/18	CD30	yes	previously untreated systemic anaplastic large cell lymphoma (sALCL) or other CD30-expressing peripheral T-cell lymphomas (PTCLs), including angioimmunoblastic T-cell lymphoma and PTCL not otherwise specified (in combination with chemotherapy)	peripheral T-cell lymphomas	yes		Treatment of anaplastic large cell lymphoma (2y - 17y); P/0013/2021	
ADCETRIS	brentuximab vedotin	SUPPL-97	03/20/18	CD30	yes	previously untreated stage III or IV classical Hodgkin lymphoma (cHL) (in combination with chemotherapy)	classical Hodgkin lymphoma	yes		Treatment of Hodgkin lymphoma (5y - 17y); P/0013/2021	
ADCETRIS	brentuximab vedotin	SUPPL-94	11/09/17	CD30	yes	patients with primary cutaneous anaplastic large cell lymphoma (pcALCL) or CD30-expressing mycosis fungoides (MF) who have received prior systemic therapy	anaplastic large cell lymphoma	yes		Treatment of anaplastic large cell lymphoma (2y - 17y); P/0013/2021	
							mycosis funcoides	yes		Treatment of Cutaneous T-Cell Lymphoma; P/0168/2015	waiver
AFINITOR	everolimus	SUPPL-36	02/26/16	mTORC1	yes	progressive, well-differentiated, non-functional, neuroendocrine tumors (NET) of gastrointestinal (GI) or lung origin with unresectable, locally advanced or metastatic disease	neuroendocrine tumorsof gastrointestinal or lung origin	yes		Treatment of renal cell carcinoma and pancreatic neuroendocrine tumour; P/2/2007	waiver
ALECENSA	alectinib	SUPPL-3	11/06/17	ALK	yes	anaplastic lymphoma kinase (ALK)-positive metastatic non-small cell lung cancer (NSCLC)	non-small cell lung cancer	yes		Treatment of non-small cell lung carcinoma (NSCLC); P/0359/2018;	waiver
ALIQOPA	copanlisib	ORIG-1	09/14/17	PI3K	yes	relapsed follicular lymphoma (FL) who have received at least two prior systemic therapies	follicular lymphoma	yes		Treatment of mature B-cell neoplasms; P/0402/2020	waiver
ALUNBRIG	brigatinib	SUPPL-8	05/22/20	ALK; EGFR	yes	anaplastic lymphoma kinase (ALK)-positive metastatic non-small cell lung cancer (NSCLC)	non-small cell lung cancer	yes		Treatment of non-small cell lung cancer; P/0483/2020	waiver
ALUNBRIG	brigatinib	ORIG-1	04/28/17	ALK; EGFR	yes	anaplastic lymphoma kinase (ALK)-positive metastatic non-small cell lung cancer (NSCLC) who have progressed on or are intolerant to crizotinib	non-small cell lung cancer	yes		Treatment of non-small cell lung cancer; P/0483/2020	waiver
ARZERRA	ofatumumab	SUPPL-62	01/19/16	CD20	yes	extended treatment of patients who are in complete or partial response after at least two	chronic lymphocytic leukemia	yes			

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						lines of therapy for recurrent or progressive chronic lymphocytic leukemia (CLL)					
ASPARLAS	calaspargase pegol-mknl	ORIG-1	12/20/18	L-asparagine	yes	acute lymphoblastic leukemia (ALL)	acute lymphoblastic leukemia	yes	pediatric and young adult patients age 1 month to 21 years		
AVASTIN	bevacizumab	SUPPL-323	06/13/18	VEGF-A	yes	stage III or IV epithelial ovarian, fallopian tube, or primary peritoneal cancer, following initial surgical resection (in combination with carboplatin + paclitaxel)	ovarian cancer	yes			Class waiver
							fallopian tube cancer	yes			Class waiver
							primary peritoneal cancer	yes			Class waiver
AYVAKIT	avapritinib	ORIG-1	01/09/20	Type 1 kinase	yes	unresectable or metastatic gastrointestinal stromal tumor (GIST) harboring a platelet-derived growth factor receptor alpha (PDGFRA) exon 18 mutation, including D842V mutations	gastrointestinal stromal tumor	yes		Treatment of all conditions included in the category of malignant neoplasms (except haematopoietic and lymphoid tissue neoplasms) (2y - 17y); P/0007/2020	
AZEDRA	iobenguane I 131	ORIG-1	07/30/18	norepinephrine analogue	no	iobenguane scan-positive, unresectable, locally advanced or metastatic pheochromocytoma or paraganglioma (PPGL) who require systemic anticancer therapy	pheochromocytoma	yes	adult and pediatric patients (12 years and older)		
							paraganglioma	yes			
BALVERSA	erdafitinib	ORIG-1	04/12/19	FGFR	yes	locally advanced or metastatic urothelial carcinoma, that has susceptible FGFR3 or FGFR2 genetic alterations, and progressed during or following at least one line of prior platinum-containing chemotherapy, including within 12 months of neoadjuvant or adjuvant platinum-containing chemotherapy	urothelial carcinoma	no		Treatment of urothelial carcinoma; P/0126/2017	waiver
BAVENCIO	avelumab	SUPPL-9	06/30/20	PD-L1	yes	maintenance treatment of locally advanced or metastatic urothelial carcinoma (UC) that has	urothelial carcinoma	no		Treatment of all conditions included in the category of malignant neoplasms (except central nervous	

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						not progressed with first-line platinum-containing chemotherapy				system tumours, haematopoietic and lymphoid tissue neoplasms) (0 - 17y); P/0504/2020	
BAVENCIO	avelumab + axitinib	SUPPL-6	05/14/19	PD-L1	yes	first line treatment of advanced renal cell carcinoma (RCC)	renal cell carcinoma	no		Treatment of all conditions included in the category of malignant neoplasms (except central nervous system tumours, haematopoietic and lymphoid tissue neoplasms) (0 - 17y); P/0504/2020	
BAVENCIO	avelumab	SUPPL-1	05/09/17	PD-L1	yes	locally advanced or metastatic urothelial carcinoma (UC) who have disease progression during or following platinum-containing chemotherapy or have disease progression within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy	urothelial carcinoma	no		Treatment of all conditions included in the category of malignant neoplasms (except central nervous system tumours, haematopoietic and lymphoid tissue neoplasms) (0 - 17y); P/0504/2020	
BAVENCIO	avelumab	ORIG-1	03/23/17	PD-L1	yes	metastatic Merkel cell carcinoma (MCC)	Merkel cell carcinoma	yes	adults and pediatric patients 12 years and older	Treatment of all conditions included in the category of malignant neoplasms (except central nervous system tumours, haematopoietic and lymphoid tissue neoplasms) (0 - 17y); P/0504/2020	
BESPONSA	ozogamicin	ORIG-1	08/17/17	CD22	yes	relapsed or refractory B-cell precursor acute lymphoblastic leukemia (ALL)	acute lymphoblastic leukemia	yes		Treatment of B cell acute lymphoblastic leukaemia (1y - 17y); P/0062/2020	
BLENREP	belantamab mafodotin-blmf	ORIG-1	08/05/20	BCMA	no	relapsed or refractory multiple myeloma after at least 4 prior therapies, including an anti-CD38 monoclonal antibody, a proteasome inhibitor, and an immunomodulatory agent	multiple myeloma	yes		Treatment of Multiple Myeloma; P/0347/2019	waiver
BLINCYTO	blinatumomab	SUPPL-13	03/29/18	CD19	yes	B-cell precursor acute lymphoblastic leukemia (ALL) in first or second complete remission with minimal residual disease (MRD) greater than or equal to 0.1%	acute lymphoblastic leukemia	yes	adult and pediatric patients	Treatment of acute lymphoblastic leukaemia (1m - 17y); P/0143/2020	

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BLINCYTO	blinatumomab	SUPPL-8	07/11/17	CD19	yes	relapsed or refractory B-cell precursor acute lymphoblastic leukemia (ALL)	acute lymphoblastic leukemia	yes	adult and pediatric patients	Treatment of acute lymphoblastic leukaemia (1m - 17y); P/0143/2020	
BOSULIF	bosutinib	SUPPL-9	12/19/17	BCR-ABL; src tyrosine kinase	yes	newly diagnosed chronic phase (CP) Philadelphia chromosome positive (Ph+) chronic myelogenous leukemia (CML)	chronic myelogenous leukemia	yes		Treatment of chronic myeloid leukaemia (CML) (1y - 17y); P/0270/2020	
BRAFTOVI	encorafenib	SUPPL-6	04/08/20	BRAF	yes	metastatic colorectal cancer (CRC) with a BRAF V600E mutation, as detected by an FDA-approved test, after prior therapy (in combination with cetuximab)	colorectal cancer	no		Treatment of colorectal carcinoma; P/0049/2019	waiver
BRAFTOVI	encorafenib	ORIG-1	06/27/18	BRAF	yes	unresectable or metastatic melanoma with a BRAF V600E or V600K mutation, as detected by an FDA-approved test (in combination with binimetinib)	melanoma	yes		Treatment of melanoma (12y - 17y); P/0054/2016	
BRUKINSA	zanubrutinib	ORIG-1	11/14/19	BTK	yes	mantle cell lymphoma (MCL) after at least one prior therapy	mantle cell lymphoma	yes		Treatment of mature B-cell neoplasms (excluding lymphoplasmacytic lymphoma) (1y - 17y); P/0398/2019	
CABOMETYX	cabozantinib	SUPPL-3	01/14/19	c-Met; VEGFR2; AXL; RET	yes	hepatocellular carcinoma (HCC) after previous treatment with sorafenib	hepatocellular carcinoma	yes		Treatment of solid malignant tumours (0 - 17y); P/0331/2019	
CABOMETYX	cabozantinib	SUPPL-2	12/19/17	c-Met; VEGFR2; AXL; RET	yes	advanced renal cell carcinoma (RCC)	renal cell carcinoma	no		Treatment of solid malignant tumours (0 - 17y); P/0331/2019	
CABOMETYX	cabozantinib	ORIG-1	04/25/16	c-Met; VEGFR2; AXL; RET	yes	advanced renal cell carcinoma (RCC) after prior anti-angiogenic therapy	renal cell carcinoma	no		Treatment of solid malignant tumours (0 - 17y); P/0331/2019	
CALQUENCE	acalabrutinib	SUPPL-6	11/21/19	BTK	yes	chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL)	chronic lymphocytic leukemia	yes		Treatment of mature B-cell neoplasms (1y - 17y); P/0062/2019	
							small lymphocytic lymphoma	no		Treatment of mature B-cell neoplasms (1y - 17y); P/0062/2019	
CALQUENCE	acalabrutinib	ORIG-1	10/31/17	BTK	yes	mantle cell lymphoma (MCL) after at least one prior therapy	mantle cell lymphoma	yes		Treatment of mature B-cell neoplasms (1y - 17y); P/0062/2019	
COPIKTRA	duvelisib	ORIG-1	09/24/18	PI3K	yes	relapsed or refractory chronic lymphocytic leukemia (CLL) or small lymphocytic	chronic lymphocytic leukemia	yes		Treatment of mature B cell malignancies; P/0428/2019	waiver

