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Failures to further developing orphan medicinal products after designation granted in Europe

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ABSTRACT

Objectives: The Research&Development process in the field of rare diseases is characterised by many well-known difficulties and a large percentage of orphan drugs does not reach the marketing approval.

This work aims at identifying orphan medicinal products that failed the Research&Development process and at investigating the reasons for failure and possible factors influencing this failure.

Design: Drugs designated under Regulation (EC) 141/2000 in the period 2000-2012 were investigated in terms of failures: 1) Marketing Authorisation failures (refused or withdrawn), and 2) drugs abandoned by the sponsor during the development.

Possible risk factors for failure were analysed using statistical validated methods.

Results: This study demonstrated that, out of 788 designations, 437 are under development and 219 failed the developmental process.

Among these failures, 34 failed the Marketing Authorisation process and 185 were abandoned during the developmental process. In the first group of drugs (Marketing Authorisation failures), 50% reached the phase II, 47% the phase III and 3% the phase I while, in the second group (abandoned drugs), apparently, the majority of orphan medicinal products never started the development process, since no data on 48,1% of them was published and the 3,2% did not progress beyond the non-clinical stage.

The reasons for Marketing Authorisation failures were: safety/efficacy issues (26), insufficient data (12), quality issues (7), regulatory issues on trials (4), commercial reasons (1). The main causes for abandoned drugs were safety/efficacy issues reported in 54 cases, inactive companies (25,4%), change of company strategy (8,1%), drug competition (10,8%). No information about the reasons for failure was available for the 23,2%.

Conclusions: This analysis demonstrated that failures accounted for 27,8% of all designations granted in Europe and the main reasons for failure are safety and efficacy issues. Moreover, the stage of development reached by the drug represents a specific risk factor for failures.

ARTICLE SUMMARY

Strengths and limitations of this study:

This is, apparently, the first report on the failures of Orphan Medicinal Products (OMPs) in the European Union (EU) based on a large amount of data and on a rigorous methodology. Limitation is represented by the well-known lack of the public availability of trial results.

Methods of the study:

1- Orphan drug designations (ODDs) issued by the European Commission (EC) in the period 2000-2012 have been identified;

2- Information on studies supporting the Marketing Authorisation (MA) was derived from official Summaries of Product Characteristics (SmPCs), clinical trial databases and literature searches;

3- ODDs have been divided in the following categories: drugs reaching the MA, drugs in development, MA failures and drugs abandoned by the sponsor;

4- ODDs have been classified by year of designation, disease area, type of sponsor (commercial or non-commercial), stage of development, age related type of condition (whether affects children or not);

5- Reasons for failures have been identified evaluating sponsor-sourced information and information derived from clinical trial databases.

INTRODUCTION

The availability of drugs for rare diseases still represents a challenging objective because the research and development in this field is characterised by many well-known difficulties. For instance, the rarity of conditions and the geographical dispersion represent hurdles for conducting adequate studies and trials. This is even more relevant if we consider that a great part of these patients are children, and paediatric trials are more challenging due to methodological,

ethical and economic reasons, especially when the youngest ones, the neonates, are involved. Therefore, pharmaceutical companies are traditionally reluctant to invest in developing specific treatments to meet the needs of the rare disease patients mainly because the market is small and of lower commercial interest.

Over the years, specific regulations have been released in Europe,[1] US,[2] Japan[3] and Australia[4] to provide incentives for companies to develop medicines for diseases with a small market, including grants, research support, fee waivers/reduction, market exclusivity, and public diffusion of orphan innovation. Notwithstanding the incentives issued at national and international level to overcome these obstacles, the number of marketed medicines for rare diseases is still limited, especially in the case of neglected diseases[5] and paediatric patients.[6] Noticeably, many drugs in Europe gain an ODD under the European Orphan Regulation (EC) No 141/2000.[1] However, a large percentage of them does not reach the marketing approval. While in some cases the failure is made evident because a MA is refused or withdrawn by the sponsor, in other cases the Research&Development (R&D) process of an OMP results interrupted, even in lack of evident reasons. Unfortunately, even if the European OMP Regulation (EC) No 141/2000[1] requires that the sponsor shall submit to the European Medicines Agency (EMA) an annual report on the state of development of the OMP (art 5), these reports are not public. Few analyses on the developmental status of OMPs and regulatory pathway have been published.[7,8,9] In conclusion, currently the real extent and reasons for the failures in the developmental process of OMPs in EU are mainly unknown.

The objective of this work is to identify the OMPs designated by the EMA that failed to reach the MA and the reasons for the failure. We considered failures both in terms of 1) drugs with a MA refused or withdrawn (MA failures), and 2) drugs abandoned by the sponsor during the development (abandoned). We also investigated the stage of the R&D process at the time of its interruption and other possible factors influencing the failure.

METHODS

The sample of our analysis is represented by the OMPs designated in the period 2000-2012 and currently listed in the European Commission (EC) Register of OMPs.[10] We limited our analysis up to 2012 considering that the start of drug clinical development may take 2-3 years from the designation to the inclusion of clinical trials in public databases.

Medicinal products (MPs) that received an ODD were included in the analysis (*Supplementary file*). We excluded from the analysis OMPs included in a MA Application (MAA) with a pending decision (last update: March, 31st 2016).

Information on the OMPs in Europe, in the considered period, were derived from EuOrphan.[11,12] EuOrphan is a database containing information on OMPs and other medicines available on the market for rare diseases both in the EU and US. It was created by Consorzio per Valutazioni Biologiche e Farmacologiche (CVBF) in the framework of a funded European IT-Technology project (eTen 510774 2003/C 118/19) as previously described.[11,12] It is populated with data derived from official sources[13,14,15] and is regularly updated to allow analyses and statistical evaluations.

OMPs were sorted by year of designation, disease area, type of sponsor (commercial or non-commercial), stage of development, age related type of condition (whether affects children or not).

Information on studies supporting the MA was derived from official SmPCs, as catalogued by EuOrphan, and clinical trial databases (EU clinical trials register[16] and Clinicaltrials.gov[17]).

The following search strategy was adopted to query clinical trial databases:

EU clinical trials register: <disease name> AND <drug name> OR Advanced Search <Orphan Designation Number>;

Clinicaltrials.gov: Advanced Search - Targeted Search: Conditions: <disease name> AND Interventions: <drug name>.

We considered trials in which the sponsor that obtained the ODD was mentioned as sponsor or collaborating organisation (e.g. company manufacturing the Investigational Medicinal Product-IMPs).

Literature data were derived from a bibliographic search performed in PubMed[18] by using an ad hoc search strategy as follows.

Search terms. Keywords derived from Medical Subject Headings (MeSH) vocabulary thesaurus were used: (MeSH <drug name> AND MeSH <condition name>) OR (<drug name> AND <condition name>). Further key words, e.g. synonyms or acronyms, were used if relevant, as raising from the analysis performed on clinical trials.

Limits. The MeSH search was "restrict to MeSH Major Topic" and to search field "Title and abstract".

Subheadings of MeSH <condition name> were limited to: 'statistical and numerical data'; 'drug therapy' AND 'therapy' OR 'prevention and control according to the orphan indication'.

Subheadings of MeSH <drug name> were limited to: 'administration and dosage'; 'adverse effects'; 'drug effects'; 'pharmacokinetics'; 'pharmacology'; 'therapeutic use'; 'toxicity'.

We considered only items published in English in the period ranging from the designation date to March 2016.

Table 1 summarises the sources used and the related information investigated.

Failure is defined as OMP that does not reach the marketing approval because: 1- the MA has been refused or withdrawn (MA failures); 2- the R&D process has been interrupted by the sponsor (abandoned).

We considered OMPs abandoned by the sponsor during the development if:

- no clinical trial has been published on the most relevant clinical trial databases (EU clinical trials register[16] and Clinicaltrials.gov[17]), in the literature (PubMed[18]) and in the official website of the sponsor in the last 3 years;

- clinical trials have been published but the clinical development has been declared terminated by the sponsor or the sponsor resulted inactive / in bankruptcy.

To investigate the reasons for failure, sponsor-sourced information (company websites and pipelines, direct communications with the sponsors) and information derived from clinical trial databases (EU clinical trials register[16] and Clinicaltrials.gov[17]) have been evaluated.

Two researchers performed the analysis and possible conflicting results were solved through discussion or the judgement of a third reviewer.

The correlation between the failure and the following factors has been analysed: the year of designation, therapeutic area, type of sponsor (commercial or non-commercial), stage of development, condition affecting children or not. The significance of the presented results has been checked with a chi squared test. The analysis of significance was performed using the R statistical software. The significance level of the tests was set to P=0.05.

RESULTS

Orphan Designations – current status

As shown in the flow chart (*Supplementary file*), in the period 2000-2012, 788 ODDs have been granted in EU: 766 ODDs are still present in the OMP register and 22 have lost the ODD after receiving the MA.

