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Orphan Drug Regulation: A missed opportunity for children and adolescents with cancer

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Abstract ***Background:*** Oncology represents a major sector in the field of orphan drug development in Europe. The objective was to evaluate whether children and adolescents with cancer benefited from the Orphan Drug Regulation.

Methods: Data on orphan drug designations (ODDs) and registered orphan drugs from 8th August 2000 to 10th September 2016 were collected from the Community Register of medicinal products for human use. Assessment history, product information and existence of paediatric investigation plans were searched and retrieved from the European Medicine Agency website.

Results: Over 16 years, 272 of 657 oncology ODDs (41%) concerned a malignant condition occurring both in adults and children. The five most common were acute myeloid leukaemia, high-grade glioma, acute lymphoblastic leukaemia, graft-versus-host disease and soft-tissue sarcomas. 74% of 31 marketing authorisations (MAs) for an indication both in adults and children (26 medicines) had no information for paediatric use in their Summary of Product Characteristics (SmPC) at the time of the first MA. Furthermore, 68% still have no paediatric information in their most recently updated SmPC, at a median of 7 years after. Only 15 ODDs (2%) pertained to a malignancy occurring specifically in children and only two drugs received an MA:

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Unituxin for high-risk neuroblastoma and Votubia for sub-ependymal giant-cell astrocytoma.
Conclusion: The Orphan Drug Regulation failed to promote the development of innovative therapies for malignancies occurring in children. Major delays and waivers occurred through the application of the Paediatric Medicines Regulation. The European regulatory environment needs to be improved to accelerate innovation for children and adolescents dying of cancer.

1. Introduction

Since 2000, the European Regulation on Orphan Medicinal Products (EC) 141/2000 has been incentivising the development and marketing authorisation (MA) of new therapies for patients who suffer from serious, rare conditions for which there are currently no satisfactory treatments. A rare condition is defined as a disease with a prevalence of less than 5 of 10,000, meaning approximately less than 250,000 patients based on a European population of 506 million. This regulation was not specifically designed to increase drug development for children. However, two-thirds of rare diseases occur in the paediatric population. Similar regulatory incentives have been operational in the United States and in Japan since 1983 and 1993, respectively [1]. Since then, many new medicinal products have received an MA for rare and ultra-rare conditions, and a very active and successful economic activity has been created with new pharmaceutical companies entirely dedicated to orphan drug development. Orphan drugs are set to represent 20% of worldwide prescription sales by 2020 (excluding generics) with an 11.7% per year market growth as compared with 5.9% for non-orphan medicines [2].

Cancer represents a large part of this activity, and in 2011, oncology products account for 41% of the orphan drug designations (ODDs) granted by the Committee of Orphan Medicinal Products at the European Medicines Agency (EMA) [3]. In 2014, six of the top 10 selling orphan drugs in the United States (US) were oncology products. In 2020, orphan drugs are set out to account for 20.2% of global prescription sales (excluding generics) and 15 of the top 20 selling orphan drugs in the world will be oncology products [2].

Cancer is a rare condition in children and adolescents (<18 years old), accounting for 2% of all cancers. Each of the more than 60 different paediatric malignancies is thus a rare or even ultra-rare disease. Despite significant progress made over the last 50 years [4], cancer remains the leading cause of death by disease over the age of 1 year, and more than 6000 young people and children die each year of cancer in Europe [5]. The outcome for some childhood malignancies, e.g. diffuse intrinsic pontine glioma (DIPG), high-grade glioma and high-risk neuroblastoma, remains tragic with no or little improvement for over the last 30 years. Cancer remains a serious, life-threatening, rare condition and innovative therapies are urgently needed.

Considering the large success of the Orphan Drug Regulation in oncology as evidenced by an increased number of medicines available for rare conditions, the goal of the study was to evaluate whether it addressed the needs of children and adolescents with cancer over the last 16 years. This was assessed by the number of oncology products relevant to paediatric malignancies, given an ODD and eventually authorised, and which had information for paediatric use in their Summary of Product Characteristics (SmPC).

2. Method

Data on ODDs and registered orphan drugs were collected from the Community Register of medicinal products for human use. They are made publicly available in accordance with Article 13 of Regulation (EC) No 726/2004 [6]. There are two lists: one for active orphan medicinal products, namely orphan designations and marketed orphan drugs under exclusivity; and the other for non-active orphan medicinal products, including withdrawn orphan designations and marketed drugs that are no longer under exclusivity. Assessment history and product information were retrieved for each drug from the European Public Assessment Reports on the EMA website. The existence of a paediatric investigation plan (PIP) was searched for each drug in the 'Opinion and decisions on paediatric investigation plans' page of the EMA website [7]. Availability of paediatric information for each drug was checked in its SmPC at the time of the first MA and in the most recently updated SmPC. Searches on all websites were performed on 10th September 2016.

