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Safety-Related Regulatory Actions for Orphan Drugs in the US and EU

A Cohort Study

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Abstract

Background: Drugs for rare diseases, so-called orphan drugs, are often intended for serious or chronically debilitating diseases. Safety information is more limited at the time of approval for orphan drugs as a result of various factors, such as the limited number of patients in clinical trials, quality of the clinical trials and special approval procedures. Several studies have been conducted on safety-related regulatory actions for drugs, but none of these have specifically focused on orphan drugs.

Objective: To determine the frequency and nature of safety-related regulatory actions for orphan drugs in the US and EU.

Methods: This cohort study examined publicly available data from the websites of US and EU regulatory authorities on orphan drugs approved in the US and/or the EU between January 2000 and December 2007. The main outcome measures were the nature, frequency and timing of safety-related regulatory actions, defined as (i) safety withdrawals; (ii) 'black-box' warnings; and (iii) written communications to healthcare professionals issued by the US FDA or the European Medicines Agency between January 2000 and June 2008.

Results: Ninety-five orphan drugs were approved during the study period (75 in the US, 44 in the EU, and 24 in both regions). Ten products (10.5%) received a safety-related regulatory action. No safety withdrawals, four black-box warnings and 12 written communications were identified. The probability of a first safety-related regulatory action for orphan drugs was 20.3% after 8 years of follow-up. Orphan drugs approved by accelerated approval (relative risk [RR] 3.32; 95% CI 1.06, 10.42), oncological products (RR 7.83; 95% CI 0.96, 63.82) and products for gastrointestinal and metabolism indications (RR 10.44; 95% CI 1.25, 87.27) may have a higher risk for a safety-related regulatory action.

Conclusions: The probability of a first safety-related regulatory action for an orphan drug was slightly lower than that reported in the literature for biologicals in one study and new molecular entities in another study. However, detection of safety issues may be complicated by the limited experience with orphan drugs in practical use due to the low prevalences of the diseases they are used for. Doctors and pharmacists should therefore be vigilant with regard to the occurrence of a safety-related issue for orphan drugs.

Orphan drugs are drugs indicated for the treatment, prevention or diagnosis of rare diseases. The number of approved orphan drugs is growing steadily since the enactment of dedicated orphan drug regulations in both the US[1] and the EU.[2] These drugs are often intended for serious or chronically debilitating diseases, for which no suitable treatment has previously been approved. In the EU, these are criteria that are required to become designated as an orphan drug,[2] whereas in the US about 85% of orphan drugs are being used for serious and/or life-threatening diseases.[3] In contrast to other drugs, these drugs are intended for use in smaller populations and, moreover, the severity of the diseases means that there is usually a high medical need for treatments for these indications.

Because of the small numbers of patients, clinical trials are often conducted with few subjects.[4-7] Therefore, the clinical development of these drugs may not have been performed as thoroughly as that for other drugs. Clinical experience of an orphan drug at the time of marketing may thus be fairly limited, with the result that knowledge on the safety profile of approved orphan drugs may be less than that for other drugs.[8-10] Consequently, unexpected safety issues may emerge more frequently during use in daily practice for orphan drugs compared with other drugs. Table I lists certain characteristics of orphan drugs that may affect the likelihood of a safety-related event. However, the high medical need for most of these orphan drugs apparently justifies approval of the product based on the available data. As with other drugs, the safety of an orphan medicinal product is carefully monitored post-approval and, if necessary, regulatory authorities will take actions to protect public health.