Overall, the R&D process was concluded with a successful MA in 132 cases and with a MA withdrawn or refused in 34 (14 received a negative opinion and 20 had the MAA withdrawal by the sponsor), while 437 ODDs resulted in R&D at the time of the analysis and for the remained 185 the R&D process resulted interrupted if:

- no trials have been published in clinical trial databases in the last 3 years (130 ODDs);
- the R&D process has been declared terminated by the sponsor (55 ODDs).

Therefore, a total of 219 ODDs resulted failed.

Data analysis by risk factors

We distributed data collected during the analysis on ODDs by year of designation (*Figure 1*), stage of development *(Figure 2)*, therapeutic area, type of sponsor and age related type of condition (*Table 2*).

Figure 1 demonstrates that the number of failures gradually increases from 2000 to 2012.

Figure 2 elucidates the developmental status of all the ODD groups and compares data among ODDs with a MA, ODDs in R&D, MA failures and ODDs abandoned. All the developmental phases are represented. Data on clinical trials revealed that, out of a total of 788 ODDs, 54 OMPs reached the phase I, 270 the phase II, 309 the phase III and 3 presented only compassionate use data (*Figure 2*).

No information on the stage of development of 106 ODDs was found.

Phase III studies prevail in the MA groups (including both ODDs with a MA and MA failures); both phases II and III are well represented in the group of R&D while the abandoned group is characterised by a very high frequency of 'no studies/not classified studies'. With regard to this group, apparently, the largest number of ODDs never started the developmental process, since for 89 out of 185 ODDs (48,1%) we did not find any data from literature, clinical trial databases or information from the sponsor. 6 out of 185 ODDs (3,2%) did not progress beyond the non-clinical stage, while 55 out of 185 ODDs (29,7%) were in phase II clinical trials at the time of the developmental process interruption.

Our data show that the percentage of failures referring to a condition affecting adults and children and the percentage of failures referring to a condition affecting only adults are not so different: 27,3% (166/609) and 29,6% (53/179) respectively (*Table 2*).

As detailed in *Table 2*, the highest percentage of failures (out of a total of 219 ODDs), occurred in renal, urinary and reproductive diseases and other diseases (40%) followed by cardiovascular and respiratory (37,3%), dermatological (35,7%), oncologic (31,7%), gastrointestinal (31,6%), neurological and psychotic (25,9%) and inborn errors of metabolism diseases (24,2%).

In particular, the rare conditions with the highest number of failures were in the oncology area and included: glioma (12); acute myelogenous leukaemia (11); pancreatic cancer (10); chronic lymphocytic leukaemia (7). In the respiratory group, 6 failures were counted for cystic fibrosis.

With regard to the sponsor, in our sample, commercial sponsors receiving the ODD are the most represented with 749 out of 788 ODDs (i.e. 95,0%, *Table* 2) while non-commercial sponsors account for only 39 out of 788 ODDs.

In particular, failures resulted the 28,3% (212/749) of ODDs sponsored by commercial sponsors and the 17,9% (7/39) of ODDs sponsored by a non-commercial entity.

Finally, our analysis demonstrated that OMPs that completed (or reached) phase III have a reduced risk of failure ($P<0.01$).

Reasons for failures

As shown in *Figure 3*, the lack of efficacy and safety has been identified as the main reason for the failure of the developmental process. This aspect varies across the therapeutic areas (*Figure 4*). We found that the 42,5% (34 out of 80 ODDs failed for safety/efficacy issues) has been designated for oncologic diseases.

Other relevant causes for failure are represented by economic issues and company strategic decisions. Companies resulting inactive (bankrupt) accounted for a large number of failures (47/185= 25,4%). In other cases, the development was abandoned following specific company strategy; as an example, 11 ODDs were abandoned because in development for other indications. Also, the number of ODDs abandoned for the drug competition, such as other OMPs with a MA or in development for the same indication, is considerable (20/185, 10,8%).

No information about the possible reasons for failure was available for the 23,2% of ODDs abandoned (*Figure 3*). In this case, we may speculate that the reason for the abandoned development is a not declared 'sponsor strategy'.

Interestingly, safety and efficacy issues are significantly more represented than other causes of failure in the ODDs group that reached the MA. In these groups, only in 1 case commercial reasons from the sponsor were declared (1).

For the abandoned drugs, the main reasons for the failure were safety/efficacy issues that were reported in 54 cases but the relevance of other causes linked to the sponsor is much more evident that includes a) the lack of any data b) inactive company c) company strategy blocking the developmental process.

For MA failures, the reasons identified were: safety/efficacy issues (26), insufficient data (12), quality issues (7), and regulatory issues on trials (4) such as no comparator trials and no

commercial protection. In only 1 case a commercial reason from the sponsor was declared (1). It is noticeable that in some cases more than one reason accounted for the failure.

DISCUSSION

Research and scientific progress in the rare disease field is a challenging objective because of the small number of patients affected by rare diseases, the need for highly specialised research centres dealing with each specific condition, and the scarce economic return.

On this basis, specific clinical studies in this field may be difficult to perform and, as a result, may be long and costly. Fagnan[19] reported that in recent years OMP trials take approximately 5.9 years from phase I to new drug application with an additional 0.8 years required for the approval process, and that the revenue from the OMPs development is not perceived as justifying the cost of the clinical trials. This recent publication enlightened that the development of OMPs resulted lower over recent years, in line with the general decline of productivity of pharmaceutical companies.

In our analysis, we found that the number of ODDs gradually increases from 2000-2012. This is consistent with the situation in the United States (US),[20] where less than 14% of OMPs has received a MA by Food and Drug Administration (FDA), and an exponential increase of ODDs has been demonstrated up to 2013. Concurrently, the annual number of orphan medicinal approvals has remained more or less constant.[21]

This analysis shown that out of a total of **788 ODDs designated in the period 2000-2012, 132 received a MA, 437 are in R&D and 219 have not reached the MA: 34 failed the MA (refused or MAA withdrawal) and 185 were abandoned during the developmental process.**

In particular, failures accounted for 27,8% of ODDs granted in Europe, including ODDs abandoned and MA failures.

The renal, cardiovascular, respiratory, dermatological, oncologic and gastrointestinal diseases, present the highest rate of failures. Poisoning/overdose diseases and haematological diseases were characterised by a lower percentage of failures (16,7% and 14,5% respectively). However, differences were not significant. In line with our data, a 2013 publication demonstrated that the success rate of market approval of OMPs developed by pharmaceutical companies is 21.8% and that the success or failure of OMP development programmes may be less likely correlated across diseases.[20]

Furthermore, we confirmed that most of the sponsors that obtained the ODD are commercial (about 90%) while, among non-commercial sponsors, hospitals and universities obtained only 30 ODDs, mostly still under research (25).

With regard to the stage of development, we demonstrated that it represents the main factor influencing the success or the failure of the R&D process because we found statistical differences (*P < 0.01) among the stages of development of OMPs. Most of failures were not likely to reach the clinical phase especially when safety/efficacy issues arose. In fact, when preliminary preclinical or early clinical studies show that both safety and efficacy issues were raised, the negative benefit/risk profile did not support the continuation of the development and the sponsor prefers to stop it.

This demonstrated that to complete the R&D process still remains a challenging issue for an orphan drug. In particular, the development of 20% of abandoned OMPs for safety/efficacy issues was stopped in the preclinical phase and the 48,1% in phase I-II clinical studies.

Our data are in line with a very recent publication from Morel and coll.[21] demonstrating that the development of more than one hundred OMPs has been discontinued mainly in phase II.

Generally speaking, our analysis shows that the main reasons for the failure in development are the safety/efficacy issues (about 30%). For six OMPs the development was terminated after the discontinuation of trials, two recommended by the Data Safety Monitoring Committee (DSMC).

Also among MA refused and MAA withdrawal, only a small part completed the developmental process when applying for a MA. This is in line with the known difficulties to follow a standardized phase I to III scheme to provide the necessary evidence to approve of OMPs. The second cause of failure is the deemed company inactivity / bankruptcy (about 25,4%), perhaps connected with the failure of the R&D program, especially in case of small companies whose efforts are mainly focused on the OMP. About the 51% of these abandoned OMPs was in the oncologic area. Often, small pharmaceutical companies may fail the developmental program of their lead OMP and for this reason go bankrupt. This means that the bankruptcy may be the cause or even the resulting effect of drug development process failure.

However, other relevant company-related causes of failure are demonstrated in our study. Among them, drug competition also represents one of the most important reasons for the failure. Other OMPs with a MA or in development for the same indication were the main causes for the discontinuation of the R&D process. Competitors in development were found both from the same sponsor and from other companies.