3. Results

3.1. Oncology ODDs

From 8th August 2000 to 10th September 2016, 1731 ODDs have been granted, of which 1363 (79%) were active at study date. Of 1731 ODDs, 657 (38%) concerned a malignant condition and 1074 (62%) a non-

malignant condition. The three most frequent non-malignant conditions with ODDs were cystic fibrosis (n = 56), Duchenne muscular dystrophy (n = 28) and amyotrophic lateral sclerosis (n = 23).

Among the 657 oncology ODDs, there were 290 (44%) for haematological malignancies, 257 (39%) for malignant solid tumours, 65 (10%) for brain and neurological tumours and 45 (7%) for supportive care and treatments used in haematopoietic stem cell transplantation (Table 1). The five most common conditions were non-Hodgkin lymphomas, acute myeloid leukaemia, high-grade glioma, pancreatic and ovarian cancers and accounted for 43% of oncology ODDs. A total of 370 oncology ODDs (56%) concerned conditions occurring only in adults.

Fifteen ODDs (2%) concerned a malignancy occurring almost exclusively in children: neuroblastoma [10], sub-ependymal giant-cell astrocytoma (SEGA) [2], medulloblastoma, hepatoblastoma and juvenile myelomonocytic leukaemia (Table 2). There was no ODD in other rare malignancies occurring in children, such as DIPG, a brain tumour occurring specifically in children with a median survival of 9 months under

Table 1
European orphan drug designations for malignant conditions as of 10th September 2016 (percentages expressed % of total).

Malignancies	N	%	Condition	N	%	Disease occurring in		
						Adults only	Children	Adults & children
Haematological malignancies and lymphomas	290	44%	Acute lymphoblastic leukaemia	24	3.7%			24
			Acute myeloid leukaemia	64	9.7%			64
			Chronic lymphocytic leukaemia	29	4.4%	29		
			Chronic myeloid leukaemia	10	1.5%			10
			Other leukaemias	5	0.8%		1	4
			Myelodysplastic syndromes	11	1.7%	11		
			Myeloproliferative syndromes	28	4.3%	28		
			Myeloma	35	5.3%	35		
			Hodgkin lymphoma	11	1.7%			11
			Non-Hodgkin lymphomas	73	11.1%	53		20
Malignant solid tumours	257	39%	Adrenal cancer	4	0.6%			4
			Biliary tract cancer	6	0.9%	6		
			Bone sarcoma	7	1.1%			7
			Melanoma	1	0.2%			1
			Gastric and oesophageal cancer	12	1.8%	12		
			Other gastrointestinal tract cancers	4	0.6%	4		
			Gastrointestinal stromal tumour	6	0.9%			6
			Genito-urinary cancers	1	0.2%	1		
			Ovarian cancer	39	5.9%	39		
			Other gynaecological cancers	2	0.3%	2		
			Head & neck cancers	4	0.6%	4		
			Hepatoblastoma	1	0.2%		1	
			Hepatocarcinoma	29	4.4%	29		
			Kidney cancer	23	3.5%	23		
			Mesothelioma	14	2.1%	14		
			Neuro-endocrine tumours	13	2.0%	13		
			Neuroblastoma	10	1.5%		10	
			Non–small cell lung cancer	6	0.9%	6		
			Pancreatic cancer	44	6.7%	44		
			Soft-tissue sarcoma	21	3.2%			21
			Thymoma	2	0.3%	2		
			Thyroid cancer	8	1.2%	8		
Brain and neurological tumours	65	10%	High-grade glioma	60	9.1%			60
			Medulloblastoma	1	0.2%		1	
			Sub-ependymal giant-cell astrocytoma	2	0.3%		2	
			Other neurological malignancies	2	0.3%	2		
Haematopoietic transplantation for malignancies and supportive care	45	7%	Haematopoietic stem cell transplantation	12	1.8%			12
			Graft-versus-host disease	23	3.5%			23
			Intoxication	3	0.5%	1		2
			Mucositis	4	0.6%	4		
			Other supportive care	3	0.5%			3
			Total	657		370	15	272
						56.3%	2.3%	41.4%

Table 2
European orphan drug designations for malignant conditions occurring specifically in children as of 10th September 2016.