Studies investigating the frequency and nature of post-approval, safety-related regulatory actions have been conducted by Giezen et al.[13] in 2008 and Lasser et al.[14] in 2002. Another study evaluated post-authorization safety studies as proposed at the time of regulatory approval.[15] None of these studies focused on orphan drugs. However, within the study by Giezen et al.,[13] 17 of 30 (57%) biologicals that obtained a 'Dear Healthcare Professional' letter (DHPL) from the US FDA, and 11 of 17 (65%) biologicals with a 'black-box' warning were orphan drugs, whereas none of the biological orphan drugs received a

Table I. Characteristics of orphan drugs that may affect the likelihood of a safety-related event

Many orphan drugs are biologicals or new chemical entities based on innovative new molecules or delivery mechanisms[3,11,12] that may have a higher chance of unexpected safety events[9]
Many orphan drugs are intended for the treatment, diagnosis or prevention of chronic or serious diseases in patients that may be more prone towards adverse events[3]
Many orphan drugs are approved based on very small-scale clinical trials, and clinical experience with orphan drugs is often limited at the time of marketing approval. Consequently, knowledge of the safety of the product is limited[4,5]
Only 57% of approved orphan drugs have been tested in a randomized clinical trial before approval.[5] In addition, Joppi et al.[4,5] describe several other deficiencies on the clinical development of orphan drugs, including lack of active controls, use of incorrect surrogate parameters and duration of trials that are too short, all of which contribute to the limited availability of clinical experience with an orphan drug
Large numbers of orphan drugs are approved as an accelerated approval (US), under exceptional circumstances (EU) or as a conditional approval (EU), possibly limiting the availability of pre-approval safety information[5]

direct healthcare professional communication (DHPC) from the European Medicines Agency (EMEA).[13] In the study by Lasser et al.,[14] 6 of the 45 (13%) black-box warnings for new molecular entities were issued for FDA-approved orphan drugs;[14] however, comparable figures on the entire group of orphan drugs are not known.

In this study, we therefore aim to determine the frequency and nature of safety-related regulatory actions for all orphan drugs approved in the US and/or EU from the initiation of the EU Regulation on Orphan Medicinal Products in January 2000.[2] Moreover, we determine whether the occurrence of safety-related regulatory actions is related to the type of molecule (biological or small molecule), type of approval and indication class.

Methods

We have included all medicinal products with an orphan designation in the US, the EU, or both regions, that have been approved for their first indication between the enforcement of the EU 'Regulation on Orphan Medicinal Products' in January 2000 to December 2007 and for which their first approved orphan indication was also within this time period. For a list of orphan drugs approved in the US and/or the EU included in this study, with further detail and approval dates, please see the Supplementary Digital Content at http://links.adisonline.com/DSZ/A21. An orphan indication was defined in this study as an indication forthcoming from an official orphan designation by the FDA or the EMEA. For most orphan drugs, the first registration is also the registration for an orphan indication, but some drugs were approved for another indication before approval for an orphan indication.

For the period January 2000 to June 2008, important safety-related regulatory actions that required urgent communication were identified, such that, for all products, at least 6 months follow-up time could be observed. Safety-related regulatory actions were classified as follows:

- Safety-related market withdrawals (US and EU).
- Post-approval black-box warnings (US).
- Written communications to healthcare professionals (DHPLs [US only] or DHPCs [EU only]).

DHPLs were identified from MedWatch (www.fda.gov/medwatch), and DHPCs were identified from the website of the Medicines Evaluation Board in the Netherlands (www.cbg-meb.nl) and European Public Assessment Reports of the EMEA (www.emea.europa.eu). The date of the letter was used as the date of the safety-related regulatory action. Letters not including safety warnings and follow-up letters of previously issued letters containing no new safety information were excluded.

Post-approval black-box warnings were identified from the labels available from the websites of the FDA Center for Drug Evaluation and Research (CDER) (www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm), MedWatch and the marketing authorization holder. The latest approved label of every orphan drug available from the CDER was searched for a black-box warning. Where a black-box warning was identified from the latest approved label, previously approved labels were checked to identify the date the black-box warning was added, which was crosschecked with the information from MedWatch. The date of the black-box warning stated on the websites of the CDER or MedWatch was included in the analysis. Where the exact date of the black-box warning could not be identified, the latest possible date the black-box warning was issued was included in the analysis.