Economic issues and lack of funding related with the development of the OMP (and not the general economic trend of the company) resulted a small part of failure reasons (3,2%), especially in the fields of oncologic, cardiovascular and respiratory diseases. For the majority of these OMPs, no clinical trial was published on the main databases.

A small number of OMPs (8,1%) failed due to company strategy, e.g. change in overall product development plan. The highest number of these drugs was in development for other indications by the same sponsor.

If we look at failed MA, other reasons for failures emerged, such as insufficient data, quality issues or regulatory issues on trials.

In the following strengths and weaknesses of this study have been discussed.

One of the main difficulties in performing this kind of analysis is the lack of sufficient publicly available information. To overcome this barrier, besides public information, we directly contacted the sponsors to investigate the stage of development of OMPs and the reasons for failures even if OMPs are still listed in the European OMPs registry.

However, this effort remains only partially successful. In particular, the search for information about the failures of trials and OMPs development faced difficulties related with the availability of results. In fact, we found no information about the failures for the 23,2% of abandoned drugs and no information on the stage of development of 48% of abandoned drugs. This aspect deals with the 'transparency' of results, a problem still under debate.

The European OMP Regulation[1] rules that the state of development of OMPs is to be provided only to EMA on a confidential basis. In addition, the EU clinical trial registry does not provide any detail about trial completion or discontinuation. On the contrary, the public availability of trial results has been made mandatory in Europe by the new EU Regulation on clinical trials (EU) 536/2014,[22] requiring the publication of summary of clinical trial results one year after the end of the trial, while respecting the personal data protection and commercially confidential information. This should improve the access to information, but we will evaluate the real outcomes of the new law in the next years, also considering that the regulation allows pharmaceutical companies to censor clinical study report before online publication.

The publication and availability for researchers of trial results and datasets still remain a sensitive issue, as also underlined by Doshi and colleagues.[23] Data sharing allows clinicians to match a patient's electronic health record directly to clinical trials and observational study data sets for better individualized therapeutic decisions. On the other hand, regulators are legally obliged to take timely decisions on the availability of drugs for patients, even under conditions of uncertainty, and the personal data protection or patient confidentiality, i.e. issues very different from commercial confidentiality, are not easy to ensure, as simply uploading trial data on a

website would entail its own problems and there is a small risk that an individual patient could be identified from an anonymized dataset.[24]

All things considered, a step further to improve the availability of data without compromising the work of regulators and companies, personal data protection, patient and commercial confidentiality, may be the publication of summaries of the main outcomes, being the publication of full trials reports probably unnecessary. Therefore, registries and databases like EuOrphan may better disseminate and make information available.

Another issue encountered in performing this study was related to the transfer of sponsorship. Over the years, 28,7% of sponsorships (226/788) has been transferred (data not shown) from the sponsor obtaining the designation and the actual one. This issue enhances the difficulties to search and obtain reliable information.

Finally, this work demonstrated to be a good exercise to better understand the risks encountered by companies willing to develop OMPs.

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COMPETING INTERESTS

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: VG, AL, DB declare that part of this work was supported by an unrestricted grant from Celgene International II Sàrl; EB owns Celgene Stock Options (<0.00001%); no other relationships or activities that could appear to have influenced the submitted work.

AUTHOR'S CONTRIBUTION

V. Giannuzzi prepared the first draft of the manuscript and performed the analysis; A. Landi performed the analysis and contributed to the draft of the manuscript; E. Bosone reviewed data and solved conflicting results; F. Giannuzzi and S. Nicotri performed the statistical analysis and prepared figures, J. Torrent Farnell reviewed regulatory data and issues; Fedele Bonifazi contributed to set up of the methodology; M. Felisi performed a consistency check with data from European Public Assessment Reports (EPAR) on paediatric medicinal products and indications; D. Bonifazi provided a general revision of the paper; A. Ceci provided a general and final review of the draft.

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DATA SHARING STATEMENT

Unpublished data from the study are not available to anyone other than authors.

ABBREVIATIONS

DSMC: Data Safety Monitoring Committee

EC: European Commission

EMA: European Medicines Agency

EPAR: European public assessment reports

EU: European Union

FDA: Food and Drug Administration

IMP: Investigational Medicinal Product

MA: Marketing Authorisation

MAA: Marketing Authorisation Application

MeSH: Medical Subject Headings

MP: Medicinal product

ODD: Orphan Drug Designation

OMP: Orphan Medicinal Product

R&D: Research and Development

SmPCs: Summaries of Product Characteristics

US: United States

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TABLES

Table 1 *– Sources used for the analysis and information investigated.*

SOURCE	INFORMATION
EuOrphan (EMA, Orphanet)	- Active substances designated as OMP; - ODDs with a MA; - ODDs withdrawn with a MA; - Dates of designation; - Rare condition(s); - Orphan indication(s) - First and current sponsors; - MA refusals and MAA withdrawals; - Reasons for withdrawals or refusals; - Clinical trials and other evidence supporting the MA - Possible competitors, i.e. other OMPs for the same indication.
Clinical trial databases (EU clinical trials register and Clinicaltrials.gov)	- Published clinical trials - Reasons for prematurely ended clinical trials
PubMed	- Published clinical trials and other studies in literature - Efficacy and safety data
Sponsor-sourced information (company websites and pipelines, direct communications with the sponsors)	- Sponsor type (commercial or non-commercial) - Stage of development of the drug - Reasons for failures

Table 2 – *Orphan drug designations by risk factors.*

RISK FACTORS	N. ODDs with a MA	N. R&D	N. FAILURES		TOT	% FAILURES
			MA failures	Abandoned		
Age related type of condition						
Not affecting children	24	102	8	45	**179**	**29,6%**
Affecting children	108	335	26	140	**609**	**27,3%**
Therapeutic Area						
Cardiovascular and respiratory diseases	10	37	3	25	**75**	**37,3**
Dermatological diseases	1	8	1	4	**14**	**35,7**
Endocrine diseases	6	16	1	4	**27**	**18,5**
Gastrointestinal diseases	2	11	0	6	**19**	**31,6**
Haematologic diseases	12	35	0	8	**55**	**14,5**
Inborn errors of metabolism diseases	32	37	6	16	**91**	**24.2**
Infectious and immunitary system diseases	8	58	1	19	**86**	**23,3**
Neurological and psychotic diseases	9	54	2	20	**85**	**25,9**
Oncologic diseases	49	147	17	74	**287**	**31,7**
Ophthalmic diseases	1	22	1	4	**28**	**17,9**
Poisoning/overdose diseases	0	5	1	0	**6**	**16,7**
Renal, urinary and reproductive diseases	0	3	1	1	**5**	**40**
Others	2	4	0	4	**10**	**40**
Sponsor type						
Commercial	132	405	34	178	**749**	**28,3**
Non-commercial	0	32	0	7	**39**	**17,9**
Sponsorship transferred	40	117	16	53	**226**	**30,5**

FIGURES

Figure 1 - Distribution of orphan designations by year.

Figure 2 - Stage of development reached by ODDs with a MA and MA failures (on the top) and ODDs resulting in R&D and abandoned (on the bottom). Statistical differences between stages of development were determined using a chi squared test (*P < 0.01).

Figure 3 - Reasons for failures of abandoned drugs (left) and Marketing Authorisation failures (right).

Figure 4 - Failures for efficacy and safety issues across therapeutic areas.

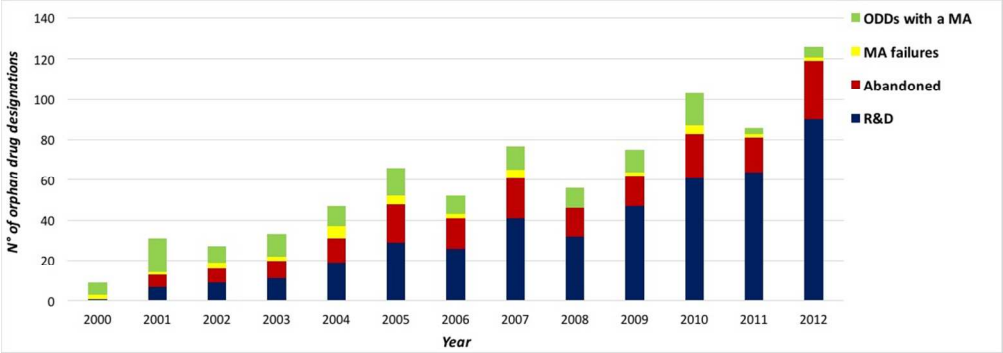

Figure 1 - Distribution of orphan designations by year

404x142mm (72 x 72 DPI)