Designated orphan indication	Product	Sponsor	EU designation	Designation date	Status	Tradename	EU centralised marketing authorisation No.	Implemented on
Treatment of hepatoblastoma	Doxorubicin	Double Bond Pharmaceutical AB	EU/3/15/1513	28/07/2015	Active			
Treatment of medulloblastoma	16-Base single-stranded peptide nucleic acid oligonucleotide linked to 7-amino acid peptide	Biogenera SpA	EU/3/10/789	01/10/2010	Active			
Treatment of neuroblastoma	Iodine (131I) iobenguane	Molecular Insight Limited	EU/3/07/525	31/01/2008	Active			
	Murine monoclonal antibody to GD2	United Therapeutics Europe Ltd	EU/3/09/644	12/06/2009	Withdrawn			
	16-base single-stranded PNA oligonucleotide linked to a 7-amino acid peptide	Biogenera SpA	EU/3/09/692	25/11/2009	Active			
	Chimeric monoclonal antibody against GD2	United Therapeutics Europe Ltd	EU/3/11/879	21/06/2011	Active	Unituxin	EU/1/15/1022	18/08/2015
	Eflornithine	Cancer Prevention Pharma Limited	EU/3/11/902	27/09/2011	Active			
	16-base single-stranded peptide nucleic acid oligonucleotide linked to 7-amino acid peptide	Biogenera SpA	EU/3/12/1016	04/07/2012	Active			
	Chimeric monoclonal antibody against GD2	APEIRON Biologics AG	EU/3/12/1062	08/11/2012	Active			
	Chimeric monoclonal antibody to O-acetyl-GD2 antigen	OGD2 Pharma	EU/3/14/1416	15/01/2015	Active			
	Sodium 2-hydroxylinoleate	Ability Pharmaceuticals SL	EU/3/15/1485	24/04/2015	Active			
	N-[5-(3,5-difluorobenzyl)-1H-indazol-3- yl]-4-(4 methylpiperazin-1-yl)-2-(tetrahydro-2H-pyran-4-ylamino) benzamide	Pharma Gateway AB	EU/3/15/1580	11/11/2015	Active			
Treatment of juvenile myelomonocytic leukaemia	GM-CSF receptor antagonist	British Biotech Pharmaceuticals Ltd	EU/3/02/089	18/03/2002	Withdrawn			
Treatment of sub-ependymal giant-cell astrocytoma (SEGA)	Everolimus	Novartis Europharm Limited	EU/3/10/764	04/08/2010	Active	Votubia	EU/1/11/710	06/09/2011
	Sirolimus	Desitin Arzneimittel GmbH	EU/3/15/1557	09/10/2015	Active			

current treatment, the worst prognosis among paediatric malignancies.

A total of 272 oncology ODDs (41%) concerned a malignant condition occurring in both children and adults, and the top five conditions were acute myeloid leukaemia, high-grade glioma, acute lymphoblastic leukaemia, graft-versus-host disease and soft-tissue sarcomas (Table 1).

3.2. Marketing authorisations for orphan oncology medicinal products

As of 10th September 2016, the register listed 155 centralised MAs for an orphan medicine, of which 116 (75%) were still under exclusivity. Sixty-five MAs (42%) were granted to 46 orphan oncology medicinal products (Fig. 1).

Over 16 years, only two medicines have been authorised for the treatment of a malignancy occurring specifically and almost exclusively in children: Unituxin (dinutuximab) (authorised in 2015), a first-in-class anti-GD2 monoclonal antibody for the treatment of high-risk neuroblastoma and Votubia (everolimus) (authorised in 2011) for the treatment of SEGA, a first paediatric indication for a mammalian target of rapamycin inhibitor. Indeed, everolimus was first authorised in 2009 (Afinitor) as an orphan drug for the treatment of renal-cell carcinoma in adults and then developed in a different malignancy in children. Both drugs were developed through PIP as an obligation under the Paediatric Medicines Regulation (PMR).

A total of 26 oncology medicinal products were granted 31 MAs for the treatment of an orphan indication occurring both in adults and children (Fig. 1): 74% concerned a haematological malignancy or haematopoietic stem cell transplantation and 19% concerned a malignant solid tumour. Twenty-three MAs (74%) did not have any recommendation for use in the paediatric population in their SmPC at the time of the first authorisation (Table 3). Glivec (imatinib) was authorised for the treatment of chronic myeloid leukaemia in paediatric patients, 13 months after its first approval for the treatment of the same disease in adults. Glivec (imatinib) was then authorised for the treatment of Philadelphia (Ph+) acute lymphoblastic leukaemia in paediatric patients after completion of a PIP in May 2013, i.e. 6.7 years after its MA variation for the treatment of adult Ph+ acute lymphoblastic leukaemia.