The nature of the safety-related regulatory action was coded at the System Organ Class (SOC) level according to the Medical Dictionary for Regulatory Activities (MedDRA) version 11.1. Moreover, for each of the selected products, information was collected on the following variables: region of approval, type of molecule, approval circumstances and indication of the product. For the region of approval, products could be approved in the US, the EU or both regions. The type of molecule could be biological (extracted or produced from living organisms[11]) or a small molecule. Two groups of approvals were defined: (i) accelerated approvals, defined

Table II. Nature and timing of orphan drugs with a post-approval, safety-related regulatory action in the US and EU

Active substance	Registered trade name	Approval date for first orphan indication	Warning	System organ class	Time to safety-related regulatory action (y)	Region of marketing approval	Safety issue included in SPC (EU) or label text (US)
Black-box warnings							
Cetuximab	Erbitux®	12 February 2004	Cardiopulmonary arrest	Cardiac disorders	2.0	US and EU[a]	In SPC since 27 February 2007
Gemtuzumab ozogamicin	Mylotarg®	17 May 2000	Hypersensitivity reactions, including anaphylaxis, infusion reactions, pulmonary events/hepatotoxicity	Immune system disorders/hepatobiliary disorders	0.8	US	
Ibritumomab tiuxetan	Zevalin®	19 February 2002	Severe cutaneous and mucocutaneous reactions	Skin and subcutaneous tissue disorders	3.6	US and EU[a]	In SPC since 15 November 2005
Laronidase	Aldurazyme®	30 April 2003	Life-threatening anaphylactic reactions	Immune system disorders	5.0	US and EU	Included in original SPC, 10 June 2003
Dear Healthcare Professional Letters							
Sodium phenylacetate/ sodium benzoate	Ammonul®	17 February 2005	Detection of particulate matter in injection product	Injury, poisoning and procedural complications	3.6	US	
Bosentan	Tracleer®	20 November 2001	Reminder of the importance of monthly liver function testing due to cases of hepatotoxicity	Investigations	4.3	US and EU	Included in original SPC, 15 May 2002
Cetuximab	Erbitux®	1 March 2006	Hypomagnesia/infusion reactions	Metabolism and nutrition disorders/general disorders and administration site conditions	1.6	US and EU[a]	Included in SPC since 13 September 2005, updated 27 February 2006
Deferasirox	Exjade®	2 November 2005	Risk for renal failure	Renal and urinary disorders	1.5	US and EU	Included in original SPC, 28 August 2006
			Risk for hepatic failure	Hepatobiliary disorders	2.1		Included in SPC since 25 July 2008
Ibritumomab tiuxetan	Zevalin®	19 February 2002	Severe cutaneous or mucocutaneous reactions	Skin and subcutaneous tissue disorders	3.7	US and EU[a]	In SPC since 15 November 2005
Imatinib	Gleevec®	10 May 2001	Severe congestive heart failure and left ventricular dysfunction	Cardiac disorders	5.4	US and EU	Direct Health Professional Communication on 11 December 2006
Zoledronic acid	Zometa®	20 August 2001	Dosage adjustments in patients with multiple myeloma and metastatic bone lesions from solid tumours	Surgical and medical procedures	3.1	US and EU[a]	Included in original SPC, 20 March 2001
			Osteonecrosis of the jaw	Musculoskeletal and connective tissue disorder	3.7		Included in original SPC, updated on 6 January 2006
			Atrial fibrillation	Cardiac disorders	6.1		Included in SPC since 19 October 2007

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Table II. Contd

Active substance	Registered trade name	Approval date for first orphan indication	Warning	System organ class	Time to safety-related regulatory action (y)	Region of marketing approval	Safety issue included in SPC (EU) or label text (US)
Direct Healthcare Professional Communications							
Imatinib	Glivec®	7 November 2001	Preclinical carcinogenicity findings	Neoplasms benign, malignant and unspecified	3.4	US and EU	Included in the label since 16 December 2004
			Heart failure and left-ventricular dysfunction	Cardiac disorders	5.1		Dear Healthcare Professional Letter on 19 October 2006
Miglustat	Zavesca®	20 November 2002	Preclinical carcinogenicity findings in rats and mice	Neoplasms benign, malignant and unspecified	4.4	US and EU	Included in the label since 29 February 2008

a Indicates the drug is approved in the EU but has not obtained orphan status.