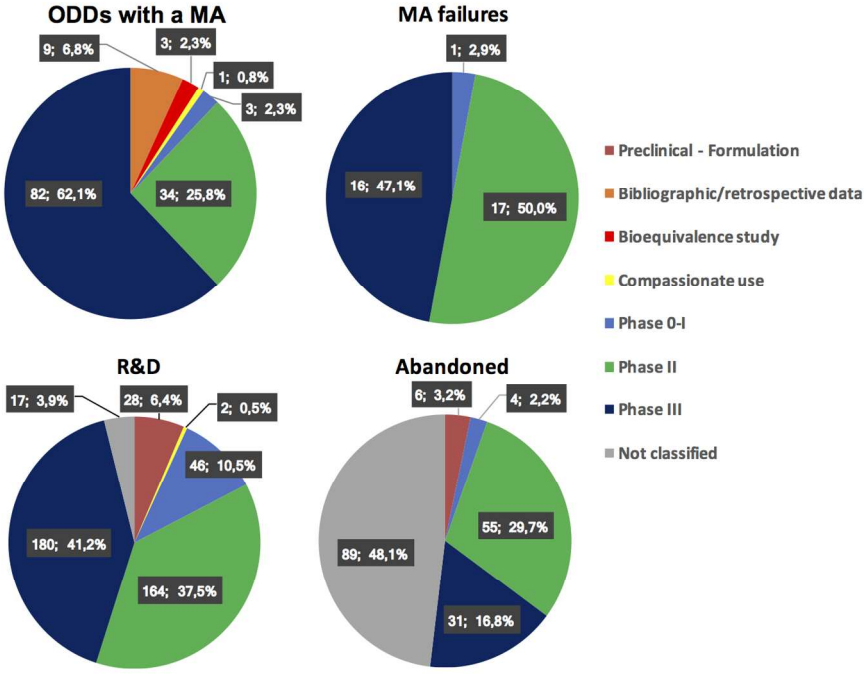

Figure 2 - Stage of development reached by ODDs with a MA and MA failures (on the top) and ODDs resulting in R&D and abandoned (on the bottom). Statistical differences between stages of development were determined using a chi squared test (*P < 0.01).

276x189mm (150 x 150 DPI)

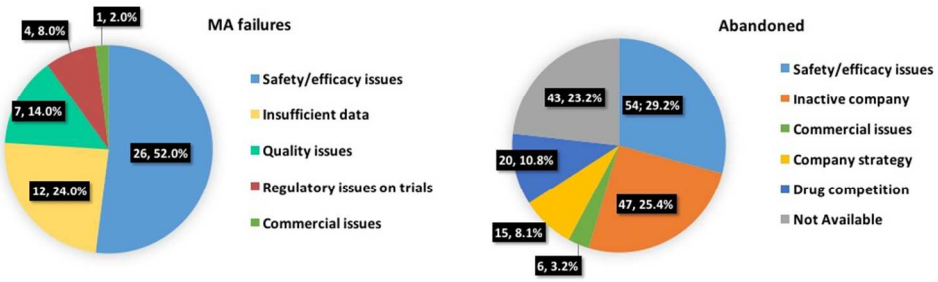

Figure 3 - Reasons for failures of abandoned drugs (left) and Marketing Authorisation failures (right).

364x101mm (72 x 72 DPI)

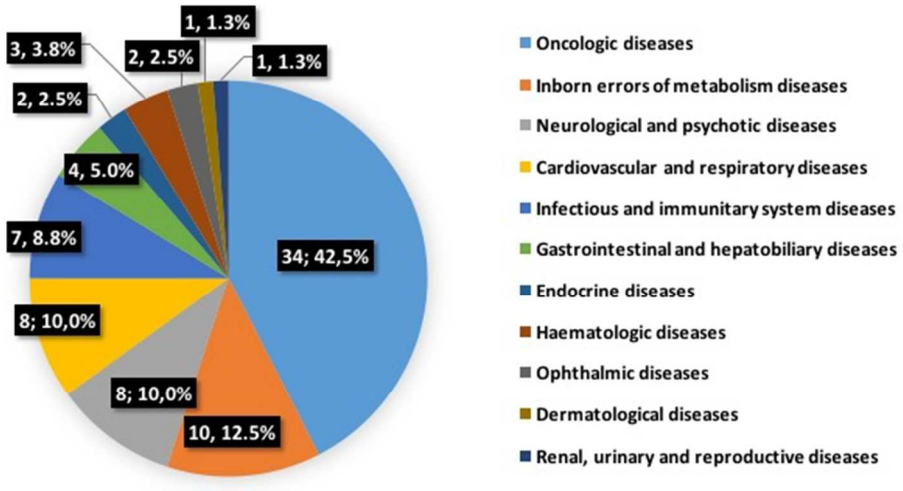

Figure 4 - Failures for efficacy and safety issues across therapeutic areas.

227x110mm (72 x 72 DPI)

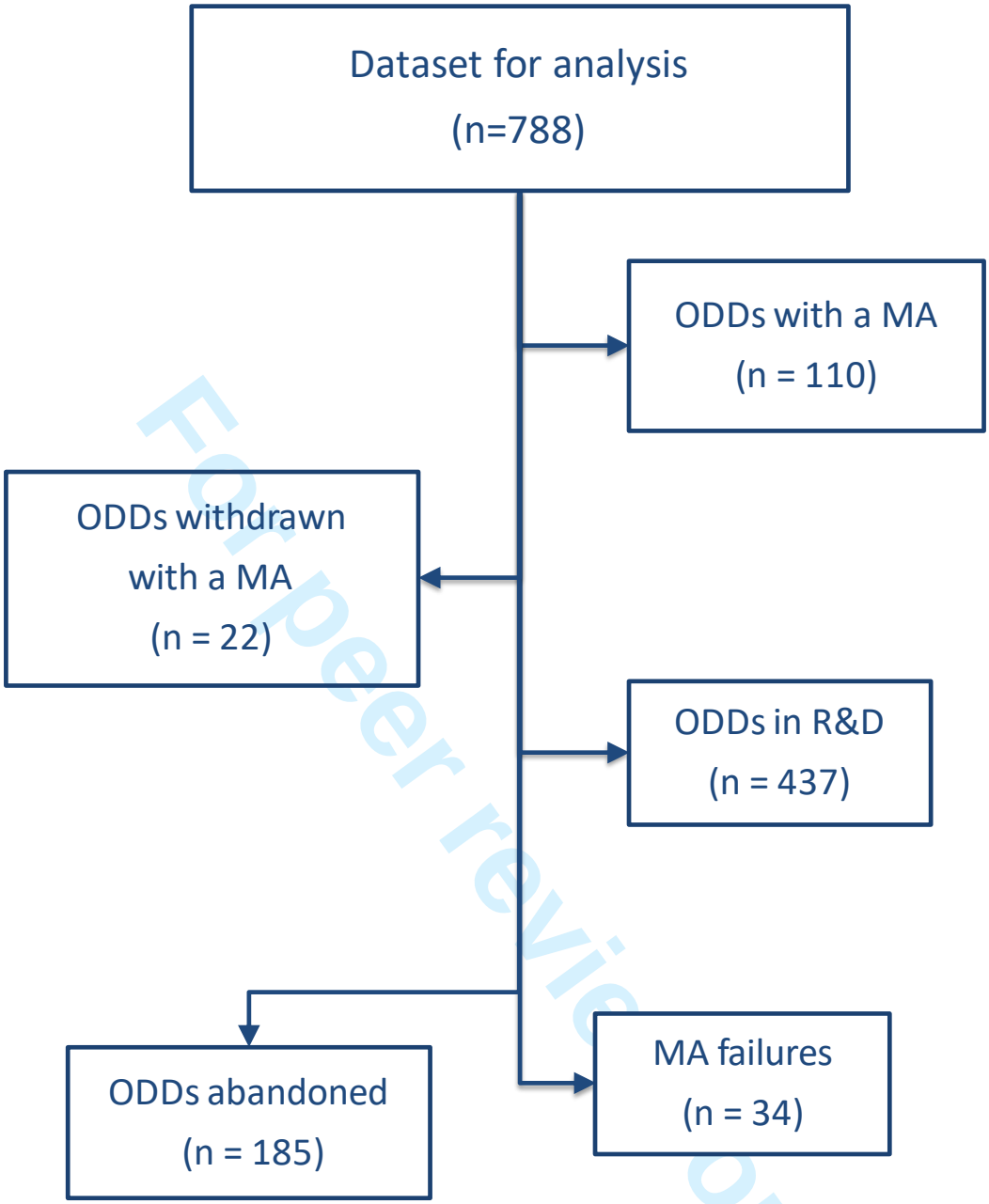

Figure 1 *- Flow chart of the dataset (in brackets the number of designations released between 2000-2012). We included 766 orphan designations currently present in the OMPs European Register and 22 OMPs that lost the designation over the year.*

BMJ Open

Failures to further developing orphan medicinal products after designation granted in Europe: an analysis of Marketing Authorisation failures and abandoned drugs

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ABSTRACT

Objectives: The Research & Development process in the field of rare diseases is characterised by many well-known difficulties, and a large percentage of orphan medicinal products does not reach the marketing approval.