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						lymphoma (SLL) after at least two prior therapies	small lymphocytic lymphoma	yes		Treatment of mature B cell malignancies; P/0428/2019	waiver
COPIKTRA	duvelisib	ORIG-1	09/24/18	PI3K	yes	relapsed or refractory follicular lymphoma (FL) after at least two prior systemic therapies	follicular lymphoma	yes		Treatment of mature B cell malignancies; P/0428/2019	waiver
CYRAMZA	ramucirumab	SUPPL-34	05/29/20	VEGFR2	yes	first line treatment of metastatic non-small cell lung cancer (NSCLC) with epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 (L858R) substitution mutations (in combination with erlotinib)	non-small cell lung cancer	no		Treatment of lung malignant neoplasms; P/0282/2017	waiver
CYRAMZA	ramucirumab	SUPPL-29	05/10/19	VEGFR2	yes	hepatocellular carcinoma (HCC) with an alpha fetoprotein (AFP) of ≥ 400 ng/mL and after treatment with sorafenib	hepatocellular carcinoma	yes		Treatment of liver cancer; P/0282/2017	waiver
DARZALEX	daratumumab	SUPPL-24	09/26/19	CD38	yes	multiple myeloma in newly diagnosed patients who are eligible for autologous stem cell transplant (in combination with bortezomib + thalidomide + dexamethasone)	multiple myeloma	yes			Class waiver
DARZALEX	daratumumab	SUPPL-20	06/27/19	CD38	yes	multiple myeloma in newly diagnosed patients who are ineligible for autologous stem cell transplant and relapsed or refractory multiple myeloma after at least one prior therapy (in combination with lenalidomide + dexamethasone)	multiple myeloma	yes			Class waiver
DARZALEX	daratumumab	SUPPL-3	11/21/16	CD38	yes	multiple myeloma after at least one prior therapy (in combination with lenalidomide/bortezomib + dexamethasone)	multiple myeloma	yes			Class waiver
DARZALEX FASPRO	daratumumab + hyaluronidase-fihj	ORIG-1	05/01/20	CD38	yes	multiple myeloma	multiple myeloma	yes			Class waiver
DAURISMO	glasdegib	ORIG-1	11/21/18	SHH	yes	newly-diagnosed acute myeloid leukemia (AML) in adult patients who are ≥75 years old or who have comorbidities that preclude use of intensive induction chemotherapy (in combination with low-dose cytarabine)	acute myeloid leukemia	yes		Treatment of acute myeloid leukaemia; P/0239/2018	waiver

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ELZONRIS	tagraxofusp-erzs	ORIG-1	12/21/18	CD123	yes	blastic plasmacytoid dendritic cell neoplasm (BPDCN)	blastic plasmacytoid dendritic cell neoplasm	yes	adults and pediatric patients 2 years and older	Treatment of blastic plasmacytoid dendritic cell neoplasm; P/0326/2018	waiver
ENHERTU	fam-trastuzumab deruxtecan-nxki	ORIG-1	12/20/19	HER2	yes	unresectable or metastatic HER2-positive breast cancer after two or more prior anti-HER2-based regimens in the metastatic setting	breast cancer	no			Class waiver
ERLEADA	apalutamide	SUPPL-1	09/17/19	Androgen receptor	no	metastatic castration-sensitive prostate cancer (mCSPC)	prostate cancer	no			Class waiver
ERLEADA	apalutamide	ORIG-1	02/14/18	Androgen receptor	no	non-metastatic castration-resistant prostate cancer (NM-CRPC)	prostate cancer	no			Class waiver
GAZYVA	obinutuzumab	SUPPL-18	11/16/17	CD20	yes	previously untreated stage II bulky, III, or IV follicular lymphoma (FL) (in combination with chemotherapy)	follicular lymphoma	yes		Treatment of mature B-cell lymphoma (6m - 17y); P/0046/2013	
GAZYVA	obinutuzumab	SUPPL-13	02/26/16	CD20	yes	relapsed or refractory follicular lymphoma (FL) after a rituximab-containing regimen (in combination with bendamustine)	follicular lymphoma	yes		Treatment of mature B-cell lymphoma (6m - 17y); P/0046/2013	
GILOTRIF	afatinib	SUPPL-14	01/12/18	HER2; EGFR	yes	first-line treatment of metastatic non-small cell lung cancer (NSCLC) which has non-resistant epidermal growth factor receptor (EGFR) mutations as detected by an FDA-approved test	non-small cell lung cancer	yes		Treatment of all conditions included in the category of malignant neoplasms (excluding central nervous system, haematopoietic and lymphoid tissue neoplasms) (1y - 17y); P/0184/2020	
GILOTRIF	afatinib	SUPPL-7	04/15/16	HER2; EGFR	yes	metastatic squamous non-small cell lung cancer (NSCLC) progressing after platinum-based chemotherapy	non-small cell lung cancer	yes		Treatment of all conditions included in the category of malignant neoplasms (excluding central nervous system, haematopoietic and lymphoid tissue neoplasms) (1y - 17y); P/0184/2020	
HALAVEN	eribulin	SUPPL-15	01/28/16	microtubules	yes	unresectable or metastatic liposarcoma after prior anthracycline-containing regimen	liposarcoma	yes		Treatment of soft tissue sarcoma (0 - 17y); P/0040/2021	
HERCEPTIN-HYLECTA	trastuzumab + hyaluronidase-oysk	ORIG-1	02/28/19	HER2	yes	adjuvant treatment of HER2 overexpressing node positive or node negative (ER/PR	breast cancer	no			

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						negative or with one high risk feature) breast cancer (in combination with doxorubicin + cyclophosphamide + paclitaxel/ docetaxel OR docetaxel + carboplatin)					
IBRANCE	palbociclib + aromatase inhibitor	SUPPL-4	03/31/17	CDK4/6	yes	hormone receptor (HR) positive, human epidermal growth factor receptor 2 (HER2) negative advanced or metastatic breast cancer (in combination with aromatase inhibitor / fulvestrant)	breast cancer	no		Treatment of breast malignant neoplasms; P/0005/2019	waiver
IBRANCE	palbociclib	SUPPL-2	02/19/16	CDK4/6	yes	hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced or metastatic breast cancer (in combination with letrozole / fulvestrant)	breast cancer	no		Treatment of breast malignant neoplasms; P/0005/2019	waiver
IDHIFA	enasidenib	ORIG-1	08/01/17	IDH2	yes	relapsed or refractory acute myeloid leukemia with an isocitrate dehydrogenase-2 (IDH2) mutation as detected by an FDA-approved test	acute myeloid leukemia	yes		Treatment of acute myeloid leukaemia (2y - 17y); P/0293/2017	
IMBRUVICA	ibrutinib	SUPPL-16	01/18/17	BTK	yes	marginal zone lymphoma (MZL) requiring systemic therapy and after at least one prior anti-CD20-based therapy	marginal zone lymphoma	yes		Treatment of mature B-cell neoplasms (1y - 17y); P/0117/2021	
IMBRUVICA	ibrutinib	SUPPL-10	05/06/16	BTK	yes	chronic lymphocytic leukemia (CLL) / small lymphocytic lymphoma (SLL) with or without a 17p deletion	chronic lymphocytic leukemia	yes		Treatment of mature B-cell neoplasms (1y - 17y); P/0117/2021	
							small lymphocytic lymphoma	yes		Treatment of mature B-cell neoplasms (1y - 17y); P/0117/2021	
IMFINZI	durvalumab	SUPPL-18	03/27/20	PD-L1	yes	first line treatment of extensive-stage small cell lung cancer (ES-SCLC) (in combination with etoposide + carboplatin/cisplatin)	small cell lung cancer	yes		Treatment of all conditions included in the category of malignant neoplasms (except central nervous system, haematopoietic and lymphoid tissue) (0 - 17y); P/0106/2021	
IMFINZI	durvalumab	SUPPL-2	02/16/18	PD-L1	yes	unresectable stage III non-small cell lung cancer (NSCLC) which has not progressed following concurrent platinum-based chemotherapy and radiation therapy	non-small cell lung cancer	no		Treatment of all conditions included in the category of malignant neoplasms (except central nervous system, haematopoietic and	

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										lymphoid tissue) (0 - 17y); P/0106/2021	
IMFINZI	durvalumab	ORIG-1	05/01/17	PD-L1	yes	locally advanced or metastatic urothelial carcinoma which has progressed during or following platinum-containing chemotherapy or which has progressed within 12 month of neoadjuvant treatment with platinum-containing chemotherapy	urothelial carcinoma	no		Treatment of all conditions included in the category of malignant neoplasms (except central nervous system, haematopoietic and lymphoid tissue) (0 - 17y); P/0106/2021	
INQOVI	decitabine + cedazuridine	ORIG-1	07/07/20	DNMT; CDA	yes	myelodysplastic syndromes (MDS)	myelodysplastic syndrome	yes		Treatment of acute myeloid leukaemia (1m - 17y); P/0234/2017	
INREBIC	fedratinib	ORIG-1	08/16/19	JAK2	yes	intermediate-2 or high-risk primary or secondary (post-polycythemia vera or post-essential thrombocythemia) myelofibrosis (MF)	myelofibrosis	yes		Treatment of essential thrombocythaemia; Treatment of polycythaemia vera; Treatment of primary myelofibrosis; P/0261/2012	waiver
JELMYTO	mitomycin	ORIG-1	04/15/20	DNA	yes	low-grade upper tract urothelial cancer (LG-UTUC)	urothelial carcinoma	yes			
JEVTANA	cabazitaxel	SUPPL-19	09/14/17	microtubules	yes	metastatic castration-resistant prostate cancer previously treated with a docetaxel-containing treatment regimen (in combination with prednisone)	prostate cancer	no			Class waiver
KADCYLA	ado-trastuzumab emtansine	SUPPL-105	05/03/19	HER2	yes	adjuvant treatment of HER2-positive early breast cancer (EBC)in patients with residual invasive disease after neoadjuvant taxane and trastuzumab-based treatment	breast cancer	no			Class waiver
KEYTRUDA	pembrolizumab	SUPPL-84	06/29/20	PD-1	yes	unresectable or metastatic microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) colorectal cancer	colorectal cancer	no		Treatment of all conditions included in the category of malignant neoplasms (except nervous system, haematopoietic and lymphoid tissue) (6m - 17y); P/0043/2018	
KEYTRUDA	pembrolizumab	SUPPL-68	06/24/20	PD-1	yes	recurrent or metastatic cutaneous squamous cell carcinoma (cSCC) that is not curable by surgery or radiation	cutaneous squamous cell carcinoma	no		Treatment of all conditions included in the category of malignant neoplasms (except nervous system, haematopoietic and lymphoid tissue) (6m - 17y); P/0043/2018	