SPC = summary of product characteristics.

as accelerated approvals (US only), conditional approvals or approvals under exceptional circumstances (both EU only); and (ii) other approvals. Finally, data on time between the first approval (orphan or regular) and the regulatory action was determined. For every unique approved product, only the data on the first approval were included in the study. Unique products were defined as products with the same active compound, indication and sponsor.

Kaplan-Meier survival curves were plotted to estimate the probability of the occurrence of a first safety-related regulatory action for the total group of orphan drugs, and by region (US and EU) and type of warning (written communications and black-box warnings). The proportional hazard assumptions proved not to be valid for some of the variables of interest. Therefore, cumulative incidence rates at the end of the study after 8.5 years, relative risks (RR) and corresponding 95% confidence intervals (CIs) were calculated for the risk of a first safety-related regulatory action for the orphan drugs with each of the above-mentioned variables.

Results

Between January 2000 and December 2007, 75 orphan drugs were approved in the US and 44 in the EU. Of these products, 24 were approved as orphan drugs in both regions, resulting in a total group of 95 unique products. Median follow-up time was 3.7 years (range 0.6–8.3 years). For ten (10.5%) of the products included in the study, one or more safety-related regulatory actions were identified. No safety-related withdrawals were observed during the study period. Of the 75 products that were approved in the US, seven products obtained a total number of ten DHPLs (table II). In addition, two of these products and two other products received a black-box warning (table II). Of the products that obtained a regulatory action, sodium phenylacetate/sodium benzoate (Ammonul®) obtained a DHPL with a warning for particulate matter in the infusion product, while bosentan (Tracleer®) obtained a DHPL reminding physicians of the importance of

liver function tests. The remaining seven products received boxed or written warnings regarding newly detected safety risks, such as infusion reactions and immunological reactions. Of the 44 products that were approved in the EU, two products received a total of three DHPCs by the EMEA, of which two were for imatinib (Gleevec®/Glivec®), which also received a DHPL from the FDA (table II). In addition, of the 13 safety-related regulatory actions unique for US-approved products, five of the underlying safety-issues were already included in the original summary of product characteristics (SPC), while six resulted in a change in the SPC around the time of the regulatory action and two were for products not approved in the EU. Both safety-related regulatory actions unique for EU-approved products resulted in a change in the US label text (table II).

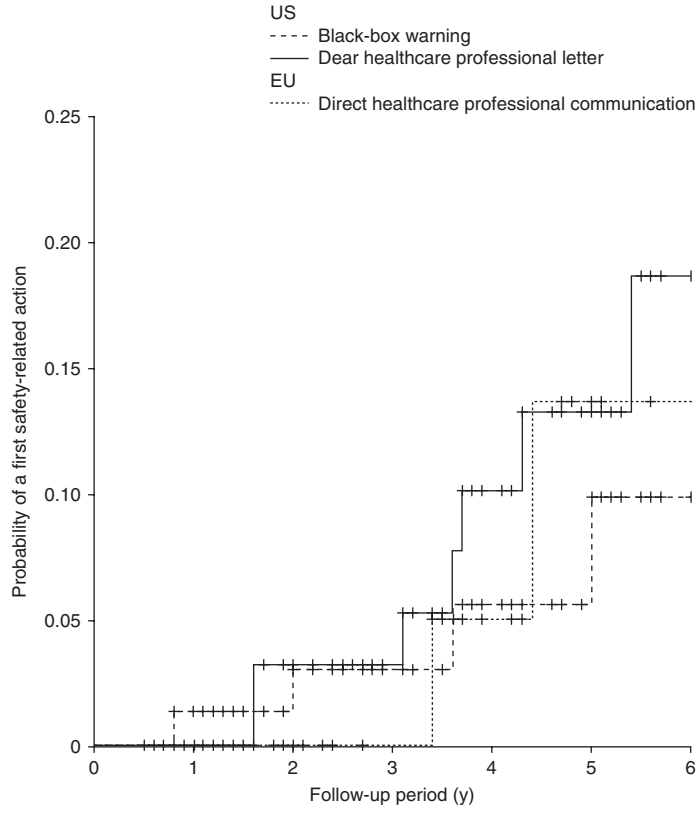
Safety-related regulatory actions for the orphan biologicals included two actions classified at the SOC level as immune system disorders, and two as skin and subcutaneous tissue disorders, although the latter involved one product. Actions for the small molecule orphan drugs included three actions classified at the SOC level as cardiac disorders and two as neoplasms, benign, malignant and unspecified (table II).