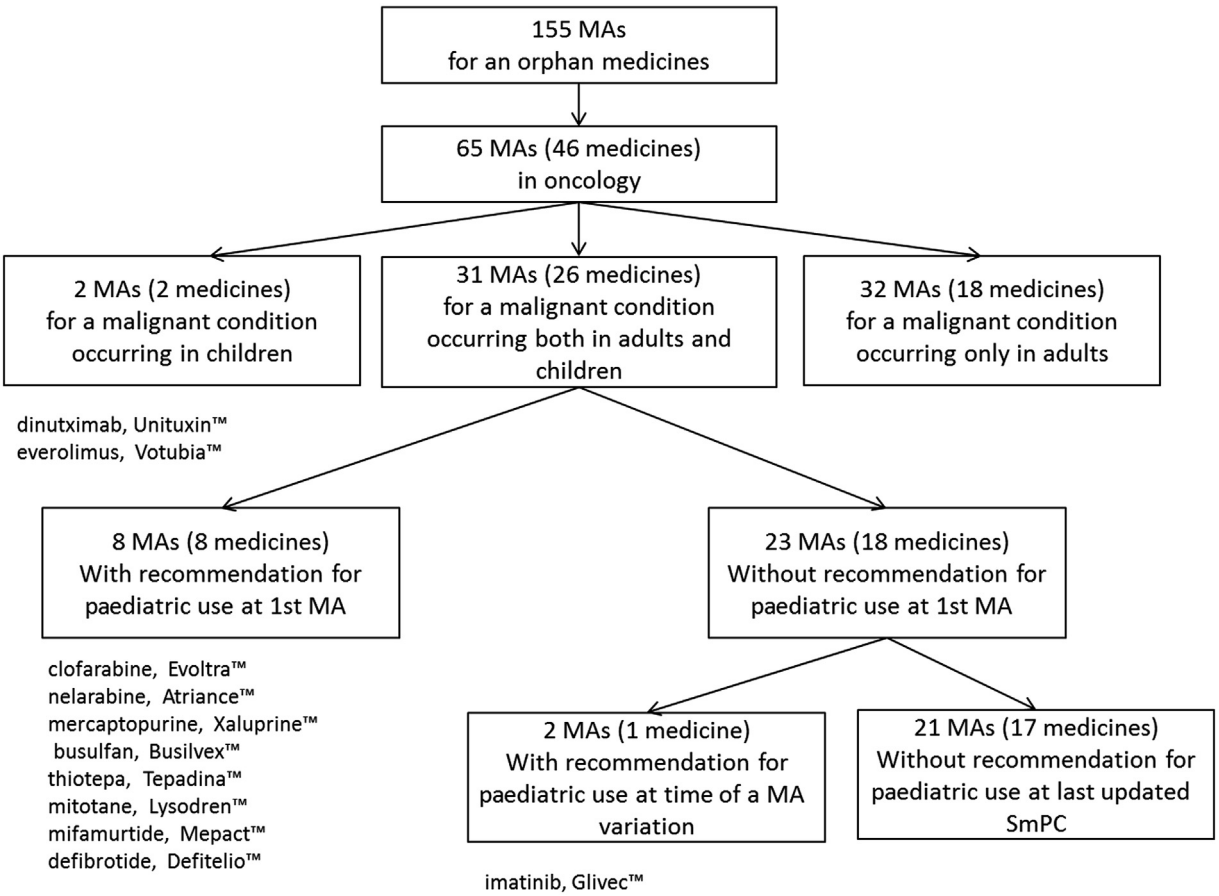

Fig. 1. Marketing authorisations for an oncology medicinal product as of 10th September 2016. MA, marketing authorisation; SmPC, Summary of Product Characteristics.

Table 3
European orphan drugs marketing authorisations for malignant conditions occurring both in children and adults as of 10th September 2016.