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KEYTRUDA	pembrolizumab	SUPPL-71	06/16/20	PD-1	yes	advanced endometrial carcinoma that is not microsatellite instability high (MSI-H) or mismatch repair deficient (dMMR), with disease progression following prior systemic therapy and which are not candidates for curative surgery or radiation (in combination with Lenvatinib)	endometrial carcinoma	no		Treatment of all conditions included in the category of malignant neoplasms (except nervous system, haematopoietic and lymphoid tissue) (6m - 17y); P/0043/2018	
KEYTRUDA	pembrolizumab	SUPPL-71	06/16/20	PD-1	yes	unresectable or metastatic tumor mutational burden-high (TMB H) [≥10 mutations/megabase (mut/Mb)] solid tumors as determined by an FDA-approved test, that have progressed following prior treatment and that have no satisfactory alternative treatment options	solid tumors	no	adult and pediatric patients	Treatment of all conditions included in the category of malignant neoplasms (except nervous system, haematopoietic and lymphoid tissue) (6m - 17y); P/0043/2018	
KEYTRUDA	pembrolizumab	SUPPL-66	01/08/20	PD-1	yes	Bacillus Calmette-Guerin (BCG)-unresponsive, high-risk, non-muscle invasive bladder cancer (NMIBC) with carcinoma in situ (CIS) with or without papillary tumors, ineligible for or without election to undergy cystectomy	bladder cancer	no		Treatment of all conditions included in the category of malignant neoplasms (except nervous system, haematopoietic and lymphoid tissue) (6m - 17y); P/0043/2018	
KEYTRUDA	pembrolizumab	SUPPL-55	07/30/19	PD-1	yes	recurrant locally advanced or metastatic squamous cell carcinoma of the esophagus with PD-L1 expression (CPS 19) as determined by an FDA-approved test, with disease progression after one or more prior lines of systemic therapy	esophageal squamous cell carcinoma	yes		Treatment of all conditions included in the category of malignant neoplasms (except nervous system, haematopoietic and lymphoid tissue) (6m - 17y); P/0043/2018	
KEYTRUDA	pembrolizumab	SUPPL-53	06/17/19	PD-1	yes	metastatic small cell lung cancer (SCLC) with disease progression on or after platinum-based chemotherapy and at least one other prior line of therapy	small cell lung cancer	yes		Treatment of all conditions included in the category of malignant neoplasms (except nervous system, haematopoietic and lymphoid tissue) (6m - 17y); P/0043/2018	
KEYTRUDA	pembrolizumab	SUPPL-52	06/10/19	PD-1	yes	metastatic or unresectable, recurrent head and neck squamous cell carcinoma (HNSCC) (with or without platinum + fluorouracil (FU))	head and neck squamous cell carcinoma	no		Treatment of all conditions included in the category of malignant neoplasms (except nervous system,	

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										haematopoietic and lymphoid tissue) (6m - 17y); P/0043/2018	
KEYTRUDA	pembrolizumab	SUPPL-54	04/19/19	PD-1	yes	advanced renal cell carcinoma (RCC) (in combination with axitinib)	renal cell carcinoma	no		Treatment of all conditions included in the category of malignant neoplasms (except nervous system, haematopoietic and lymphoid tissue) (6m - 17y); P/0043/2018	
KEYTRUDA	pembrolizumab	SUPPL-47	04/11/19	PD-1	yes	first-line treatment of stage III non-small cell lung cancer (NSCLC) in patients who are not candidates for surgical resection or definitive chemoradiation, or metastatic NSCLC expressing PD-L1 (TPS ≥ 1%) as determined by an FDA-approved test, with no EGFR or ALK genomic tumor aberrations	non-small cell lung cancer	no		Treatment of all conditions included in the category of malignant neoplasms (except nervous system, haematopoietic and lymphoid tissue) (6m - 17y); P/0043/2018	
KEYTRUDA	pembrolizumab	SUPPL-40	02/15/19	PD-1	yes	adjuvant treatment of melanoma with involvement of lymph node(s) following complete resection	melanoma	yes		Treatment of all conditions included in the category of malignant neoplasms (except nervous system, haematopoietic and lymphoid tissue) (6m - 17y); P/0043/2018	
KEYTRUDA	pembrolizumab	SUPPL-45	12/19/18	PD-1	yes	recurrent locally advanced or metastatic Merkel cell carcinoma (MCC)	Merkel cell carcinoma	yes	adult and pediatric patients	Treatment of all conditions included in the category of malignant neoplasms (except nervous system, haematopoietic and lymphoid tissue) (6m - 17y); P/0043/2018	
KEYTRUDA	pembrolizumab	SUPPL-42	11/09/18	PD-1	yes	hepatocellular carcinoma (HCC) after previous treatment with sorafenib	hepatocellular carcinoma	yes		Treatment of all conditions included in the category of malignant neoplasms (except nervous system, haematopoietic and lymphoid tissue) (6m - 17y); P/0043/2018	
KEYTRUDA	pembrolizumab	SUPPL-41	10/30/18	PD-1	yes	first-line treatment of metastatic squamous non-small cell lung cancer (NSCLC) (in combination with carboplatin + paclitaxel /nab-paclitaxel)	non-small cell lung cancer	no		Treatment of all conditions included in the category of malignant neoplasms (except nervous system, haematopoietic and lymphoid tissue) (6m - 17y); P/0043/2018	

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KEYTRUDA	pembrolizumab	SUPPL-35	08/20/18	PD-1	yes	first-line treatment of metastatic, non-squamous non-small cell lung cancer (NSqNSCLC), with no EGFR or ALK genomic tumor aberrations (in combination with pemetrexed + platinum)	non-small cell lung cancer	no		Treatment of all conditions included in the category of malignant neoplasms (except nervous system, haematopoietic and lymphoid tissue) (6m - 17y); P/0043/2018	
KEYTRUDA	pembrolizumab	SUPPL-30	06/13/18	PD-1	yes	refractory primary mediastinal large B-cell lymphoma (PMBCL)	primary mediastinal large B-cell lymphoma	yes	adult and pediatric patients		
KEYTRUDA	pembrolizumab	SUPPL-34	06/12/18	PD-1	yes	recurrent or metastatic cervical cancer with disease progression on or after chemotherapy and tumor expression of PD-L1 (CPS ≥1) as determined by an FDA-approved test	cervical cancer	no		Treatment of all conditions included in the category of malignant neoplasms (except nervous system, haematopoietic and lymphoid tissue) (6m - 17y); P/0043/2018	
KEYTRUDA	pembrolizumab	SUPPL-24	09/22/17	PD-1	yes	recurrent locally advanced or metastatic, gastric or gastroesophageal junction adenocarcinoma expressing PD-L1 (CPS ≥1 as determined by an FDA-approved test) with disease progression on or after two or more prior lines of therapy including fluoropyrimidine- and platinum-containing chemotherapy and if appropriate, HER2/neu-targeted therapy	gastric or gastroesophageal junction adenocarcinoma	yes		Treatment of all conditions included in the category of malignant neoplasms (except nervous system, haematopoietic and lymphoid tissue) (6m - 17y); P/0043/2018	
KEYTRUDA	pembrolizumab	SUPPL-14	05/23/17	PD-1	yes	unresectable or metastatic, microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) solid tumors that have progressed following prior treatment and with no satisfactory treatment options, or colorectal cancer that has progressed following treatment with a fluoropyrimidine, oxaliplain, and irinotecan	solid tumors	no	adult and pediatric patients	Treatment of all conditions included in the category of malignant neoplasms (except nervous system, haematopoietic and lymphoid tissue) ((6m - 17y); P/0043/2018	
KEYTRUDA	pembrolizumab	SUPPL-17	05/18/17	PD-1	yes	locally advanced or metastatic urothelial carcinoma not eligible for cisplatin-containing chemotherapy or which has progressed during or following platinum-containing	urothelial carcinoma	no		Treatment of all conditions included in the category of malignant neoplasms (except nervous system,	

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						chemotherapy or within 12 months of neoaduvant or adjuvant treatment with platinum-containing chemoterapy				haematopoietic and lymphoid tissue) (6m - 17y); P/0043/2018	
KEYTRUDA	pembrolizumab	SUPPL-16	05/10/17	PD-1	yes	first-line treatment of metastatic non-squamous non-small cell lung cancer (NSCLC) (in combination with pemetrexed + carboplatin)	non-small cell lung cancer	no		Treatment of all conditions included in the category of malignant neoplasms (except nervous system, haematopoietic and lymphoid tissue) (6m - 17y); P/0043/2018	
KEYTRUDA	pembrolizumab	SUPPL-15	03/14/17	PD-1	yes	refractory classical Hodgkin lymphoma (cHL)	classical Hodgkin lymphoma	yes	adult and pediatric patients	Treatment of Hodgkin lymphoma (3y - 17y); P/0008/2018	
KEYTRUDA	pembrolizumab	SUPPL-8	10/24/16	PD-1	yes	first line treatment of metastatic non-small cell lung cancer (NSCLC) with high PD-L1 expression (TPS ≥ 1%) as determined by an FDA-approved test, with disease progression on or after platinum-containing chemotherapy	non-small cell lung cancer	no		Treatment of all conditions included in the category of malignant neoplasms (except nervous system, haematopoietic and lymphoid tissue) (6m - 17y); P/0043/2018	
KEYTRUDA	pembrolizumab	SUPPL-9	08/05/16	PD-1	yes	recurrent or metastatic head and neck squamous cell carcinoma (HNSCC) which has progressed on or after platinum-containing chemotherapy	head and neck squamous cell carcinoma	no		Treatment of all conditions included in the category of malignant neoplasms (except nervous system, haematopoietic and lymphoid tissue) (6m - 17y); P/0043/2018	
KISQALI	ribociclib	SUPPL-1	07/18/18	CDK4/6	yes	HR-positive, HER2-negative advanced or metastatic breast cancer, as initial endocrine based therapy or following disease progression on endocrine therapy (in combination with fulvestrant)	breast cancer	no		Treatment of breast cancer; P/0218/2020	waiver
KISQALI	ribociclib	ORIG-1	03/13/17	CDK4/6	yes	hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced or metastatic breast cancer (in combination with aromatase inhibitor)	breast cancer	no		Treatment of breast cancer; P/0218/2020	waiver
KOSELUGO	selumetinib	ORIG-1	04/10/20	MEK	yes	neurofibromatosis type 1 (NF1) with symptomatic, inoperable plexiform neurofibromas (PN)	neurofibromatosis type 1	yes	pediatric patients, 2 years of age and older	Treatment of neurofibromatosis type 1 (1y - 17y); P/0279/2019	

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KYMRIAH	tisagenlecleucel	SUPPL-1	05/01/18	CD19	yes	relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy including diffuse large B-cell lymphoma (DLBCL) not otherwise specified, high grade B-cell lymphoma and DLBCL arising from follicular lymphoma	large B-cell lymphoma	yes		Treatment of mature B-cell neoplasms (patients weighing at least 6kg); P/0323/2019	
KYMRIAH	tisagenlecleucel	ORIG-1	08/30/17	CD19	yes	B-cell precursor acute lymphoblastic leukemia (ALL) that is refractory or in second or later relapse	acute lymphoblastic leukemia	yes	patients up to age 25 years	Treatment of B cell acute lymphoblastic leukaemia/lymphoblastic lymphoma (patients weighing at least 6kg); P/0008/2019	
LARTRUVO	olaratumab	ORIG-1	10/19/16	PDGF-R α	yes	soft tissue sarcoma (STS) with a histologic subtype for which an anthracycline-containing regimen is appropriate and which is not amenable to curative treatment with radiotherapy or surgery (in combination with doxorubicin)	soft tissue sarcoma	yes		Treatment of soft tissue sarcoma; P/0112/2019	waiver
LENVIMA	lenvatinib	SUPPL-7	08/15/18	VEGFR1/2/3	yes	unresectable hepatocellular carcinoma (HCC)	hepatocellular carcinoma	yes		Treatment of all conditions included in the category of malignant neoplasms except haematopoietic and lymphoid tissue neoplasms, papillary thyroid cancer, follicular thyroid cancer and osteosarcoma (2y - 17y); P/0210/2020	
LENVIMA	lenvatinib	SUPPL-3	05/13/16	VEGFR1/2/3	yes	advanced renal cell carcinoma following one prior anti-angiogenic therapy (in combination with everolimus)	renal cell carcinoma	no		Treatment of all conditions included in the category of malignant neoplasms except haematopoietic and lymphoid tissue neoplasms, papillary thyroid cancer, follicular thyroid cancer and osteosarcoma (2y - 17y); P/0210/2020	
LIBTAYO	cemiplimab-rwlc	ORIG-1	09/28/18	PD-1	yes	metastatic cutaneous squamous cell carcinoma (CSCC) or locally advanced CSCC in	cutaneous squamous cell carcinoma	no		Treatment of all conditions included in the category of malignant neoplasms (except haematopoietic	