This work aims at identifying orphan medicinal products that failed the developmental process, and investigating reasons for and possible factors influencing failures.

Design: Drugs designated in Europe under Regulation (EC) 141/2000 in the period 2000-2012 were investigated in terms of the following failures: 1) Marketing Authorisation failures (refused or withdrawn), and 2) drugs abandoned by sponsors during development.

Possible risk factors for failure were analysed using statistically validated methods.

Results: This study points out that 437 out of 788 designations are still under development, while 219 failed the developmental process. Among the latter, 34 failed the Marketing Authorisation process and 185 were abandoned during the developmental process. In the first group of drugs (Marketing Authorisation failures), 50% reached phase II, 47% phase III and 3% phase I, while in the second group (abandoned drugs) the majority of orphan medicinal products apparently never started the development process, since no data on 48.1% of them was published and the 3.2% did not progress beyond the non-clinical stage.

The reasons for failures of Marketing Authorisation were: efficacy/safety issues (26), insufficient data (12), quality issues (7), regulatory issues on trials (4), commercial reasons (1). The main causes for abandoned drugs were efficacy/safety issues, reported in 54 cases, inactive companies (25.4%), change of company strategy (8.1%), drug competition (10.8%). No information concerning reasons for failure was available for 23.2% of the analysed products.

Conclusions: This analysis shows that failures occurred in 27.8% of all designations granted in Europe, the main reasons being safety and efficacy issues. Moreover, the stage of development reached by drugs represents a specific risk factor for failures.

ARTICLE SUMMARY

Strengths and limitations of this study:

Strengths:

- This report about failures of Orphan Medicinal Products (OMPs) in the European Union (EU) is based on a large amount of data and on a rigorous methodology;
- Information on studies supporting Marketing Authorisation (MA) was derived from official Summaries of Product Characteristics (SmPCs), clinical trial databases and literature searches;
- Orphan Drug Designations (ODDs) have been classified by year of designation, disease area, type of sponsor (commercial or non-commercial), stage of development, age-related type of condition (whether they affects children or not).

Limitations:

- Public information on drug development, as well as on trial results, is not mandatory, therefore not always publicly available;

1- As the developmental phase, and reasons for failures have been identified through, sponsor-sourced information, clinical trial databases and literature, we considered as 'abandoned' drugs even those whose preclinical and clinical studies are ongoing but no information has been made available from the sponsor.

INTRODUCTION

The availability of drugs for rare diseases still represents a challenging objective, since because Research & Development (R&D) in this field is characterised by many well-known difficulties. For instance, rarity of conditions and geographical dispersion represent hurdles for conducting adequate studies and trials. This is even more relevant if we consider that alarge part of these patients are children, since paediatric trials are more challenging due to methodological, ethical and economic reasons, especially when neonates are involved. Therefore, pharmaceutical companies were traditionally reluctant to invest in developing specific treatments for rare diseases, mainly because of the smallness of the market and/or lower commercial interest.

Over the years, specific regulations have been released in Europe,[1] US,[2] Japan[3] and Australia[4], in order to provide incentives for companies to develop medicines for diseases with small market, including grants, research support, fee waivers/reduction, market exclusivity, and public diffusion of orphan innovation. Notwithstanding the incentives issued at national and international level to overcome such obstacles, the number of marketed medicines for rare diseases is still limited, especially for the ones targeted at paediatric patients.[5] Noticeably, many drugs in Europe gain an Orphan Drug Designation (ODD) under the European Orphan Regulation (EC) No 141/2000.[1] However, a large percentage of them does not reach marketing approval. While in some cases the failure is made evident, since MA is refused or withdrawn by the sponsor, in other cases the R&D process of an Orphan Medicinal Product (OMP) is interrupted with apparently no reason. Unfortunately, even if the European OMP Regulation (EC) No 141/2000[1] requires the sponsor to submit to the European Medicines Agency (EMA) an annual report on the state of development of the OMP (art 5), such reports are not public. Few analyses on the developmental status of OMPs and regulatory pathway have been published.[6,7,8,9] In conclusion, the real extent and reasons for the failures in the developmental process of OMPs in EU are currently mainly unknown.

The aim of this work is to identify the OMPs designated by the EMA that failed to reach the MA, and the reasons for their failure. We considered failed those drugs 1) with a refused or withdrawn MA (MA failures), and 2) abandoned by the sponsor during development (abandoned). In the first case, they reached the submission and/or the assessment from the Committee for Medicinal Products for Human Use (CHMP), but finally resulted failed because the MA approval was refused or the MA has been withdrawn; in the second case they did not reach the CHMP assessment.

We also investigated the stage of the R&D process at the time of its interruption and other possible factors influencing the failure.

METHODS

The sample we consider in our analysis is represented by OMPs designated in the period 2000-2012, and currently listed in the European Commission (EC) Register of OMPs.[10] We did not consider OMPs designated after 2012 since the beginning of drug clinical development may take 2-3 years from the designation to the inclusion of clinical trials in public databases.

Medicinal products (MPs) that received an ODD are included in the study (*Supplementary file*). We excluded from the analysis OMPs included in an MA Application (MAA) with a pending decision (last update: March, 31st 2016).

Information on the OMPs in Europe, in the considered period, has been derived from EuOrphan.[11,12] EuOrphan is a database containing information on OMPs and other medicines available on the market for rare diseases in both the EU and the US. It was created by the *Consorzio per Valutazioni Biologiche e Farmacologiche* (CVBF) within a funded European IT-Technology project (eTen 510774 2003/C 118/19), as previously described.[11,12] It is populated with data derived from official sources [13,14,15] and is regularly updated to allow analyses and statistical evaluations.

OMPs have been sorted by year of designation, disease area, type of sponsor (commercial or non-commercial), stage of development, age-related type of condition (affecting children or not).

Information on studies supporting the MA has been derived from official SmPCs, as catalogued by EuOrphan, and clinical trial databases (EU clinical trials register[16] and Clinicaltrials.gov[17]).

The following search strategy has been adopted to query clinical trial databases:

EU clinical trials register: <disease name> AND <drug name> OR Advanced Search <Orphan Designation Number>;

Clinicaltrials.gov: Advanced Search - Targeted Search: Conditions: <disease name> AND Interventions: <drug name>.

We considered trials in which the sponsor that obtained the ODD was mentioned as sponsor or collaborating organisation (e.g. company manufacturing the Investigational Medicinal Product-IMPs).

Literature data have been derived from a bibliographic search performed in PubMed[18] by using an ad hoc search strategy as follows.

Search terms. Keywords derived from Medical Subject Headings (MeSH) vocabulary thesaurus were used: (MeSH <drug name> AND MeSH <condition name>) OR (<drug name> AND <condition name>). Further keywords, e.g. synonyms or acronyms, were used when relevant.

Limits. The MeSH search was "restricted to MeSH Major Topic" and to search field "Title and abstract".

Subheadings of MeSH <condition name> were limited to: 'statistical and numerical data'; 'drug therapy' AND 'therapy' OR 'prevention and control according to the orphan indication'.

Subheadings of MeSH <drug name> were limited to: 'administration and dosage'; 'adverse effects'; 'drug effects'; 'pharmacokinetics'; 'pharmacology'; 'therapeutic use'; 'toxicity'.

We have considered only items published in English during the period ranging from the designation date to March 2016.

used sources and related investigated information are summarised in *Table 1*.

We assumed that the development of a drug was successfully completed if an MA has been issued by the EC. Failure is defined as an OMP not reaching marketing approval because: 1- the MA has been refused or withdrawn (MA failures); 2- the R&D process has been interrupted by the sponsor (abandoned).

We considered OMPs as abandoned by the sponsor during development if:

- no clinical trial has been published on the most relevant clinical trial databases (EU clinical trials register[16] and Clinicaltrials.gov[17]), in the literature (PubMed[18]), or on the official website of the sponsor during the last 3 years;

- clinical trials have been published, but the clinical development has been declared terminated by the sponsor, or the sponsor resulted inactive / in bankruptcy.

To investigate the reasons for failure, sponsor-sourced information (company websites and pipelines, direct communications with the sponsors) and information derived from clinical trial databases (EU clinical trials register[16] and Clinicaltrials.gov[17]) have been evaluated.

Two researchers performed the analysis and conflicts were solved through discussion or by asking the opinion of a third reviewer.

The correlation between the failure and the following factors has been analysed: year of designation, therapeutic area, type of sponsor (commercial or non-commercial), stage of development, condition (affecting children or not). The significance of the results has been checked with a chi squared test. The significance analysis has been performed using the R statistical software. The significance level of the tests was set to P=0.05.

RESULTS

Orphan Designations – current status

As shown in the flow chart (*Supplementary file*), 788 ODDs have been granted in EU during the period 2000-2012: 766 ODDs still are in the OMP register and 22 have lost the ODD after receiving the MA.