The overall probability for obtaining a first safety-related regulatory action for orphan drugs was 3.5% after 3 years of follow-up and 20.3% after 8 years of follow-up. Figure 1 shows the probabilities to obtain a first safety-related action (written communication or black-box warning) for orphan drugs approved in the US or EU. For the orphan drugs approved in the US, the probability, after 6 years, to obtain a first DHPL was 18.6% and for a black-box warning, the probability was 10.0%. For orphan drugs approved in the EU, the probability of a DHPC after 6 years was 13.6%. Table III provides an overview of the characteristics of the orphan drugs included in the study. Biological orphan drugs do not have a statistically significantly higher RR to obtain a safety-related regulatory action compared with small molecules (RR 1.68; 95% CI 0.51, 5.49). Of the 95 orphan drugs in the study, 22 were approved under accelerated conditions, either as an accelerated approval (n = 11) by the FDA, or as a conditional approval (n = 2) or an approval under exceptional circumstances (n = 10) by the EMEA. The RR for these products approved in an accelerated course was 3.32 (95% CI 1.06, 10.42) compared with otherwise approved products. Finally, of all ten products with at least one safety-related regulatory action issued by the FDA or the EMEA, five were oncological orphan drugs (Anatomical Therapeutic Chemical [ATC] class L01/L02) and four were indicated for gastrointestinal or metabolic diseases (ATC class A). The RR to obtain a first safety-related regulatory action for oncological products was 7.83 (95% CI 0.96, 63.82), and the RR for gastrointestinal and metabolic diseases was 10.44 (95% CI 1.25, 87.27) compared with products indicated for other disease classes. In a separate analysis, we compared the RR to obtain a DHPC for the European orphan drugs (n = 44) with the risk of obtaining a DHPL for the US orphan drugs (n = 75). In the current study, it was found that EMEA-approved orphan drugs may have a lower risk (RR 0.49) for a written safety communication than FDA-approved orphan drugs, although this was not statistically significant (95% CI 0.11, 2.24).

Discussion

In the current study, we found the probability of obtaining a first safety-related event to be 3.5% after 3 years and 20.3% after 8 years for all orphan drugs. We found no statistically significant association between the region of approval of an orphan drug or the type of molecule of the product and the risk for a safety-related regulatory action. However, we did find an association of a higher risk for orphan drugs approved under accelerated circumstances and with orphan drugs intended for gastrointestinal and metabolic indications. In addition, orphan drugs intended for oncological indications may also have an increased risk of a safety-related regulatory action.

Our results indicate a slightly lower frequency and probability of safety-related regulatory actions for orphan drugs than was found for biologicals by Giezen et al.[13] and than that found for



Number of orphan drugs at risk							
US							
Black-box warning	75	70	59	45	33	22	13
Dear healthcare professional letter	75	62	58	46	33	21	11
EU							
Direct healthcare professional communication	44	38	27	20	14	8	4

Fig. 1. Kaplan-Meier analysis of the probability to obtain a first safety-related regulatory action for orphan drugs.