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						patients who are not candidates for curative surgery or curative radiation				and lymphoid tissue neoplasms) (0 - 17y); P/0385/2017	
LONSURF	trifluridine + tipiracil	SUPPL-8	02/22/19	DNA	yes	metastatic gastric or gastroesophageal junction (GEJ) adenocarcinoma previously treated with at least two prior lines of chemotherapy that included a fluoropyrimidine, a platinum, either a taxane or irinotecan, and if appropriate, HER2/neu-targeted therapy	gastric or gastroesophageal junction adenocarcinoma	yes			Class waiver
LORBRENA	lorlatinib	ORIG-1	11/02/18	ALK; ROS1	yes	anaplastic lymphoma kinase (ALK)-positive metastatic non-small cell lung cancer (NSCLC) which has progressed on crizotinib and at least one other ALK inhibitor for metastatic disease; or alectinib as the first ALK inhibitor therapy for metastatic disease; or ceritinib as the first ALK inhibitor therapy for metastatic disease	non-small cell lung cancer	yes		Treatment of lung cancer; P/0006/2021	waiver
LUMOXITI	moxetumomab pasudotox-tdfk	ORIG-1	09/13/18	CD22	yes	relapsed or refractory hairy cell leukemia (HCL) after at least two prior systemic therapies, including treatment with a purine nucleoside analog (PNA)	hairy cell leukemia	yes		Treatment of hairy cell leukaemia; P/0228/2019	waiver
LUTATHERA	lutetium Lu 177 dotatate	ORIG-1	01/26/18	Somatostatin receptors	yes	somatostatin receptor-positive gastroenteropancreatic neuroendocrine tumors (GEP-NETs), including foregut, midgut, and hindgut neuroendocrine tumors	gastroenteropancreatic neuroendocrine tumors	yes			Class waiver
LYNPARZA	olaparib	SUPPL-14	05/19/20	PARP	yes	deleterious or suspected deleterious germline or somatic homologous recombination repair (HRR) gene-mutated metastatic castration-resistant prostate cancer (mCRPC) which has progressed following prior treatment with enzalutamide or abiraterone	prostate cancer	no		Treatment of all conditions included in the category of malignant neoplasms (except central nervous system tumours, haematopoietic and lymphoid tissue neoplasms) (6m - 17y); P/0250/2020	
LYNPARZA	olaparib	SUPPL-13	05/08/20	PARP	yes	maintenance treatment of advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer after complete or partial response to first-line platinum-based chemotherapy and	ovarian cancer	yes		Treatment of all conditions included in the category of malignant neoplasms (except central nervous system tumours, haematopoietic	

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						which is associated with homologous recombination deficiency (HRD) positive status defined by either a deleterious or suspected deleterious BRCA mutation, and/or genomic instability (in combination with bevacizumab)				and lymphoid tissue neoplasms) (6m - 17y); P/0250/2020	
							fallopian tube cancer	yes		Treatment of all conditions included in the category of malignant neoplasms (except central nervous system tumours, haematopoietic and lymphoid tissue neoplasms) (6m - 17y); P/0250/2020	
							primary peritoneal cancer	yes		Treatment of all conditions included in the category of malignant neoplasms (except central nervous system tumours, haematopoietic and lymphoid tissue neoplasms) (6m - 17y); P/0250/2020	
LYNPARZA	olaparib	SUPPL-10	12/27/19	PARP	yes	maintenance treatment of deleterious or suspected deleterious germline BRCA-mutated (gBRCAm) metastatic pancreatic adenocarcinoma which has not progressed on at least 16 weeks of a first-line platinum-based chemotherapy regimen	pancreatic adenocarcinoma	yes		Treatment of all conditions included in the category of malignant neoplasms (except central nervous system tumours, haematopoietic and lymphoid tissue neoplasms) (6m - 17y); P/0250/2020	
LYNPARZA	olaparib	SUPPL-6	12/19/18	PARP	yes	maintenance treatment of deleterious or suspected deleterious germline or somatic BRCA-mutated (gBRCAm or sBRCAm) advanced epithelial ovarian, fallopian tube or primary peritoneal cancer after complete or partial response to first-line platinum-based chemotherapy	ovarian cancer	yes		Treatment of all conditions included in the category of malignant neoplasms (except central nervous system tumours, haematopoietic and lymphoid tissue neoplasms) (6m - 17y); P/0250/2020	
							fallopian tube cancer	yes		Treatment of all conditions included in the category of malignant neoplasms (except central nervous system tumours, haematopoietic and lymphoid tissue neoplasms) (6m - 17y); P/0250/2020	
							primary peritoneal cancer	yes		Treatment of all conditions included in the category of malignant	

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										neoplasms (except central nervous system tumours, haematopoietic and lymphoid tissue neoplasms) (6m - 17y); P/0250/2020	
LYNPARZA	olaparib	SUPPL-1	01/12/18	PARP	yes	deleterious or suspected deleterious germline BRCA-mutated (gBRCAm), HER2-negative metastatic breast cancer after treatment with chemotherapy in the neoadjuvant, adjuvant, or metastatic setting	breast cancer	no		Treatment of all conditions included in the category of malignant neoplasms (except central nervous system tumours, haematopoietic and lymphoid tissue neoplasms) (6m - 17y); P/0250/2020	
LYNPARZA	olaparib	ORIG-1	08/17/17	PARP	yes	deleterious or suspected deleterious germline BRCA-mutated (gBRCAm) advanced ovarian cancer after three or more prior lines of chemotherapy	ovarian cancer	yes		Treatment of all conditions included in the category of malignant neoplasms (except central nervous system tumours, haematopoietic and lymphoid tissue neoplasms) (6m - 17y); P/0250/2020	
LYNPARZA	olaparib	ORIG-1	08/17/17	PARP	yes	maintenance treatment of recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer after complete or partial response to platinum-based chemotherapy	ovarian cancer	yes		Treatment of all conditions included in the category of malignant neoplasms (except central nervous system tumours, haematopoietic and lymphoid tissue neoplasms) (6m - 17y); P/0250/2020	
							fallopian tube cancer	yes		Treatment of all conditions included in the category of malignant neoplasms (except central nervous system tumours, haematopoietic and lymphoid tissue neoplasms) (6m - 17y); P/0250/2020	
							primary peritoneal cancer	yes		Treatment of all conditions included in the category of malignant neoplasms (except central nervous system tumours, haematopoietic and lymphoid tissue neoplasms) (6m - 17y); P/0250/2020	

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MONJUVI	tafasitamab-cxix	ORIG-1	07/31/20	CD19	yes	relapsed or refractory diffuse large B-cell lymphoma (DLBCL) not otherwise specified, including DLBCL arising from low grade lymphoma, and not eligible for autologous stem cell transplant (ASCT) (in combination with lenalidomide)	diffuse large B-cell lymphoma	yes		Treatment of diffuse large B-cell lymphoma; P/0294/2019	waiver
MYLOTARG	gemtuzumab ozogamicin	SUPPL-4	06/16/20	CD33	yes	CD33-positive acute myeloid leukemia (AML)	acute myeloid leukemia	yes	adults and pediatric patients 1 month and older	Treatment of acute myeloid leukaemia (1m - 17y); P/0326/2017	
MYLOTARG	gemtuzumab ozogamicin	ORIG-1	09/01/17	CD33	yes	CD33-positive acute myeloid leukemia (AML)	acute myeloid leukemia	yes		Treatment of acute myeloid leukaemia (1m - 17y); P/0326/2017	
MYLOTARG	gemtuzumab ozogamicin	ORIG-2	09/01/17	CD33	yes	relapsed or refractory CD33-positive AML	acute myeloid leukemia	yes	adults and in pediatric patients 2 years and older	Treatment of acute myeloid leukaemia (1m - 17y); P/0326/2017	
NERLYNX	neratinib	SUPPL-5	02/25/20	HER2; EGFR	yes	advanced or metastatic HER2-positive breast cancer after two or more prior anti-HER2 based regimens in the metastatic setting (in combination with capecitabine)	breast cancer	no		Treatment of breast cancer; P/0246/2020	waiver
NERLYNX	neratinib	ORIG-1	07/17/17	HER2; EGFR	yes	early stage HER2-overexpressed/amplified breast cancer, to follow adjuvant trastuzumab based therapy	breast cancer	no		Treatment of breast cancer; P/0246/2020	waiver
NUBEQA	darolutamide	ORIG-1	07/30/19	Androgen receptor	no	non-metastatic castration-resistant prostate cancer	prostate cancer	no			Class waiver
OPDIVO	nivolumab	SUPPL-81	06/10/20	PD-1	yes	unresectable advanced, recurrent or metastatic esophageal squamous cell carcinoma (ESCC) after prior fluoropyrimidine- and platinum-based chemotherapy	esophageal squamous cell carcinoma	no		Treatment of all conditions included in the category of malignant neoplasms (except nervous system, haematopoietic and lymphoid tissue) (6m - 17y); P/0432/2020	

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OPDIVO	nivolumab	SUPPL-80	05/15/20	PD-1	yes	first-line treatment of metastatic non-small cell lung cancer with PD-L1 (≥1%) expression (in combination with ipilimumab)	non-small cell lung cancer	no		Treatment of all conditions included in the category of malignant neoplasms (except nervous system, haematopoietic and lymphoid tissue) (6m - 17y); P/0432/2020	
OPDIVO	nivolumab	SUPPL-67	08/16/18	PD-1	yes	metastatic small cell lung cancer (SCLC) with progression after platinum-based chemotherapy and at least one other line of therapy	small cell lung cancer	yes		Treatment of all conditions included in the category of malignant neoplasms (except nervous system, haematopoietic and lymphoid tissue) (6m - 17y); P/0432/2020	
OPDIVO	nivolumab	SUPPL-55	12/20/17	PD-1	yes	adjuvant treatment of melanoma with involvement of lymph nodes or metastatic disease after complete resection	melanoma	yes		Treatment of melanoma (12y - 17y); P/0070/2021	
OPDIVO	nivolumab	SUPPL-41	09/22/17	PD-1	yes	hepatocellular carcinoma (HCC) after previous treatment with sorafenib	hepatocellular carcinoma	yes		Treatment of all conditions included in the category of malignant neoplasms (except nervous system, haematopoietic and lymphoid tissue) (6m - 17y); P/0432/2020	
OPDIVO	nivolumab	SUPPL-34	07/31/17	PD-1	yes	microsatellite instability high (MSI-H) or mismatch repair deficient (dMMR) metastatic colorectal cancer (CRC) that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan	colorectal cancer	no	adult and patients 12 years and older	Treatment of all conditions included in the category of malignant neoplasms (except nervous system, haematopoietic and lymphoid tissue) (6m - 17y); P/0432/2020	
OPDIVO	nivolumab	SUPPL-24	02/02/17	PD-1	yes	locally advanced or metastatic urothelial carcinoma following disease progression during or following platinum-containing chemotherapy or disease progression within 12 months or neoadjuvant or adjuvant treatment with platinum-containing therapy	urothelial carcinoma	no		Treatment of all conditions included in the category of malignant neoplasms (except nervous system, haematopoietic and lymphoid tissue) (6m - 17y); P/0432/2020	
OPDIVO	nivolumab	SUPPL-22	11/10/16	PD-1	yes	recurrent or metastatic squamous cell carcinoma of the head and neck (SCCHN) with disease progression on or after platinum-based therapy	head and neck squamous cell carcinoma	no		Treatment of all conditions included in the category of malignant neoplasms (except nervous system, haematopoietic and lymphoid tissue) (6m - 17y); P/0432/2020	