Paediatric Regulation requirements	Product	Tradename	Sponsor	Designated orphan indication	EU Designation	Designation date	EU Centralised marketing authorisation Nr	Implemented on	Paediatric information in SmPC at first authorisation	PIP date	Paediatric information in most recently updated SmPC
Not applicable	Arsenic trioxide	Trisenox	Cephalon Europe	Treatment of acute promyelocytic leukaemia	EU/3/00/008	18/10/2000	EU/1/02/204	07/03/2002	No		No
	Busulfan (intravenous use)	Busilvex	Pierre Fabre Médicament	Conditioning treatment before conventional haematopoietic progenitor cell transplantation	EU/3/00/011	29/12/2000	EU/1/03/254	11/07/2003	Yes		Yes
	Imatinib mesylate	Glivec	Novartis Europharm Limited	Treatment of chronic myeloid leukaemia	EU/3/01/021	14/02/2001	EU/1/01/198	12/11/2001	No	02/12/2009	Yes
	Ecteinascidin 743	Yondelis	Pharma Mar S.A.	Treatment of soft-tissue sarcoma	EU/3/01/039	30/05/2001	EU/1/07/417	20/09/2007	No		No
	Dexrazoxane	Savene	Clinigen Healthcare Limited	Treatment of anthracycline extravasations	EU/3/01/059	19/09/2001	EU/1/06/350	02/08/2006	No		No
	Imatinib	Glivec	Novartis Europharm Limited	Treatment of malignant gastrointestinal stromal tumours	EU/3/01/061	20/11/2001	EU/1/01/198	27/05/2002	No	02/12/2009	No
	Clofarabine	Evoltra	Genzyme Europe B.V.	Treatment of acute lymphoblastic leukaemia	EU/3/01/082	05/02/2002	EU/1/06/334	31/05/2006	Yes		Yes
	Mitotane	Lysodren	Laboratoire HRA Pharma	Treatment of adrenal cortical carcinoma	EU/3/02/102	12/06/2002	EU/1/04/273	30/04/2004	Yes		Yes
	5-Aminolevulinic acid hydrochloride	Gliolan	Medac Gesellschaft für klinische Spezialpräparate mbH	Intra-operative photodynamic diagnosis of residual glioma	EU/3/02/121	13/11/2002	EU/1/07/413	12/09/2007	No		No
	Muramyl tripeptide phosphatidyl ethanolamine	Mepact	Takeda France SAS	Treatment of osteosarcoma	EU/3/04/206	21/06/2004	EU/1/08/502	23/03/2009	Yes		Yes
	Defibrotide	Defitelio	Gentium S.r.I.	Treatment of hepatic veno-occlusive disease	EU/3/04/212	29/07/2004	EU/1/13/878	22/10/2013	Yes		Yes
	Sunitinib	Sutent	Pfizer Limited	Treatment of malignant gastrointestinal stromal tumours	EU/3/05/267	10/03/2005	EU/1/06/347	15/01/2007	No	24/02/2009	No
	Histamine dihydrochloride	Ceplene	Meda AB	Treatment of acute myeloid leukaemia	EU/3/05/272	11/04/2005	EU/1/08/477	09/10/2008	No		No
	Nelarabine	Atriance	Novartis Europharm Limited	Treatment of acute lymphoblastic leukaemia	EU/3/05/293	16/06/2005	EU/1/07/403	24/08/2007	Yes		Yes
	Imatinib mesylate	Glivec	Novartis Europharm Limited	Treatment of acute lymphoblastic leukaemia	EU/3/05/304	26/08/2005	EU/1/01/198	18/09/2006	No	02/12/2009	Yes
	Dasatinib	Sprycel	Bristol-Myers Squibb	Treatment of acute	EU/3/05/338	23/12/2005	EU/1/06/363	22/11/2006	No	03/11/2009	No