Overall, the R&D process was concluded with a successful MA in 132 cases (as detailed in the flowchart *Supplementary file*, 110 ODDs received an MA and are still listed in the OMP Register, 22 ODDs received an MA but the designation has been withdrawn) and with a withdrawn or refused MA in 34 cases (14 received a negative opinion and 20 had the MAA withdrawn by the sponsor); 437 ODDs resulted under R&D when we performed the analysis. For the remaining 185, the R&D process was considered interrupted if:

- no trials have been published in clinical trial databases during the last 3 years (130 ODDs) or;
- the R&D process has been declared terminated by the sponsor (55 ODDs).

Therefore, a total of 219 ODDs resulted in failure.

Data analysis by risk factors

We have organised data by year of designation (*Figure 1*), stage of development *(Figure 2)*, therapeutic area, type of sponsor, and age-related type of condition (*Table 2*).

Figure 1 shows that the number of failures gradually increases from 2000 to 2012.

Figure 2 emphasizes the developmental status of all ODD groups and shows a comparison among ODDs with an MA, ODDs in R&D, MA failures and abandoned ODDs. All the developmental phases are represented. Data on clinical trials revealed that, out of a total of 788 ODDs, 54 OMPs reached phase I, 270 reached phase II, 309 reached phase III and three were only included in compassionate use programmes (*Figure 2*).

No information about the stage of development of 106 ODDs was found.

Phase III studies prevail in the MA groups (including both ODDs with an MA and MA failures); both phases II and III are well represented in the R&D group while the abandoned group is characterised by a very high frequency of 'no studies/not classified studies'. In this group, the majority of ODDs apparently never started the developmental process, since for 89 out of 185 ODDs (48.1%) we found no data in literature, clinical trial databases or information from the sponsor. 6 out of 185 ODDs (3.2%) did not progress beyond the non-clinical stage, while 55 out of 185 ODDs (29.7%) were in phase II clinical trials when the developmental process stopped.

Our data show that the percentage of failures referring to a condition affecting adults and children and the percentage of failures referring to a condition affecting adults only are close to each other: 27.3% (166/609) and 29.6% (53/179) respectively (*Table 2*).

As detailed in *Table 2*, the highest percentage of failures (out of a total of 219 ODDs), occurred in renal, urinary and reproductive diseases and other diseases (40%), followed by cardiovascular and respiratory (37.3%), dermatological (35.7%), oncologic (31.7%), gastrointestinal (31.6%), neurological and psychotic (25.9%) and inborn errors of metabolism diseases (24.2%).

In particular, the rare conditions with the highest number of failures were in the oncology area and included: glioma (12), acute myelogenous leukaemia (11), pancreatic cancer (10), chronic lymphocytic leukaemia (7). In the respiratory group, 6 failures were for cystic fibrosis.

Concerning the sponsor, commercial sponsors receiving ODD are the most represented with 749 out of 788 ODDs (95.0%, *Table* 2), while non-commercial sponsors account for only 39 out of 788 ODDs.

In particular, 28.3% (212/749) of ODDs sponsored by commercial sponsors and the 17.9% (7/39) of ODDs sponsored by a non-commercial entity ended up in failures.

Finally, our analysis demonstrated that OMPs that completed (or reached) phase III have a reduced risk of failure ($P<0.01$).

Reasons for failures

As shown in *Figure 3*, lack of efficacy and safety has been identified as the main reason for failure of the developmental process. This aspect varies across therapeutic areas (*Figure 4*). For example, we have found that 42.5% (34 out of 80) of ODDs referred to oncologic diseases failed for efficacy/safety issues.

Other relevant causes for failure are economic issues and strategic decisions. Inactive companies (due to bankrupt) accounted for a large number of failures (47/185, 25.4%). In other cases, the development was abandoned because of a specific strategy; for example, 11 ODDs were abandoned during the developmental phase for other indications.

Moreover, the number of ODDs abandoned because of competitor drugs, such as other OMPs with an MA or under development for the same therapeutic indication, is considerable (20/185, 10.8%).

No information about the possible reasons for failure was available for 23.2% of abandoned ODDs (*Figure 3*). In this case, no conclusions can be drawn.

Interestingly, safety and efficacy issues are significantly more represented than other causes of failure in the ODD groups that reached MA. In these groups, commercial reasons were declared by the sponsor in just one case (1).

For the abandoned drugs, the main reasons for failure were efficacy/safety issues, reported in 54 cases. Other relevant causes were linked to sponsors, i.e. a) lack of data, b) inactive company, c) company strategy blocking the developmental process.

For MA failures, the identified reasons were: efficacy/safety issues (26), insufficient data (12), issues related with the quality of the IMP (e.g. manufacturing issues) (7), and regulatory issues on trials (4), such as trials without a control arm or not compliant with Good Clinical Practice (GCP) and/or no commercial protection (i.e. market exclusivity granted for other products

already authorised for the same condition). In just one case a commercial reason was declared by the sponsor (1). It is noticeable that in some cases more than one reason accounted for the failure.

DISCUSSION

Research and scientific progress in the rare disease field is challenging since a small number of patients are affected by such diseases, highly specialised research centres dealing with specific conditions are needed, and economic return is scarce.

Specific clinical studies may be long, costly, and difficult to be performed. Fagnan[19] reported that in recent years OMP trials take approximately 5.9 years from phase I to new drug application, with an additional 0.8 years required for the approval process, and that the revenue from the OMPs development is not perceived as justifying the cost of the clinical trials.

In our analysis, we have found that the number of ODDs gradually increases from 2000 to2012. This is consistent with the situation in the United States (US), where less than 14% of OMPs has received an MA by Food and Drug Administration (FDA), and an exponential increase of ODDs has been demonstrated up to 2013; concurrently, the annual number of orphan medicinal approvals has remained more or less constant.[20]

If we look at non-orphans, the recent EMA reports [21, 22] indicate that the percentage of Marketing Authorisation Applications (MAAs) receiving a positive opinion from EMA out of the total number of MAAs submitted is similar between orphan and non-orphan drugs in the last years: 59% and 73% respectively (2016); 83% and 89% respectively (2015); 85% and 86% respectively (2014).

The present analysis has shown that out of a total of **788 ODDs designated during the period 2000-2012, 132 received an MA, 437 are in R&D, and 219 have not reached MA: 34 failed**

the MA (refused or MAA withdrawal) and 185 were abandoned during the developmental process.

In particular, failures accounted for 27.8% of ODDs granted in Europe, including abandoned ODDs and MA failures.

Renal, cardiovascular, respiratory, dermatological, oncologic and gastrointestinal diseases, have the highest rate of failures, while poisoning/overdose and haematological diseases were characterised by a lower percentage of failures (16.7% and 14.5% respectively). However, differences were not significant. In line with our data, a publication from 2014 demonstrated that the success rate of market approval for OMPs developed by pharmaceutical companies is 21.8% and the success or failure of OMP development programmes may be unlikely correlated with the type of disease.[20]

Furthermore, we confirmed that most of the sponsors that obtained the ODD are commercial (about 90%), in line with a previous publication [12], while hospitals and universities obtained only 30 ODDs, mostly still under research (25).

We demonstrated that the stage of development represents the main factor influencing the success or failure of the R&D process of OMPs, since differences among various stages are statistically significant ($P < 0.01$). Most of the failures could not reach the clinical phase, especially if efficacy/safety issues arose. In fact, when in preliminary preclinical or early clinical studies both efficacy and safety issues were raised, the sponsors stopped the development due to a negative benefit/risk balance.

This demonstrates that completing the R&D process still remains a challenging issue for an orphan medicinal product. In particular, the development of abandoned OMPs for efficacy/safety issues was stopped in the preclinical phase in 20% of the cases and in phase I-II clinical studies in 48.1%.

Our data are in line with a very recent publication by Morel and coll.[9] demonstrating that the development of more than one hundred OMPs has been discontinued mainly in phase II.

Overall, our analysis shows that the main reasons for failure during the developmental phase are efficacy/safety issues (about 30%). For six OMPs the development was terminated after the discontinuation of trials, two recommended by the Data Safety Monitoring Committee (DSMC). Moreover, only a small part of refused MA and MAA withdrawals completed the developmental process when applying for an MA. This is in line with the known difficulties in providing the necessary evidences for OMPs approval when a standardized phase I to III scheme is followed. The second reason for failure is company inactivity / bankruptcy (about 25.4%), perhaps connected to the failure of the R&D program, especially in case of small companies whose efforts are mainly focused on a single OMP. About 51% of these abandoned OMPs was in the oncologic area. Often, small pharmaceutical companies may fail the developmental program of their lead OMP and consequently go bankrupt. This means that the bankruptcy may be the cause or even the resulting effect of the failure of the drug development.