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OPDIVO	nivolumab	SUPPL-19	05/17/16	PD-1	yes	classical Hodgkin lymphoma (cHL) that has relapsed or progressed after autologous hematopoietic stem cell transplantation (HSCT) and post-transplantation brentuximab vedotin	classical Hodgkin lymphoma	yes		Treatment of malignant neoplasms of lymphoid tissue (6m - 17y); P/0433/2020	
OPDIVO	nivolumab	SUPPL-82	05/26/20	PD-1	yes	first line treatment of metastatic or recurrent non-small cell lung cancer (NSCLC), with no epidermal growth factor receptor (EGFR) or anaplastic lymphoma kinase (ALK) genomic tumor aberrations (in combination with ipilimumab + 2 cycles of platinum-doublet chemotherapy)	non-small cell lung cancer	no		Treatment of all conditions included in the category of malignant neoplasms (except nervous system, haematopoietic and lymphoid tissue) (6m - 17y); P/0432/2020	
OPDIVO	nivolumab	SUPPL-78	03/10/20	PD-1	yes	hepatocellular carcinoma (HCC) after previous treatment with sorafenib (in combination with ipilimumab)	hepatocellular carcinoma	yes		Treatment of all conditions included in the category of malignant neoplasms (except nervous system, haematopoietic and lymphoid tissue) (6m - 17y); P/0432/2020	
OPDIVO	nivolumab	SUPPL-58	04/16/18	PD-1	yes	intermediate or poor risk, previously untreated advanced renal cell carcinoma (in combination with ipilimumab)	renal cell carcinoma	no		Treatment of all conditions included in the category of malignant neoplasms (except nervous system, haematopoietic and lymphoid tissue) (6m - 17y); P/0432/2020	
PADCEV	enfortumab vedotin-ejfv	ORIG-1	12/18/19	Nectin-4	no	locally advanced or metastatic urothelial carcinoma after treatment with programmed death receptor-1 (PD-1) or programmed death-ligand 1 (PD-L1) inhibitor, and a platinum-containing chemotherapy in the neoadjuvant/adjuvant, locally advanced or metastatic setting	urothelial carcinoma	no		Treatment of urothelial carcinoma; P/0114/2018	waiver
PEMAZYRE	pemigatinib	ORIG-1	04/17/20	FGFR2	yes	previously treated, unresectable locally advanced or metastatic cholangiocarcinoma with a fibroblast growth factor receptor 2 (FGFR2) fusion or other rearrangementas detected by an FDA-approved test	cholangiocarcinoma	yes		Treatment of cholangiocarcinoma; P/0386/2018	waiver

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PERJETA	pertuzumab	SUPPL-118	12/20/17	HER2	yes	adjuvant treatment of HER2-positive early breast cancer at high risk of recurrence (in combination with trastuzumab + chemotherapy)	breast cancer	no			Class waiver
PHESGO	pertuzumab + trastuzumab + hyaluronidase–zzxf	ORIG-1	06/29/20	HER2	yes	HER2-positive metastatic breast cancer in patients who have not received prior anti-HER2 therapy or chemotherapy for metastatic disease (in combination with docetaxel)	breast cancer	no			Class waiver
PHESGO	pertuzumab + trastuzumab + hyaluronidase–zzxf	ORIG-1	06/29/20	HER2	yes	neoadjuvant treatment of HER2-positive, locally advanced, inflammatory, or early stage breast cancer as part of a complete treatment regiment for early breast cancer; adjuvant treatment of HER2-positive early breast cancer at high risk of recurrence (in combination with chemotherapy)	breast cancer	no			Class waiver
PIQRAY	alpelisib	ORIG-1	05/24/19	PI3K	yes	treatment of postmenopausal women, and men, with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative, PIK3CA-mutated, advanced or metastatic breast cancer as detected by an FDA-approved test following progression on or after an endocrine-based regimen (in combination with fulvestrant)	breast cancer	no		Treatment of breast cancer; P/0079/2017	waiver
POLIVY	polatuzumab vedotin-piiq	ORIG-1	06/10/19	CD79b	yes	relapsed or refractory diffuse large B-cell lymphoma (DLBCL), not otherwise specified, after at least two prior therapies (in combination with bendamustine + rituximab)	diffuse large B-cell lymphoma	yes		Treatment of mature B-cell neoplasms; P/0117/2018	waiver
POMALYST	pomalidomide	SUPPL-23	05/14/20	Cereblon	yes	AIDS-related Kaposi sarcoma after failure of highly active antiretroviral therapy and Kaposi sarcoma in adult patients who are HIV-negative	Kaposi sarcoma	yes			
POTELIGEO	mogamulizumab-kpkc	ORIG-1	08/08/18	CCR4	no		mycosis fungoides	yes		Treatment of Cutaneous T-Cell Lymphoma; P/0261/2015	waiver

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						relapsed or refractory mycosis fungoides (MF) or Sézary syndrome (SS) after at least one prior systemic therapy	Sézary syndrome	yes		Treatment of Cutaneous T-Cell Lymphoma; P/0261/2015	waiver
QINLOCK	ripretinib	ORIG-1	05/15/20	KIT; PDGFRA	yes	advanced gastrointestinal stromal tumor (GIST) after prior treatment with 3 or more kinase inhibitors, including imatinib	gastrointestinal stromal tumor	yes		Treatment of gastrointestinal stromal tumours; P/0122/2020	waiver
RETEVMO	selpercatinib	ORIG-1	05/08/20	RET-kinase	yes	advanced or metastatic RET-mutant medullary thyroid cancer (MTC) requiring systemic therapy	thyroid cancer	yes	Adult and pediatric patients ≥12 years of age	Treatment of all conditions included in the category of malignant neoplasms (except haematopoietic and lymphoid tissue neoplasms) (6m - 17y); P/0369/2019	
RETEVMO	selpercatinib	ORIG-1	05/08/20	RET-kinase	yes	metastatic RET fusion-positive non-small cell lung cancer (NSCLC)	non-small cell lung cancer	yes		Treatment of all conditions included in the category of malignant neoplasms (except haematopoietic and lymphoid tissue neoplasms) (6m - 17y); P/0369/2019	
REVLIMID	lenalidomide	SUPPL-57	05/28/19	Cereblon	yes	previously treated follicular lymphoma (FL) and previously treated marginal zone lymphoma (MZL) (in combination with rituximab)	follicular lymphoma	yes		Treatment of mature B-cell neoplasms; P/0279/2017	waiver
							marginal zone lymphoma	yes		Treatment of mature B-cell neoplasms; P/0279/2017	waiver
REVLIMID	lenalidomide	SUPPL-49	02/22/17	Cereblon	yes	maintenance therapy of multiple myeloma following autologous hematopoietic stem cell transplantation (auto-HSCT)	multiple myeloma	yes		Treatment of mature B-cell neoplasms; P/0279/2017	waiver
RITUXAN HYCELA	rituximab and hyaluronidase human combination	ORIG-1	06/22/17	CD20	yes	treatment of follicular lymphoma, diffuse large B-cell lymphoma, and chronic lymphocytic leukemia	follicular lymphoma	yes			
							diffuse large B-cell lymphoma	yes			
							chronic lymphocytic leukemia	no			
ROZLYTREK	entrectinib	ORIG-1	08/15/19	Tyrosine kinases (TRK A/B/C; ROS1; ALK)	yes	metastatic ROS1-positive non-small cell lung cancer (NSCLC)	non-small cell lung cancer	yes		Treatment of all conditions induded in the category of malignant neoplasms (except haematopoietic and lymphoid tissue neoplasms) (0 - 17y); P/0092/2020	

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ROZLYTREK	entrectinib	ORIG-1	08/15/19	Tyrosine kinases (TRK A/B/C; ROS1; ALK)	yes	solid tumors that have a neurotrophic tyrosine receptor kinase (NTRK) gene fusion without a known acquired resistance mutation, are metastatic or where surgical resection is likely to result in severe morbidity, and have either progressed following treatment or have no satisfactory alternative therapy	solid tumors	yes	adults and pediatric patients 12 years of age and older	Treatment of all conditions induded in the category of malignant neoplasms (except haematopoietic and lymphoid tissue neoplasms) (0 - 17y); P/0092/2020	
RUBRACA	rucaparib	SUPPL-4	05/15/20	PARP-1	yes	deleterious BRCA mutation (germline and/or somatic)-associated metastatic castration-resistant prostate cancer (mCRPC) after androgen receptor-directed therapy and a taxane-based chemotherapy	prostate cancer	no		Treatment of prostate malignant neoplasms; P/0242/2020	waiver
RUBRACA	rucaparib	SUPPL-3	04/06/18	PARP-1	yes	deleterious BRCA mutation (germline and/or somatic) associated epithelial ovarian, fallopian tube, or primary perioneal cancer after two or more chemotherapies	ovarian cancer	yes		Treatment of ovarian cancer; P/0242/2020	waiver
							fallopian tube cancer	no		Treatment of fallopian tube cancer; P/0242/2020	waiver
							primary peritoneal cancer	no		Treatment of primary peritoneal cancer; P/0242/2020	waiver
RUBRACA	rucaparib	SUPPL-3	04/06/18	PARP-1	yes	maintenance treatment of recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer after complete or partial response to platinum-based chemotherapy	ovarian cancer	yes		Treatment of ovarian cancer; P/0242/2020	waiver
							fallopian tube cancer	no		Treatment of fallopian tube cancer; P/0242/2020	waiver
							primary peritoneal cancer	no		Treatment of primary peritoneal cancer; P/0242/2020	waiver
RUBRACA	rucaparib	ORIG-1	12/19/16	PARP-1	yes	deleterious BRCA mutation (germline and/or somatic) associated advanced ovarian cancer after two or more chemotherapies	ovarian cancer	yes		Treatment of ovarian cancer; P/0242/2020	waiver
RYDAPT	midostaurin	ORIG-2	04/28/17	CD135; FLT3	yes	newly diagnosed acute myeloid leukemia (AML) that is FLT3 mutation positive as detected by a FDA approved test (in combination with cytarabine + daunorubicin induction + cytarabine consolidation chemotherapy)	acute myeloid leukemia	yes		Treatment of acute myeloid leukaemia (3m - 17y); P/0086/2021	