new molecular entities by Lasser et al.[14] Giezen et al.[13] found the probability of a first safety-related regulatory action, including written communications to healthcare professionals in the US and the EU, and black-box warnings in the US, was up to 29%, 10 years after the approval, and 27%, 8 years after the approval, for biologicals in general, including orphan biologicals (Giezen TJ, unpublished observations, and Giezen et al.[13]). Distributed by the type of safety action, probabilities after 6 years were 23% for a DHPL, 13% for a black-box warning and 10% for a DHPC in the study by Giezen et al.[13] Moreover, Lasser et al.[14] found the probability of a black-box warning or withdrawal due to a safety reason was up to 9% for new molecular entities, 6 years after approval.[14]

Given the severe nature of many of the diseases for which these drugs are indicated, the number of safety-related regulatory actions is relatively low. One may therefore be tempted to conclude that orphan drugs are relatively safe drugs. However, the results presented should be interpreted with caution since practical use is different for orphan drugs compared with other drugs; consequently, knowledge on adverse

Table III. Relative risks and corresponding 95% CIs for the risk of a first safety-related regulatory action for orphan drugs

Characteristics of selected orphan drugs	Total number of orphan drugs (n = 95)	No. of orphan drugs with a safety-related regulatory action	Median follow-up time [y (range)]	Event rate	Relative risk (95% CI)
Type of molecule					
Small molecule	68	6	3.7 (0.6–8.2)	0.09	1 (reference)
Biological	27	4	3.7 (0.8–8.3)	0.15	1.68 (0.51, 5.49)
Approval circumstances					
Normal approval	73	5	3.8 (0.6–8.3)	0.07	1 (reference)
Accelerated approval (accelerated [US only], exceptional or conditional [EU only])	22	5	3.5 (0.8–7.2)	0.23	3.32 (1.06, 10.42)
Indication group of the orphan drug					
Other indications	47	1	3.9 (0.8–8.3)	0.02	1 (reference)
Gastrointestinal and metabolism (ATC class A)	18	4	3.9 (0.6–8.0)	0.22	10.44 (1.25, 87.27)
Oncology (ATC class L01/L02)	30	5	3.3 (0.7–7.8)	0.17	7.83 (0.96, 63.82)
Region of approval[a]					
US	75	7	2.6 (0.6–6.9)	0.09	1 (reference)
EU	44	2	3.7 (0.5–8.3)	0.05	0.49 (0.11, 2.24)

a Limited to written safety communications.

ATC = Anatomical Therapeutic Chemical.

effects may still be incomplete, even in the years after approval. For orphan drugs, real-life utilization of the product still only involves relatively modest numbers of patients. This is illustrated by the numbers of study subjects in pivotal trials, as reported by Joppi et al.[4] and their estimated treatment populations. For example, two orphan drugs that are available for the treatment of Fabry's disease (agalsidase alfa [Replagal®, EU only] and agalsidase beta [Fabrazyme®]) have been studied in pivotal trials with 41 and 56 patients, respectively.[4] The prevalence of this disease is 1 in 40 000, resulting in an estimated maximum treatment population of 7500 patients in the US and 12 500 in the EU. Another example is the orphan drugs approved for the treatment of pulmonary arterial hypertension, a disease with a prevalence of 6–15 per million.[16] For this disease, five orphan medicinal products were approved in the EU (corresponding number of patients in pivotal trials): ambrisentan (Volibris®, 261 patients); bosentan (Tracleer®, 32 patients); iloprost (Ventavis®, 203 patients); sildenafil (Revatio®, 278 patients); and sitaxentan (Thelin®, 516 patients).[4,17] It should be noted that the number of patients actually treated with an orphan drug is usually much lower than the calculated prevalence of the indication.[18] As a consequence of this, the chances of finding serious adverse drug effects during clinical use are not very high and, consequently, safety-related regulatory actions may be taken later than would be expected.[9,10] Thus, the fact that we find lower frequencies of safety-related regulatory actions does not necessarily mean that the risks are less for orphan drugs.