Nevertheless, other relevant company-related causes of failure are shown in our study. Among them, drug competition plays one of the most important roles. Other OMPs with an MA or in development for the same therapeutic indication were the main causes for the discontinuation of the R&D process. Competitors in the developmental phase were found from both the same sponsor and other companies.

Economic issues and lack of funding related to OMP development (and not to the general economic trend of the company) accounted for a small part of the failures (3.2%), especially among oncologic, cardiovascular and respiratory diseases. For the majority of such OMPs, no clinical trial has been published on the main databases. These data support the relevance of incentive issues within the EU for drugs gaining the ODD under Regulation (EC) No 141/2000.[1] These drugs are entitled to receive incentives such as fee waivers/reduction, 10-

year market exclusivity, free of charge protocol assistance and public funding for research support. During the last years, the EC have planned research programmes, such as the Sixth and Seventh Framework Programmes and the ongoing Horizon 2020 to grant funding for OMP development. Importantly, additional funds are requested to be provided by each Member State [12]. This would have promoted the study of medicines for rare diseases by pharmaceutical companies, SMEs and research groups, as well as the creation of research consortia. This was proven to be successful for paediatric research [23]. It would be interesting to evaluate the mentioned measures within 5-10 years.

A small number of OMPs (8.1%) failed due to company strategy, e.g. change in the overall product development plan. In fact, most of them were found in development for other indications.

Other reasons for MA failures emerged, such as insufficient data, quality issues or issues on trials and products.

In the following paragraphs, strengths and weaknesses of this study are discussed.

One of the main difficulties in performing this kind of analysis is the lack of publicly available information. To overcome this issue, we directly contacted the sponsors to investigate the stage of development of OMPs and the reasons for failures, even when OMPs were still listed in the European OMPs Registry. Unfortunately, we cannot exclude that a drug we defined 'abandoned' is actually in the preclinical or clinical phase, but there is no evidence about that. However, this effort has only been partially successful. In particular, the search for information about failures of trials and OMP development faced some difficulties related to the availability of results. In fact, we have found no information about failures for 23.2% and about the stage of development of 48% of abandoned drugs. This aspect deals with the 'transparency' of results, a problem still under debate.

The European OMP Regulation[1] dictates that the developmental stage of OMPs has to be provided only to the EMA on a confidential basis. In addition, the EU clinical trial registry does not provide any detail about trial completion or discontinuation. On the contrary, public availability of trial results has been made mandatory in Europe by the new EU Regulation on clinical trials (EU) 536/2014 [24] requiring publication of summary of clinical trial results one year after the end of each trial, while respecting personal data protection and commercially confidential information. This should improve access to information, but the real outcomes of the new law will be clear only in the next years, also considering that the regulation allows pharmaceutical companies to censor clinical study reports before online publication.

Publication and availability for researchers of trial results and datasets still represent sensitive issues, as also underlined by Doshi and colleagues.[25] Data sharing allows clinicians to directly match the electronic health record of a patient to clinical trials and observational study data sets for better individualized therapeutic decisions. On the other hand, regulators are legally obliged to take timely decisions on the availability of drugs for patients, even under conditions of uncertainty, and personal data protection or patient confidentiality (i.e. issues completely different with respect to commercial confidentiality) are not easily to ensure, as uploading trial data on a website would entail its own problems, since an individual patient could be identified from an anonymized dataset.[26]

Hence, a step further to improve the availability of data without compromising the work of regulators and companies, personal data protection, patient and commercial confidentiality, may consist in publishing summaries of the main outcomes, being the publication of full trial reports probably unnecessary. Therefore, registries and databases like EuOrphan may be useful to better disseminate and make information available.

Another issue faced when performing the present study was related to sponsorship transfer. Over the years, 28.7% of sponsorships (226/788) has been transferred (data not shown) from the

sponsor obtaining the designation to the actual one, and this makes it more difficult to obtain reliable information.

Finally, this work allows to better understand the risks encountered by companies willing to develop OMPs.

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COMPETING INTERESTS

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: VG, AL, DB declare that part of this work was supported by an unrestricted grant from Celgene International II Sàrl; EB owns Celgene Stock Options (<0.00001%); no other relationships or activities that could appear to have influenced the submitted work.

AUTHOR'S CONTRIBUTION

V. Giannuzzi prepared the first draft of the manuscript and performed the analysis; A. Landi performed the analysis and contributed to the draft of the manuscript; E. Bosone reviewed data and solved conflicting results; F. Giannuzzi and S. Nicotri performed the statistical analysis and prepared figures, J. Torrent Farnell reviewed regulatory data and issues; Fedele Bonifazi contributed to set up of the methodology; M. Felisi performed a consistency check with data from European Public Assessment Reports (EPAR) on paediatric medicinal products and indications; D. Bonifazi provided a general revision of the paper; A. Ceci provided a general and final review of the draft.

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DATA SHARING STATEMENT

Unpublished data from the study are not available to anyone other than authors.

ABBREVIATIONS

CHMP: Committee for Medicinal Products for Human Use

GCP: Good Clinical Practice

DSMC: Data Safety Monitoring Committee

EC: European Commission

EMA: European Medicines Agency

EPAR: European public assessment reports

EU: European Union

FDA: Food and Drug Administration

IMP: Investigational Medicinal Product

MA: Marketing Authorisation

MAA: Marketing Authorisation Application

MeSH: Medical Subject Headings

MP: Medicinal product

ODD: Orphan Drug Designation

OMP: Orphan Medicinal Product

R&D: Research and Development

SmPCs: Summaries of Product Characteristics

US: United States

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TABLES

Table 1 *– Sources used for the analysis and information investigated.*

SOURCE	INFORMATION
EuOrphan (EMA, Orphanet)	- Active substances designated as OMP; - ODDs with a MA; - ODDs withdrawn with a MA; - Dates of designation; - Rare condition(s); - Orphan indication(s) - First and current sponsors; - MA refusals and MAA withdrawals; - Reasons for withdrawals or refusals; - Clinical trials and other evidence supporting the MA - Possible competitors, i.e. other OMPs for the same indication.
Clinical trial databases (EU clinical trials register and Clinicaltrials.gov)	- Published clinical trials - Reasons for prematurely ended clinical trials
PubMed	- Published clinical trials and other studies in literature - Efficacy and safety data
Sponsor-sourced information (company websites and pipelines, direct communications with the sponsors)	- Sponsor type (commercial or non-commercial) - Stage of development of the drug - Reasons for failures

Table 2 – *Orphan drug designations by risk factors.*

RISK FACTORS	N. ODDs with a MA	N. R&D	N. FAILURES		TOT	% FAILURES
			MA failures	Abandoned		
Age related type of condition						
Not affecting children	24	102	8	45	**179**	**29.6%**
Affecting children	108	335	26	140	**609**	**27.3%**
Therapeutic Area						
Cardiovascular and respiratory diseases	10	37	3	25	**75**	**37.3**
Dermatological diseases	1	8	1	4	**14**	**35.7**
Endocrine diseases	6	16	1	4	**27**	**18.5**
Gastrointestinal diseases	2	11	0	6	**19**	**31.6**
Haematologic diseases	12	35	0	8	**55**	**14.5**
Inborn errors of metabolism diseases	32	37	6	16	**91**	**24.2**
Infectious and immunitary system diseases	8	58	1	19	**86**	**23.3**
Neurological and psychotic diseases	9	54	2	20	**85**	**25.9**
Oncologic diseases	49	147	17	74	**287**	**31.7**
Ophthalmic diseases	1	22	1	4	**28**	**17.9**
Poisoning/overdose diseases	0	5	1	0	**6**	**16.7**
Renal, urinary and reproductive diseases	0	3	1	1	**5**	**40**
Others	2	4	0	4	**10**	**40**
Sponsor type						
Commercial	132	405	34	178	**749**	**28.3**
Non-commercial	0	32	0	7	**39**	**17.9**
Sponsorship transferred	40	117	16	53	**226**	**30.5**

FIGURES

Figure 1 - Distribution of orphan designations by year.

Figure 2 - Stage of development reached by ODDs with a MA and MA failures (on the top) and ODDs resulting in R&D and abandoned (on the bottom). Statistical differences between stages of development were determined using a chi squared test (*P < 0.01).

Figure 3 - Reasons for failures of abandoned drugs (left) and Marketing Authorisation failures (right).

Figure 4 - Failures for efficacy and safety issues across therapeutic areas.