INN	Active substance	Submission	Approval Date (MM/DD/YY)	Target	Relevant target?	Indication in label	Associated condition	Orphan designation granted?	Paediatric indication in label	EU PIP (condition (age group); decision number)	EU Waiver
RYDAPT	midostaurin	ORIG-1	04/28/17	CD135; FLT3	yes	aggressive systemic mastocytosis (ASM), systemic mastocytosis with associated hematological neoplasm (SM-AHN), or mast cell leukemia	mastocytosis	yes		Treatment of malignant mastocytosis; P/0086/2021	waiver
SARCLISA	isatuximab-irfc	ORIG-1	03/02/20	CD38	yes	multiple myeloma after at least two prior therapies including lenalidomide and a proteasome inhibitor (in combination with pomalidomide + dexamethasone)	multiple myeloma	yes		Treatment of malignant neoplasms of the haematopoietic and lymphoid tissue (1m - 17y); P/0193/2019	
SPRYCEL	dasatinib	SUPPL-21	12/21/18	Tyrosine kinases (Bcr-Abl; Src kinases)	yes	newly diagnosed Philadelphia chromosome-positive (Ph+) acute lymphoblastic leukemia (ALL) (in combination with chemotherapy)	acute lymphoblastic leukemia	yes	pediatric patients 1 year of age and older	Treatment of Philadelphia-chromosome (BCR-ABL translocation)-positive acute lymphoblastic leukaemia (1y - 17y); P/0042/2018	
SPRYCEL	dasatinib	SUPPL-20	11/09/17	Tyrosine kinases (Bcr-Abl; Src kinases)	yes	Philadelphia chromosome-positive (Ph+) chronic myeloid leukemia (CML) in the chronic phase	chronic myeloid leukemia	yes	pediatric patients	Treatment of Philadelphia-chromosome (BCR-ABL translocation)-positive chronic myeloid leukaemia (1y - 17y); P/0042/2018	
STIVARGA	regorafenib	SUPPL-7	04/27/17	VEGFR2; TIE2	yes	hepatocellular carcinoma (HCC) after previous treatment with sorafenib	hepatocellular carcinoma	yes		Treatment of all conditions contained in the category of malignant neoplasms (except haematopoietic and lymphoid tissue) (6m - 17y); P/0141/2020	
SUTENT	sunitinib malate	SUPPL-33	11/16/17	Tyrosine kinases (VEGFR1/2/3; PDGFR; KIT; CSF-1R; FLT3; RET)	yes	adjuvant treatment of patients at high risk of recurrent renal cell carcinoma following nephrectomy	renal cell carcinoma	no			
TABRECTA	capmatinib	ORIG-1	05/06/20	c-Met	yes	metastatic non-small cell lung cancer (NSCLC) with a mutation that leads to mesenchymal-epithelial transition (MET) exon 14 skipping as detected by an FDA-approved test	non-small cell lung cancer	yes		Treatment of lung malignant neoplasms; P/0305/2017	waiver
TAFINLAR	dabrafenib	SUPPL-10	05/04/18	BRAF	yes	locally advanced or metastatic anaplastic thyroid cancer with BRAF V600E mutation and	thyroid cancer	yes		Treatment of solid malignant tumours (excluding melanoma) (1y - 17y); P/0410/2020	

INN	Active substance	Submission	Approval Date (MM/DD/YY)	Target	Relevant target?	Indication in label	Associated condition	Orphan designation granted?	Paediatric indication in label	EU PIP (condition (age group); decision number)	EU Waiver
						with no satisfactory locoregional treatment options (in combination with trametinib)					
TAFINLAR	dabrafenib	SUPPL-8	04/30/18	BRAF	yes	adjuvant treatment of melanoma with BRAF V600E or V600K mutations as detected by an FDA-approved test (in combination with trametinib)	melanoma	yes		Treatment of melanoma (12y - 17y); P/0410/2020	
TAFINLAR	dabrafenib	SUPPL-6	06/22/17	BRAF	yes	metastatic non-small cell lung cancer (NSCLC) with BRAF V600E mutation as detected by an FDA-approved test (in combination with trametinib)	non-small cell lung cancer	yes		Treatment of solid malignant tumours (excluding melanoma) (1y - 17y); P/0410/2020	
TAGRISSO	osimertinib	SUPPL-8	04/18/18	EGFR	yes	metastatic non-small cell lung cancer (NSCLC) with epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 L858R mutations as detected by an FDA-approved test	non-small cell lung cancer	yes		Treatment of solid malignant tumours (excluding melanoma) (1y - 17y); P/0410/2020	
TALZENNA	talazoparib	ORIG-1	10/16/18	PARP	yes	deleterious or suspected deleterious germline BRCA-mutated (gBRCAm), HER2 negative locally advanced or metastatic breast cancer	breast cancer	no			Class waiver
TARCEVA	erlotinib	SUPPL-25	10/18/16	EGFR	yes	non-small cell lung cancer (NSCLC) with epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 (L858R) substitution mutations as detected by an FDA-approved test, receiving first-line, maintanance, or second or greated treatment after progression following at least one prior chemotherapy regimen	non-small cell lung cancer	no			Class waiver
TASIGNA	nilotinib	SUPPL-27	03/22/18	BCR-ABL	yes	newly diagnosed Philadelphia chromosome positive chronic myeloid leukemia in chronic phase (Ph+ CML-CP) and Ph+CML-CP resistant or intolerant to tyrosine-kinase inhibitor (TKI) therapy	chronic myeloid leukemia	yes	pediatric patients 1 year of age or older	Treatment of chronic myeloid leukaemia (1y - 17y); P/0297/2015	
TAZVERIK	tazemetostat	ORIG-1	06/18/20	EZH2	yes	relapsed or refractory (R/R) follicular lymphoma (FL) positive for an EZH2 mutation as detected by an FDA-approved test and after at least two prior systemic therapies or in	follicular lymphoma	yes			

INN	Active substance	Submission	Approval Date (MM/DD/YY)	Target	Relevant target?	Indication in label	Associated condition	Orphan designation granted?	Paediatric indication in label	EU PIP (condition (age group); decision number)	EU Waiver
						patients who have no satisfactory alternative treatment options					
TAZVERIK	tazemetostat	ORIG-1	01/23/20	EZH2	yes	metastatic or locally advanced epithelioid sarcoma not eligible for complete resection	epithelioid sarcoma	yes	adults and pediatric patients aged 16 years and older		
TECARTUS	brexucabtagene autoleucel	ORIG-1	07/24/20	CD19	yes	relapsed or refractory mantle cell lymphoma (MCL)	mantle cell lymphoma	yes		Treatment of mantle cell lymphoma; P/0433/2019	waiver
TECENTRIQ	atezolizumab	SUPPL-28	07/30/20	PD-L1	yes	BRAF V600 mutation-positive unresectable or metastatic melanoma (in combination with cobimetinib + vemurafenib)	melanoma	yes		Treatment of all conditions included in the category of malignant neoplasms (except central nervous system tumours, haematopoietic and lymphoid tissue neoplasms) (0 - 17y); P/0207/2019	
TECENTRIQ	atezolizumab	SUPPL-27	05/18/20	PD-L1	yes	first-line treatment of metastatic non-small cell lung cancer (NSCLC) with high PD-L1 expression (PD-L1 stained ≥ 50% of tumor cells [TC ≥ 50%] or PD-L1 stained tumor-infiltrating immune cells [IC] covering ≥ 10% of the tumor area [IC ≥ 10%]), as determined by an FDA_approved test, with no EGFR or ALK genomic tumor aberrations	non-small cell lung cancer	no		Treatment of all conditions included in the category of malignant neoplasms (except central nervous system tumours, haematopoietic and lymphoid tissue neoplasms) (0 - 17y); P/0207/2019	
TECENTRIQ	atezolizumab	SUPPL-21	12/03/19	PD-L1	yes	first-line treatment of metastatic non-squamous non-small cell lung cancer (NSCLC) with no EGFR or ALK genomic tumor aberrations (in combination with paclitaxel + carboplatin)	non-small cell lung cancer	no		Treatment of all conditions included in the category of malignant neoplasms (except central nervous system tumours, haematopoietic and lymphoid tissue neoplasms) (0 - 17y); P/0207/2019	
TECENTRIQ	atezolizumab	SUPPL-19	03/18/19	PD-L1	yes	first-line treatment of extensive-stage small cell lung cancer (ES-SCLC) (in combination with carboplatin + etoposide)	small cell lung cancer	no		Treatment of all conditions included in the category of malignant neoplasms (except central nervous system tumours, haematopoietic	

INN	Active substance	Submission	Approval Date (MM/DD/YY)	Target	Relevant target?	Indication in label	Associated condition	Orphan designation granted?	Paediatric indication in label	EU PIP (condition (age group); decision number)	EU Waiver
										and lymphoid tissue neoplasms) (0 - 17y); P/0207/2019	
TECENTRIQ	atezolizumab	SUPPL-18	03/08/19	PD-L1	yes	unresectable locally advanced or metastatic triple-negative breast cancer which is PD-L1 positive as determined by an FDA-approved test (in combination with paclitaxel)	breast cancer	no		Treatment of all conditions included in the category of malignant neoplasms (except central nervous system tumours, haematopoietic and lymphoid tissue neoplasms) (0 - 17y); P/0207/2019	
TECENTRIQ	atezolizumab	SUPPL-9	12/06/18	PD-L1	yes	metastatic non-squamous, non-small cell lung cancer (NSq NSCLC) with no EGFR or ALK genomic tumor aberrations (in combination with bevacizumab + paclitaxel + carboplatin)	non-small cell lung cancer	no		Treatment of all conditions included in the category of malignant neoplasms (except central nervous system tumours, haematopoietic and lymphoid tissue neoplasms) (0 - 17y); P/0207/2019	
TECENTRIQ	atezolizumab	ORIG-1	10/18/16	PD-L1	yes	metastatic non-small cell lung cancer (NSCLC) after disease progression during or following platinum-containing chemotherapy	non-small cell lung cancer	no		Treatment of all conditions included in the category of malignant neoplasms (except central nervous system tumours, haematopoietic and lymphoid tissue neoplasms) (0 - 17y); P/0207/2019	
TECENTRIQ	atezolizumab	ORIG-1	05/18/16	PD-L1	yes	locally advanced or metastatic urothelial carcinoma after disease progression during or following platinum-containing chemotherapy or disease progression within 12 months of neoadjuvant or adjuvant treatment with platinum-containung chemotherapy	urothelial carcinoma	no		Treatment of all conditions included in the category of malignant neoplasms (except central nervous system tumours, haematopoietic and lymphoid tissue neoplasms) (0 - 17y); P/0207/2019	
TECENTRIQ	atezolizumab	SUPPL-25	05/29/20	PD-L1	yes	unresectable or metastatic hepatocellular carcinoma (HCC) without prior systemic therapy (in combination with bevacizumab)	hepatocellular carcinoma	yes		Treatment of all conditions included in the category of malignant neoplasms (except central nervous system tumours, haematopoietic and lymphoid tissue neoplasms) (0 - 17y); P/0207/2019	