			Pharma EEIG	lymphoblastic leukaemia							
	Dasatinib	Sprycel	Bristol-Myers Squibb Pharma EEIG	Treatment of chronic myeloid leukaemia	EU/3/05/339	23/12/2005	EU/1/06/363	22/11/2006	No	03/11/2009	No
	Nilotinib	Tasigna	Novartis Europharm Limited	Treatment of chronic myeloid leukaemia	EU/3/06/375	22/05/2006	EU/1/07/422	21/11/2007	No	37/3/2009	No
	Thiotepa	Tepadina	ADRIENNE S.r.I.	Conditioning treatment before haematopoietic progenitor cell transplantation	EU/3/06/424	29/01/2007	EU/1/10/622	17/03/2010	Yes		Yes
	Azacitidine	Vidaza	Celgene Europe Limited	Treatment of acute myeloid leukaemia	EU/3/07/509	29/11/2007	EU/1/08/488	22/12/2008	No	23/11/2015	No
Applicable	Herpes simplex 1 virus-thymidine kinase and truncated low affinity nerve growth factor receptor transfected donor lymphocytes	Zalmoxis	MolMed S.p.A.	Adjunctive treatment in haematopoietic cell transplantation	EU/3/03/168	20/10/2003	EU/1/16/1121	23/08/2016	No	06/03/2014	No
	Plerixafor	Mozobil	Genzyme Europe B.V.	Treatment to mobilise progenitor cells before stem cell transplantation	EU/3/04/227	20/10/2004	EU/1/09/537	04/08/2009	No	23/02/2009	No
	Decitabine	Dacogen	Janssen-Cilag International NV	Treatment of acute myeloid leukaemia	EU/3/06/370	08/06/2006	EU/1/12/792	24/09/2012	No	04/03/2011	No
	Brentuximab	Adcetris	Takeda Pharma A/S	Treatment of anaplastic large cell lymphoma	EU/3/08/595	15/01/2009	EU/1/12/794	30/10/2012	No	21/11/2012	No
	Brentuximab	Adcetris	Takeda Pharma A/S	Treatment of Hodgkin lymphoma	EU/3/08/596	15/01/2009	EU/1/12/794	30/10/2012	No	21/11/2012	No
	Mercaptopurine (oral suspension)	Xaluprine	Nova Laboratories Limited	Treatment of acute lymphoblastic leukaemia	EU/3/09/628	30/04/2009	EU/1/11/727	13/03/2012	Yes	20/04/2009	Yes
	Blinatumomab	Blincyto	Amgen Europe B.V.	Treatment of acute lymphoblastic leukaemia	EU/3/09/650	24/07/2009	EU/1/15/1047	25/11/2015	No	13/05/2014	No
	Ponatinib	Iclusig	ARIAD Pharma Ltd	Treatment of acute lymphoblastic leukaemia	EU/3/09/715	02/02/2010	EU/1/13/839	03/07/2013	No	04/07/2012	No
	Ponatinib	Iclusig	ARIAD Pharma Ltd	Treatment of chronic myeloid leukaemia	EU/3/09/716	02/02/2010	EU/1/13/839	03/07/2013	No	04/07/2012	No
	Bosutinib	Bosulif	Pfizer Limited	Treatment of chronic myeloid leukaemia	EU/3/10/762	04/08/2010	EU/1/13/818	02/04/2013	No	03/09/2010	No
	Ibrutinib	Imbruvica	Janssen-Cilag International NV	Treatment of lymphoplasmacytic lymphoma	EU/3/14/1264	29/04/2014	EU/1/14/945	07/07/2015	No	30/10/2015	No