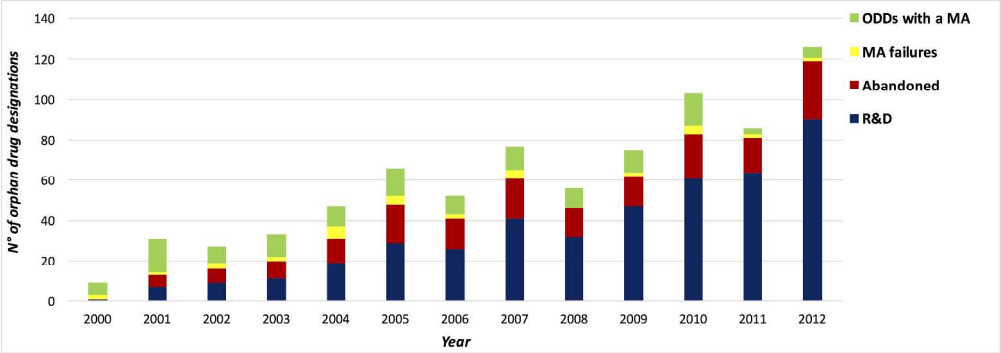

Figure 1

404x142mm (300 x 300 DPI)

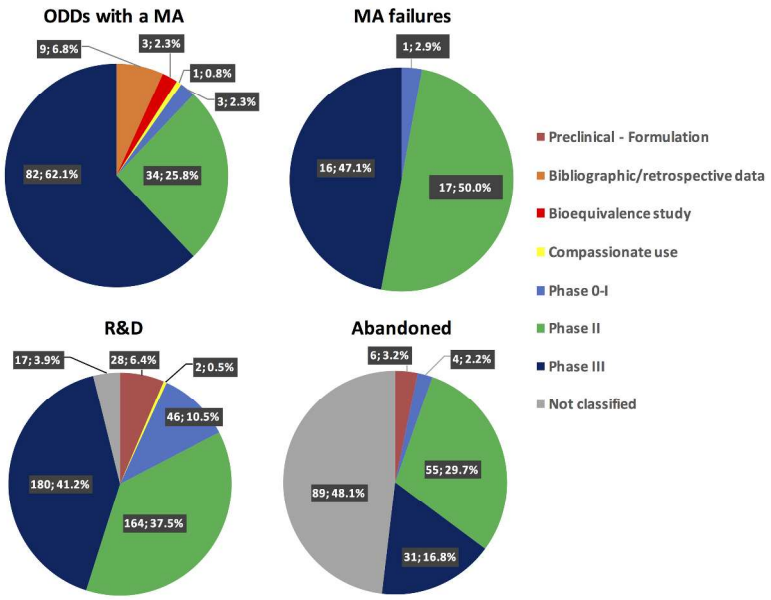

Figure 2

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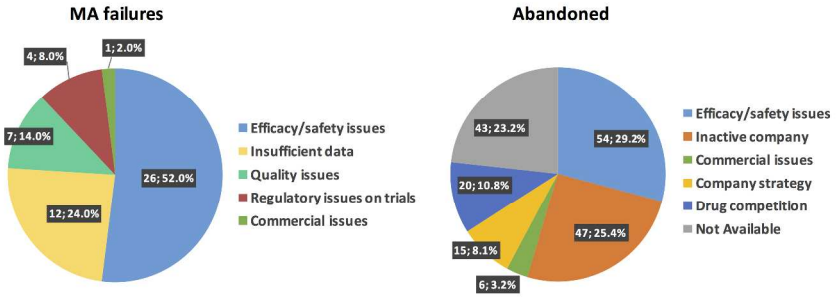

Figure 3

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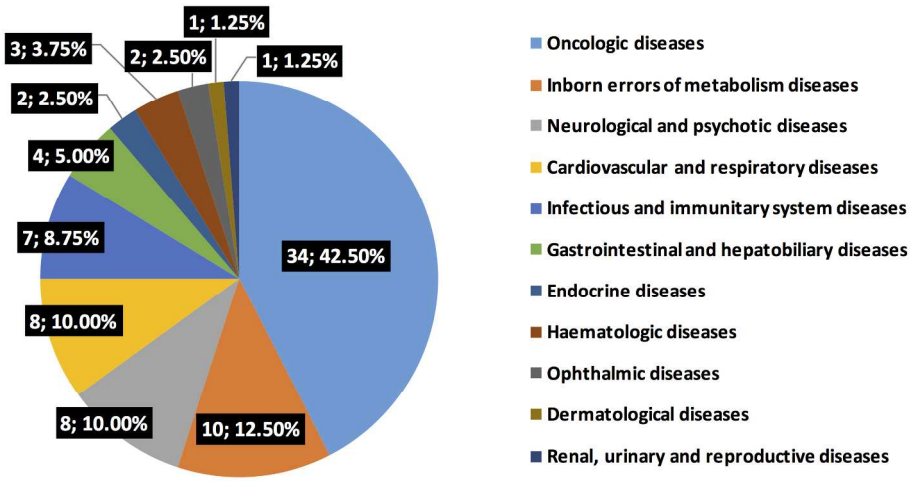

Figure 4

227x110mm (300 x 300 DPI)

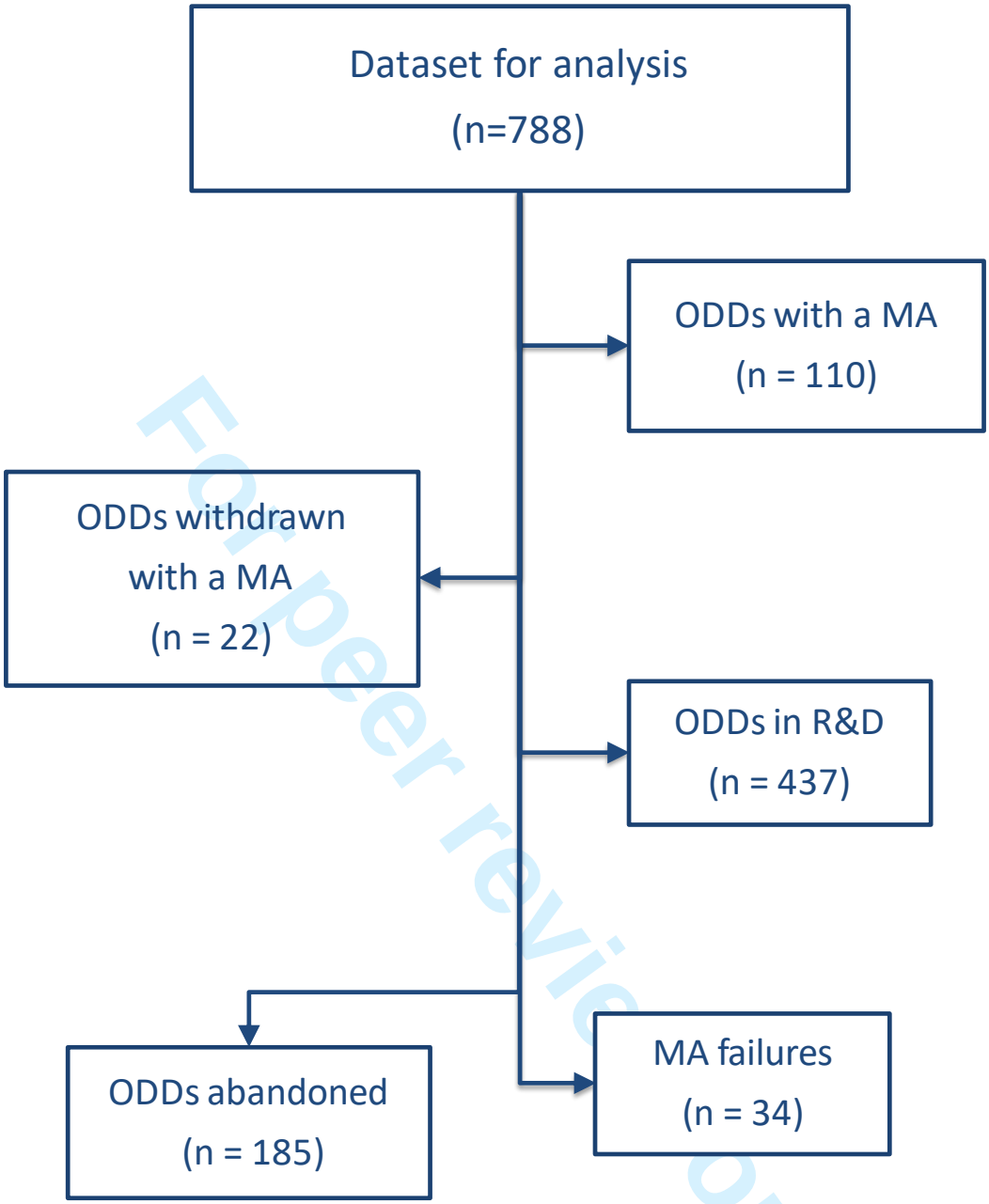

Figure 1 *- Flow chart of the dataset (in brackets the number of designations released between 2000-2012). We included 766 orphan designations currently present in the OMPs European Register and 22 OMPs that lost the designation over the year.*