INN	Active substance	Submission	Approval Date (MM/DD/YY)	Target	Relevant target?	Indication in label	Associated condition	Orphan designation granted?	Paediatric indication in label	EU PIP (condition (age group); decision number)	EU Waiver
TIBSOVO	ivosidenib	SUPPL-1	05/02/19	IDH1	yes	newly diagnosed acute myeloid leukemia (AML) with a susceptible IDH1 mutation as detected by an FDA-approved test	acute myeloid leukemia	yes		Treatment of acute myeloid leukaemia (2y - 17y); P/0280/2018	
TIBSOVO	ivosidenib	ORIG-1	07/20/18	IDH1	yes	relapsed or refractory acute myeloid leukemia (AML) with a susceptible IDH1 mutation as detected by an FDA-approved test	acute myeloid leukemia	yes		Treatment of acute myeloid leukaemia (2y - 17y); P/0280/2018	
TRODELVY	sacituzumab govitecan-hziy	ORIG-1	04/22/20	Trop-2	no	metastatic triple-negative breast cancer after at least two prior therapies for metastatic disease	breast cancer	no		Treatment of breast cancer; P/0018/2020	waiver
TUKYSA	tucatinib	ORIG-1	04/17/20	HER2	yes	advanced unresectable or metastatic HER2-positive breast cancer after one or more prior anti-HER2-based regimens in the metastatic setting (in combination with trastuzumab + capecitabine)	breast cancer	no		Treatment of breast malignant neoplasms; P/0036/2018	waiver
TURALIO	pexidartinib	ORIG-1	08/02/19	CSF-1R	yes	symptomatic tenosynovial giant cell tumor (TGCT) associated with severe morbidity or functional limitations and not amenable to improvement with surgery	tenosynovial giant cell tumor	yes		Treatment of benign soft tissue neoplasms; P/0044/2019	waiver
VENCLEXTA	venetoclax	SUPPL-13	05/15/19	Bcl-2	yes	chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL)	chronic lymphocytic leukemia	yes		Treatment of malignant neoplasms of the haematopoietic and lymphoid tissue (0 - 17y); P/0375/2020	
							small lymphocytic lymphoma	no		Treatment of malignant neoplasms of the haematopoietic and lymphoid tissue (0 - 17y); P/0375/2020	
VENCLEXTA	venetoclax	SUPPL-9	11/21/18	Bcl-2	yes	newly diagnosed acute myeloid leukemia (AML) (in combination with azacitidine or decitabine or low-dose cytarabine)	acute myeloid leukemia	yes		Treatment of malignant neoplasms of the haematopoietic and lymphoid tissue (0 - 17y); P/0375/2020	
VENCLEXTA	venetoclax	SUPPL-5	06/08/18	Bcl-2	yes	chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL) with or without 17p deletion after at least one prior therapy	chronic lymphocytic leukemia	yes		Treatment of malignant neoplasms of the haematopoietic and lymphoid tissue (0 - 17y); P/0375/2020	
							small lymphocytic lymphoma	no		Treatment of malignant neoplasms of the haematopoietic and lymphoid tissue (0 - 17y); P/0375/2020	

INN	Active substance	Submission	Approval Date (MM/DD/YY)	Target	Relevant target?	Indication in label	Associated condition	Orphan designation granted?	Paediatric indication in label	EU PIP (condition (age group); decision number)	EU Waiver
VENCLEXTA	venetoclax	ORIG-1	04/11/16	Bcl-2	yes	chronic lymphocytic leukemia (CLL) with 17p deletion, as detected by an FDA-approved test, after at least one prior therapy	chronic lymphocytic leukemia	yes		Treatment of malignant neoplasms of the haematopoietic and lymphoid tissue (0 - 17y); P/0375/2020	
VERZENIO	abemaciclib	ORIG-1	09/28/17	CDK4/6	yes	HR-positive, HER2-negative advanced or metastatic breast cancer with disease progression following endocrine therapy (in combination with fulvestrant)	breast cancer	no		Treatment of breast cancer; P/0202/2019	waiver
VERZENIO	abemaciclib	ORIG-1	09/28/17	CDK4/6	yes	HR-positive, HER2-negative advanced or metastatic breast cancer with disease progression following endocrine therapy and prior chemotherapy in the metastatic setting	breast cancer	no		Treatment of breast cancer; P/0202/2019	waiver
VITRAKVI	larotrectinib	ORIG-1	11/26/18	TRK A/B/C	yes	solid tumors that have a neurotrophic receptor tyrosine kinase (NTRK) gene fusion without a known acquired resistance mutation, that are either metastatic or where surgical resection is likely to result in severe morbidity and have no satisfactory alternative treatments or that have progressed following treatment	solid tumors	yes	adult and pediatric patients	Treatment of all conditions included in the category of malignant neoplasms (except central nervous system tumours, haematopoietic and lymphoid tissue neoplasms) (0 - 17y); P/0076/2021	
VIZIMPRO	dacomitinib	ORIG-1	09/27/18	EGFR	yes	metastatic non-small cell lung cancer (NSCLC) with epidermal growth factor receptor (EGFR) exon 19 deletion or exon 21 L858R substitution mutations as detected by an FDA-approved test	non-small cell lung cancer	yes			Class waiver
VYXEOS	liposome-encapsulated combination of daunorubicin and cytarabine	ORIG-1	08/03/17	Topoisomerase II; DNA polymerase	yes	newly diagnosed therapy-related AML (t-AML) or AML with myelodysplasia-related changes (AML-MRC)	acute myeloid leukemia	yes		Treatment of acute myeloid leukaemia (1m - 17y); P/0292/2019	
XALKORI	crizotinib	SUPPL-16	03/11/16	ALK; ROS1	yes	metastatic ROS1-positive non-small cell lung cancer (NSCLC)	non-small cell lung cancer	yes		Treatment of lung malignant neoplasms; P/0361/2018	waiver
XOSPATA	gilteritinib	ORIG-1	11/28/18	FLT3	yes	relapsed or refractory acute myeloid leukemia (AML) with a FLT3 mutation as detected by an FDA-approved test	acute myeloid leukemia	yes		Treatment of acute myeloid leukaemia (6m - 17y); P/0110/2021	

INN	Active substance	Submission	Approval Date (MM/DD/YY)	Target	Relevant target?	Indication in label	Associated condition	Orphan designation granted?	Paediatric indication in label	EU PIP (condition (age group); decision number)	EU Waiver
XPOVIO	selinexor	SUPPL-1	06/22/20	XPO1	yes	relapsed or refractory diffuse large B-cell lymphoma (DLBCL), not otherwise specified, including DLBCL arising from follicular lymphoma, after at least two lines of systemic therapy	diffuse large B-cell lymphoma	yes			
XPOVIO	selinexor	ORIG-1	07/03/19	XPO1	yes	relapsed or refractory multiple myeloma (RRMM) after at least four prior therapies and which is refractory to at least two proteasome inhibitors, at least two immunomodulatory agents, and an anti-CD38 monoclonal antibody (in combination with dexamethasone)	multiple myeloma	yes		Treatment of Multiple Myeloma; P/0384/2018	waiver
XTANDI	enzalutamide	SUPPL-15	12/16/19	Androgen receptor	no	metastatic castration-sensitive prostate cancer (mCSPC)	prostate cancer	no			Class waiver
XTANDI	enzalutamide	SUPPL-14	07/13/18	Androgen receptor	no	castration-resistant prostate cancer (CRPC)	prostate cancer	no			Class waiver
YERVOY	ipilimumab	SUPPL-96	07/10/18	CTLA4	yes	microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) metastatic colorectal cancer (mCRC) that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan (in combination with nivolumab)	colorectal cancer	no	adult and pediatric patients 12 years of age and older	Treatment of all conditions included in the category of malignant neoplasms (except melanoma, nervous system, haematopoietic and lymphoid tissue) (2y - 17y); P/0085/2015	
YESCARTA	axicabtagene ciloleucel	ORIG-1	10/18/17	CD19	yes	relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy, including diffuse large B-cell lymphoma (DLBCL) not otherwise specified, primary mediastinal large B-cell lymphoma, high-grade B-cell lymphoma, and DLBCL arising from follicular lymphoma	large B-cell lymphoma	yes		Treatment of mature B-cell neoplasms (patients weighing at least 6 kg); P/0132/2020	
ZEJULA	niraparib	SUPPL-17	04/29/20	PARP-1/2	yes	maintenance treatment of advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer which is in a complete or partial response to first-line platinum-based chemotherapy	ovarian cancer	yes		Treatment of all conditions included in the category of malignant neoplasms (except haematopoietic and lymphoid tissue neoplasms) (0 - 17y); P/0313/2019	

INN	Active substance	Submission	Approval Date (MM/DD/YY)	Target	Relevant target?	Indication in label	Associated condition	Orphan designation granted?	Paediatric indication in label	EU PIP (condition (age group); decision number)	EU Waiver
							fallopian tube cancer	no		Treatment of all conditions included in the category of malignant neoplasms (except haematopoietic and lymphoid tissue neoplasms) (0 - 17y); P/0313/2019	
							primary peritoneal cancer	no		Treatment of all conditions included in the category of malignant neoplasms (except haematopoietic and lymphoid tissue neoplasms) (0 - 17y); P/0313/2019	
ZEJULA	niraparib	SUPPL-14	04/29/20	PARP-1/2	yes	advanced ovarian, fallopian tube, or primary peritoneal cancer after three of more prior chemotherapy regimens and which is associated with homologous recombination deficiency (HRD) positive status defined by either a deleterious or suspected deleterious BRCA mutation, or genomic instability and progression more than six months after response to the last platinum-based chemotherapy	ovarian cancer	yes		Treatment of all conditions included in the category of malignant neoplasms (except haematopoietic and lymphoid tissue neoplasms) (0 - 17y); P/0313/2019	
							fallopian tube cancer	no		Treatment of all conditions included in the category of malignant neoplasms (except haematopoietic and lymphoid tissue neoplasms) (0 - 17y); P/0313/2019	
							primary peritoneal cancer	no		Treatment of all conditions included in the category of malignant neoplasms (except haematopoietic and lymphoid tissue neoplasms) (0 - 17y); P/0313/2019	
ZEJULA	niraparib	ORIG-1	04/29/20	PARP-1/2	yes	maintenance treatment of recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer which is in a complete or partial response to platinum-based chemotherapy	ovarian cancer	yes		Treatment of all conditions included in the category of malignant neoplasms (except haematopoietic and lymphoid tissue neoplasms) (0 - 17y); P/0313/2019	
							fallopian tube cancer	no		Treatment of all conditions included in the category of malignant neoplasms (except haematopoietic	

INN	Active substance	Submission	Approval Date (MM/DD/YY)	Target	Relevant target?	Indication in label	Associated condition	Orphan designation granted?	Paediatric indication in label	EU PIP (condition (age group); decision number)	EU Waiver
										and lymphoid tissue neoplasms) (0 - 17y); P/0313/2019	
							primary peritoneal cancer	no		Treatment of all conditions included in the category of malignant neoplasms (except haematopoietic and lymphoid tissue neoplasms) (0 - 17y); P/0313/2019	
ZELBORAF	vemurafenib	SUPPL-16	11/06/17	BRAF	yes	Erdheim-Chester Disease (ECD) with BRAF V600 mutation	Erdheim-Chester Disease	yes			
ZEPZELCA	lurbinectedin	ORIG-1	06/15/20	DNA	yes	metastatic small cell lung cancer (SCLC) with disease progression on or after platinum-based chemotherapy	small cell lung cancer	yes		Treatment of small cell lung cancer; P/0446/2020	waiver
ZYKADIA	ceritinib	SUPPL-9	05/26/17	ALK	yes	metastatic non-small cell lung cancer (NSCLC) which is anaplastic lymphoma kinase (ALK)-positive, as detected by an FDA-approved test	non-small cell lung cancer	yes			Class waiver
ZYTIGA	abiraterone acetate	SUPPL-24	02/07/18	CYP17A1	no	metastatic high-risk castration-sensitive prostate cancer (CSPC) (in combination with prednisone)	prostate cancer	no		Treatment of prostate malignant neoplasms; P/0244/2020	waiver