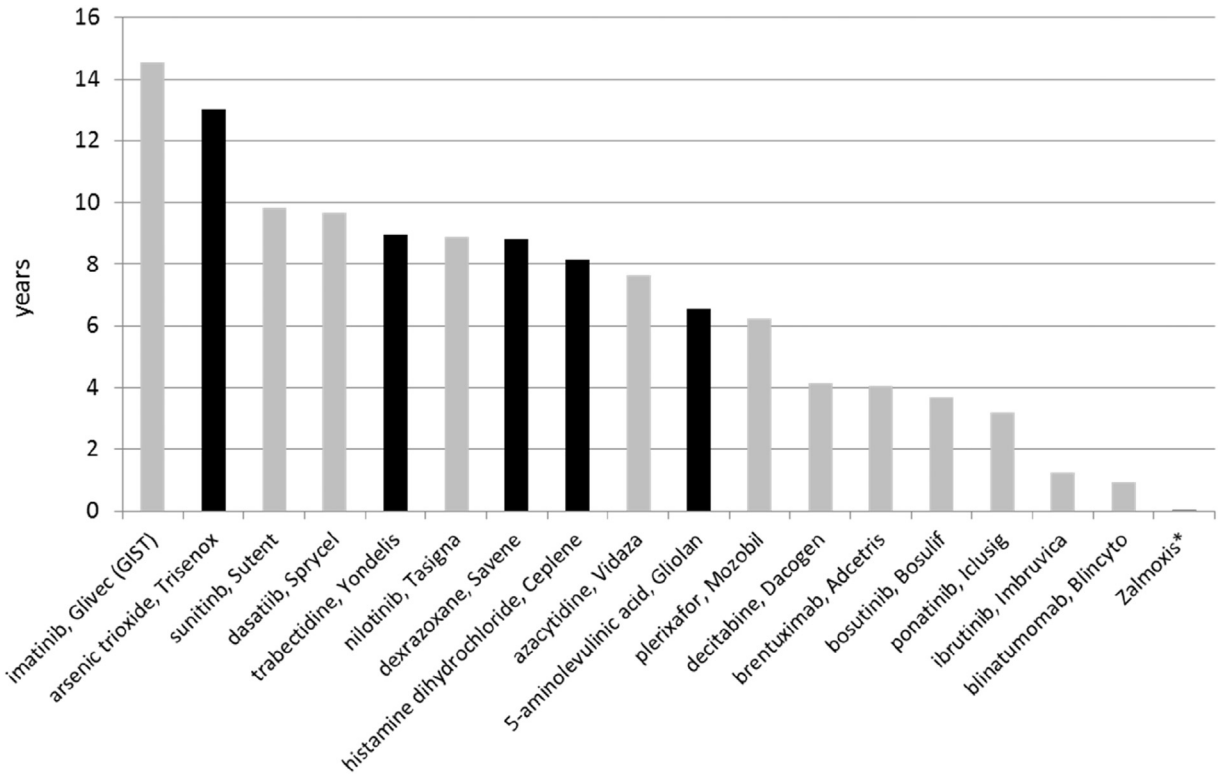

Fig. 2. Time elapsed in years between the first marketing approval and the most recently updated Summary of Product Characteristics still without any recommendation for paediatric use for 16 orphan oncology drugs approved for the treatment of a condition occurring both in adults and children (Grey – medicines with an agreed PIP; Black – medicines without a PIP) (generic names of medicines are provided with their trade names in Europe; *, Herpes simplex 1 virus-thymidine kinase and truncated low-affinity nerve growth factor receptor transfected donor lymphocytes).

None of the remaining 21 MAs had either any relevant paediatric information in their last updated SmPC, i.e. at a median time of 7.1 years, ranging from 1 month to 14.5 years, after the first MA in adults (Fig. 2).

3.3. Impact of the Paediatric Medicines Regulation

Seventeen (65%) of the 26 orphan oncology drugs for malignancies occurring in children and adults were first authorised before the requirement of the PMR came into force (26th July 2008) and five (29%) have an ongoing PIP that was approved after their first MA. Nine (35%) were first authorised after 26th July 2008, and all have an agreed PIP. However, the PIP was completed at the time of the first filing for only one orphan compound: Xaluprine (mercaptopurine), a new age-appropriate oral formulation of mercaptopurine for the treatment of acute lymphoblastic leukaemia. None of the others have information yet for paediatric use in their updated SmPC (Fig. 2). Thus, paediatric trials within all the 14 PIPs, except one started after the orphan drugs were granted their MA in adults. Even though the same disease occurred both in adults and children, the paediatric development was thus always significantly delayed.

4. Discussion

After 16 years, the Orphan Drug Regulation has been a major success in oncology as exemplified by 41% (657) of ODDs and 42% (65) of MAs for an anticancer orphan medicinal product. This is in line with the acceleration of therapeutic innovation with new effective medicines such as targeted therapies and immunotherapies. However, the results are disappointing with regard to paediatric malignancies. Only eight (30%) of the 26 orphan oncology medicinal products for the treatment of a condition occurring both in children and in adults, had a recommendation for paediatric use in their first European MA. This suggests that most companies developing oncology drugs, in an orphan condition which also occurs in children, first develop the drug in adults, as a priority towards first MA that will trigger the orphan drug exclusivity [1]. Indeed, these orphan cancer indications in adults generate a significant return on investment, as shown by the annual Orphan Drug Report [2]. Some orphan oncology drugs are blockbusters and generate more than $1 billion annual sales [8]. Paediatric development is only started through a PIP after the drug is registered for MA in adults. Indeed, the Orphan Drug Regulation is a voluntary instrument based on incentives, and there is no obligation to

develop orphan drugs in the paediatric population. Consequently, the development of these innovative oncology drugs is significantly delayed in children, as for many other oncology drugs without an orphan designation [9]. In 2014, Kreeftmeijer-Vegter *et al.* [10] showed that the Paediatric Regulation did not significantly increase the number of ODDs with potential paediatric indications and did not lead to more MAs for orphan drugs in children. We conclude that in paediatric oncology the development of orphan drugs is now driven by the obligation of the PMR rather than the attractiveness of incentives in the Orphan Drug Regulation, a voluntary instrument.

The Orphan Drug Regulation has significantly incentivised Research and Development programs in rare and ultra-rare diseases in children. As an example, 56 ODDs have been granted for cystic fibrosis and 28 for Duchenne muscular dystrophy. Of seven ODDs for Gaucher disease, three medicines have already received an MA. Medicines have been authorised for ultra-rare conditions such as hypophosphatasia [11]. In contrast, there was only one ODD for medulloblastoma, a brain tumour with an incidence of six per million, one ODD for the treatment of hepatoblastoma with an incidence of 1.4 per million and no ODD for other paediatric malignancies such as DIPG. The only successful example is the development of anti-GD2 monoclonal antibodies for the treatment of neuroblastoma with four ODDs and one already approved medicine, Unituxin (dinutuximab). On 8th May 2017, dinutuximab beta (Isqette) was granted an MA in Europe. Thus, the Orphan Regulation failed to incentivise pharmaceutical and biotech companies to invest in the development of innovative therapies for the rare malignancies occurring specifically in children, in contrast to non-malignant conditions in children.