Grey text means: not scored/counted towards number of unique conditions; Coloured background means: excluded because the product is not directed at a relevant target

Annex 2: Number of PDCO opinions on PIPs from 2008 until 2020

Year	Number of total PIP opinions			Positive opinions			Negative opinion			New application		
	Total	Oncology	% Oncology	Total	Oncology	% Oncology	Total	Oncology	% Oncology	Total	Oncology	% Oncology
2008	128	14	10,94	0	0		128	14	10,94	124	14	11,29
2009	249	21	8,43	4	0	0,00	245	21	8,57	196	18	9,18
2010	367	24	6,54	5	1	20,00	362	23	6,35	253	17	6,72
2011	310	37	11,94	5	1	20,00	305	36	11,80	152	19	12,50
2012	303	40	13,20	4	1	25,00	299	39	13,04	134	20	14,93
2013	340	32	9,41	7	0	0,00	333	32	9,61	149	13	8,72
2014	345	35	10,14	6	1	16,67	339	34	10,03	144	15	10,42
2015	331	35	10,57	6	0	0,00	325	35	10,77	125	15	12,00
2016	378	38	10,05	7	1	14,29	371	37	9,97	143	11	7,69
2017	402	64	15,92	12	0	0,00	390	64	16,41	169	32	18,93
2018	422	79	18,72	11	1	9,09	411	78	18,98	187	50	26,74
2019	410	102	24,88	16	2	12,50	394	100	25,38	182	61	33,52
2020	519	102	19,65	6	1	16,67	513	101	19,69	263	68	25,86

Year	New application - study			New application - waiver			PIP modification		
	Total	Oncology	% Oncology	Total	Oncology	% Oncology	Total	Oncology	% Oncology
2008	85	8	9,41	39	6	15,38	4	0	0,00
2009	131	12	9,16	65	6	9,23	49	3	6,12
2010	202	10	4,95	51	7	13,73	109	6	5,50
2011	107	14	13,08	45	5	11,11	153	17	11,11
2012	87	12	13,79	47	8	17,02	165	19	11,52
2013	96	9	9,38	53	4	7,55	184	19	10,33
2014	91	9	9,89	53	6	11,32	195	19	9,74
2015	71	8	11,27	54	7	12,96	200	20	10,00
2016	90	9	10,00	53	2	3,77	228	26	11,40
2017	86	17	19,77	83	15	18,07	221	32	14,48
2018	86	15	17,44	101	35	34,65	224	28	12,50
2019	65	18	27,69	117	43	36,75	212	39	18,40
2020	141	24	17,02	122	44	36,07	250	33	13,20

Annex 3: FDA approved oncology products (original submissions) between August 2020 and December 2021

INN	Active substance	Submission	Approval Date (MM/DD/YY)	Submission date (MM/DD/YY)	Falling under RACE for Children Act	Target	Relevant target	Pediatric	Indication in label
BLENREP	belantamab mafodotin-blmf	ORIG-1	08/05/20	12/05/09	no	BCMA	no	Orphan exemption	Treatment of adult patients with relapsed or refractory multiple myeloma who have received at least 4 prior therapies including an anti-CD38 monoclonal antibody, a proteasome inhibitor, and an immunomodulatory agent.
GAVRETO	pralsetinib	ORIG-1	09/04/20		no	RET	yes	Orphan exemption	Treatment of adult patients with metastatic rearranged during transfection (RET) fusion-positive non-small cell lung cancer (NSCLC) as detected by an FDA approved test.
DANYELZA	naxitamab-gqgk	ORIG-1	11/25/20	03/31/20	no	GD2	yes	Orphan exemption	Treatment of pediatric patients 1 year of age and older and adult patients with relapsed or refractory high-risk neuroblastoma in the bone or bone marrow who have demonstrated a partial response, minor response, or stable disease to prior therapy.
MARGENZA	margetuximab	ORIG-1	12/16/20	12/18/19	no	HER2	yes	Waiver (highly impracticable)	Treatment of adult patients with metastatic HER2-positive breast cancer who have received two or more prior anti-HER2 regiments, at least one of which was for metastatic disease.
ORGOVYX	relugolix	ORIG-1	12/18/20	04/20/20	no	GNRHR	no	Waiver (does not occur)	Treatment of adult patients with advanced prostate cancer.

INN	Active substance	Submission	Approval Date (MM/DD/YY)	Submission date (MM/DD/YY)	Falling under RACE for Children Act	Target	Relevant target	Pediatric	Indication in label
TEPMETKO	tepotinib	ORIG-1	02/03/21	06/29/20	no	MET	yes	Orphan exemption	Treatment of adult patients with metastatic non-small cell lung cancer (NSCLC) harboring mesenchymalepithelial transition (MET) exon 14 skipping alterations.
UKONIQ	umbralisib	ORIG-1	02/05/21	06/15/20	no	PI3Kδ, casein kinase CK1ε	yes	Orphan exemption	Treatment of adult patients with relapsed or refractory marginal zone lymphoma (MZL) who have received at least one prior anti-CD20-based regimen, or relapsed or refractory follicular lymphoma (FL) who have received at least three prior lines of systemic therapy.
BREYANZI	lisocabtagene maraleucel	ORIG-1	02/05/21	12/18/19	no	CD-19	yes	Orphan exemption	Treatment of adult patients with relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy, including diffuse large B cell lymphoma (DLBCL) not otherwise specified (including DLBCL arising from indolent lymphoma), high-grade B-cell lymphoma, primary mediastinal large B-cell lymphoma, and follicular lymphoma grade 3B. Lisocabtagene maraleucel is not indicated for the treatment of patients with primary central nervous system (CNS) lymphoma.
PEPAXTO	melphalan flufenamide	ORIG-1	02/26/21	06/30/20	no	DNA	yes	Orphan exemption	Treatment of adult patients with relapsed or refractory multiple myeloma who have received at least four prior lines of therapy and whose disease is refractory to at least one proteasome inhibitor, one immunomodulatory agent, and one CD38-directed monoclonal antibody.

INN	Active substance	Submission	Approval Date (MM/DD/YY)	Submission date (MM/DD/YY)	Falling under RACE for Children Act	Target	Relevant target	Pediatric	Indication in label
FOTIVDA	tivozanib	ORIG-1	03/10/21	03/31/20	no	VEGFR-1/2/3, c-kit, PDGFRβ	yes	Waiver (highly impracticable)	Treatment of adult patients with relapsed or refractory advanced renal cell carcinoma (RCC) following two or more prior systemic therapies.
ABECMA	idecabtagene vicleucel	ORIG-1	03/26/21	07/27/20	no	BCMA	no	Orphan exemption	Treatment of adult patients with relapsed or refractory multiple myeloma after four or more prior lines of therapy including an immunomodulatory agent, a proteasome inhibitor, and an anti-CD38 monoclonal antibody.
JEMPERLI	dostarlimab-gxly	ORIG-1	04/22/21	12/19/19	no	PD-1	yes	Waiver (highly impracticable)	Treatment of adult patients with mismatch repair deficient (dMMR) recurrent or advanced endometrial cancer, as determined by an FDA-approved test, that has progressed on or following prior treatment with a platinum-containing regimen.
ZYLONTA	loncastuximab tesirine-lpyl	ORIG-1	04/23/21	09/21/20	yes	CD-19, DNA	yes	Study	Treatment of adult patients with relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy, including diffuse large B-cell lymphoma (DLBCL) not otherwise specified, DLBCL arising from low grade lymphoma, and high-grade B-cell lymphoma.
RYBREVANT	amivantamab-vmjw	ORIG-1	05/21/21	11/24/20	yes	EGFR, MET receptor	yes	Waiver (highly impracticable)	Treatment of adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with epidermal growth factor receptor (EGFR) exon 20 insertion mutations, as detected by an FDA-approved test, whose disease has progressed on or after platinum-based chemotherapy.

INN	Active substance	Submission	Approval Date (MM/DD/YY)	Submission date (MM/DD/YY)	Falling under RACE for Children Act	Target	Relevant target	Pediatric	Indication in label
LUMAKRAS	sotorasib	ORIG-1	05/28/21	12/16/20	yes	KRAS	yes	Waiver (highly impracticable)	Treatment of adult patients with KRAS G12C-mutated locally advanced or metastatic non-small cell lung cancer (NSCLC), as determined by an FDA-approved test, who have received at least one prior systemic therapy.
TRUSELTIQ	infigratinib	ORIG-1	05/28/21	09/29/20	yes	FGFR	yes	Study	Treatment of adults with previously treated, unresectable locally advanced or metastatic cholangiocarcinoma with a fibroblast growth factor receptor 2 (FGFR2) fusion or other rearrangement as detected by an FDA-approved test.
RYLAZE	asparaginase erwinia chrysanthemi (recombinant)-rywn	ORIG-1	06/30/21	04/30/21	yes	L-asparagine	yes	Study	Treatment of acute lymphoblastic leukemia (ALL) and lymphoblastic lymphoma (LBL) in adult and pediatric patients 1 month or older who have developed hypersensitivity to E. coli-derived asparaginase.
WELIREG	belzutifan	ORIG-1	08/13/21	01/15/21	yes	HIF-2a	no	Waiver (highly impracticable)	Treatment of adult patients with von Hippel-Lindau (VHL) disease who require therapy for associated renal cell carcinoma (RCC), central nervous system (CNS) hemangioblastomas, or pancreatic neuroendocrine tumors (pNET), not requiring immediate surgery.
EXKIVITY	mobocertinib	ORIG-1	09/15/21	02/26/21	yes	EGFR	yes	Waiver (highly impracticable)	Treatment of adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with epidermal growth factor receptor (EGFR) exon 20 insertion mutations, as detected by an FDA-approved test, whose

INN	Active substance	Submission	Approval Date (MM/DD/YY)	Submission date (MM/DD/YY)	Falling under RACE for Children Act	Target	Relevant target	Pediatric	Indication in label
									disease has progressed on or after platinum-based chemotherapy.
TIVDAK	tisotumab vedotin-tftv	ORIG-1	09/20/21	02/10/21	yes	tissue factor (TF), microtubules	yes	Study	Treatment of adult patients with recurrent or metastatic cervical cancer with disease progression on or after chemotherapy.
SCEMBLIX	asciminib	ORIG-1	10/29/21	06/24/21	yes	ABL/BCR-ABL1	yes	Study	Treatment of adult patients with Philadelphia chromosome-positive chronic myeloid leukemia (Ph+ CML) in chronic phase (CP), previously treated with two or more tyrosine kinase inhibitors (TKIs), or Ph+ CML in CP with the T315I mutation.

Coloured background means this submission fell under the provisions of the RACE for Children Act AND the product is directed at a relevant molecular target.

Eidesstattliche Erklärung

Hiermit erkläre ich an Eides statt, die Arbeit selbstständig verfasst und keine anderen als die angegebenen Hilfsmittel verwendet zu haben.

München,

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Dr. Maria Huthmacher