Our study aimed at evaluating the impact of the Orphan Drug Regulation on the three situations for new oncology drug development for children. The first concerns a drug developed in rare conditions occurring both in adults and children, such as leukaemia, bone and soft-tissue sarcomas, central nervous system tumours and some lymphomas. Our study showed that, the Orphan Drug Regulation, which relies on voluntary measures, does not facilitate the development of these drugs in children, whereas the PMR obligates their paediatric development. However, major drawbacks have been identified in the implementation of the Paediatric Regulation [9], and it is critical that its timescale is reinforced to avoid major delays in starting paediatric trials (Box 1).

The second situation concerns drugs with a mechanism of action relevant for different adult and paediatric malignancies due to tumour biology: e.g. anaplastic lymphoma kinase (ALK) inhibition for the treatment of ALK+ lung cancer in adults and ALK-mutated neuroblastoma in children. If both diseases are rare, it is unlikely that the company will apply for two ODDs, and if the disease in adult is frequent, it is unlikely that the company will apply for an ODD for the paediatric condition as all resources will be focussed on the adult development. In the worst case scenario, the company will request a class waiver through the PMR because the condition in adults does not occur in children, as for crizotinib, the first-in-class ALK inhibitor [12]. There are many examples of class-waivered oncology drugs for which the company did not consider a paediatric development through an ODD [13]. The solution is to implement mechanism of action driven paediatric development plans within the PMR and to eliminate waivers based only on the grounds that 'the condition does not exist in children' [14].

The third situation concerns oncology drugs with a target or mechanism of action, which is unique to the biology of a paediatric tumour, such as anti-GD2 in neuroblastoma. This is a situation whose frequency is likely to increase because ongoing prospective programs of whole exome and RNA sequencing of paediatric patients' tumours at relapse will generate large databases of well clinically annotated molecular information that will be exploited to identify new pathways and new potentially druggable targets that will be specific for paediatric tumours [14]. Theoretically, this is a situation that should be addressed through the Orphan Drug Regulation, but only 15 of 1731 ODDs (0.8%) concerned a specific paediatric malignancy over the 16 years. There is a major need to incentivise better paediatric drug development for life-threatening conditions, such as paediatric cancers. In the US, the Priority Review Voucher program was set up in 2007 to promote development of new treatments for neglected tropical diseases and was extended in 2012 to rare life-threatening paediatric diseases [15]. After designation, a Priority Review Voucher is granted to a drug when its first MA concerned a neglected disease or a rare paediatric disease. The use of the voucher accelerates the

Box 1. Proposed solutions to improve and accelerate new oncology drug development for children and adolescents.

1. Mandatory paediatric investigation of drugs based on 'drug mechanism of action' rather than adult disease
2. Prioritisation of compounds to be evaluated or not in children, based on tumour biology, medical needs and feasibility
3. Reduction in the delays in starting paediatric development of potentially life-saving innovative drugs
4. Breaking the 18-year dogma by allowing adolescents to participate in adults' trials when medically and scientifically justified
5. More effective and flexible rewards to better incentivise the development of new and specific paediatric medicines and drug repositioning

regulatory review by the US Food and Drug Administration (FDA) for a different drug from the standard 10 month period to 6 month. This voucher is transferable and can be sold. Unituxin (dinutuximab) was granted a Priority Review Voucher that was subsequently sold to Abbvie for $350 million. The European regulatory review process by EMA is different from the FDA, and accelerated regulatory review cannot be set up because the duration of evaluation periods is fixed by law for any agent submitted for an MA. However, better rewards and incentives than the 6-month extension applied at the end of the supplementary protection certificate to any drug with a completed PIP would better attract companies and investors to develop medicines for paediatric life-threatening rare diseases, such as cancer.

In conclusion, the voluntary Orphan Drug Regulatory program has not had a significant impact on the development of innovative therapies for children and adolescents with cancer. The obligations and rewards set up by the PMR appear to have greater traction with the pharmaceutical industry, but major issues have been identified in the field of paediatric oncology that delay or waive the development of therapeutic innovations. The urgent needs of children dying of cancer are still not addressed, and changes in the regulatory environment are urgently needed to accelerate innovation.

Conflict of interest statement

None declared.

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