This is best illustrated by the two ATC classes of orphan drugs that we identified with a higher risk for a safety-related regulatory action compared with orphan drugs in other ATC classes (oncological indications; gastrointestinal and metabolic indications). These two classes are being represented by drugs with a relatively high utilization. Oncological orphan drugs are a special class in this respect. Although indicated for rare indications, these drugs are generally focused on a wide range of rare oncological indications, in trials before approval, but also after approval by way of indication extensions for other rare oncological indications. In addition, many of these products are frequently used for off-label indications, which further increases clinical experience.[12] An important example in this group, imatinib (Gleevec® [US]/Glivec® [EU]), has been

on the market in the US since May 2001 and in the EU since November 2001. From that time, the initial indication has been extended to encompass a wide range of oncological indications and thus it is being used in the treatment of large numbers of patients.[19] The amount of clinical experience that has been built with this drug is therefore relatively large.[20] It is the only orphan drug on the market in both the EU and the US that obtained a safety warning in both regions, a DHPL in the EU and a DHPC in the US. For orphan drugs that are used by large patient populations, the chances of detecting any safety issues are higher. This illustrates the relationship between clinical experience with a drug and the identification of risk and thus the obtaining of a safety-related regulatory action.

Moreover, a large number of orphan drugs have been approved as an accelerated approval by the FDA, or under exceptional circumstances or as a conditional approval by the EMEA. These are all dedicated approval programmes aimed at making available promising products for life-threatening diseases, based on preliminary evidence prior to formal demonstration of patient benefit.[21,22] Therefore, these approvals usually involve a high number of postmarketing obligations in which the sponsor must demonstrate safe and efficacious use of the product for the intended indication in a larger than normal number of patients. The higher risk of these products for a safety-related regulatory action may therefore be a consequence of both the even more limited knowledge on the safety profile of these products and the close monitoring of use in daily practice, as part of the postmarketing obligations for these products. To ensure adequate pharmacovigilance involving orphan drugs, several manufacturers now have dedicated risk-management strategies in place, the aim of which is to ensure a more sensitive detection of adverse events,[23,24] or they are exploring ways of using pharmacogenomics as part of pharmacovigilance,[25] while other manufacturers base their risk management strategies on spontaneous reporting of adverse events.[24] Further improving dedicated pharmacovigilance for orphan drugs will be the next step that we will hopefully be able to explore further in the upcoming years. Recently presented plans by the EMEA and FDA to improve pharmacovigilance and risk management may play a role in this.[26-28]

The relatively large share of safety-related regulatory actions classified as immune system disorders for orphan biologicals is also observed by Giezen et al.[13] in their study on biologicals. Moreover, most regulatory actions for small-molecule orphan drugs were classified as cardiac disorders, which correlate to the findings for new molecular entities as found by Lasser et al.[14] Consequently, based on the limited data available, the nature of safety-related regulatory actions for orphan drugs does not seem to be different from other, non-orphan drugs.

Lasser et al.[14] suggest that clinicians should be reluctant to use new drugs when older, safer alternatives are available, and that patients should be informed about the risks of new drugs. This is exactly the challenge that clinicians face when treating a patient with an orphan drug. The same applies to regulators when assessing a potential orphan drug. However, alternatives are usually not available for the treatment of serious and chronically debilitating rare diseases. Consequently, the assessment of benefits and risks for an orphan drug may be more positive given the amount of information available compared with that for regular drugs. The large number of accelerated approvals for orphan drugs also illustrates this. The fact that a treatment is available for a specific rare disease is often already a large step forward for doctors and patients.

A number of limitations of the present study should be addressed. First, the relatively short duration of follow-up for some of the products, the relatively small sample size and, consequently, the small number of safety-related regulatory actions identified, resulting in broad and non-significant 95% CIs, makes interpretation of non-statistically significant findings challenging. However, it was decided only to include orphan drugs from the year 2000 onwards because that was the time the European Regulation on Orphan Medicinal products commenced and, consequently, the presented data are all that was available from that time. Second, definitions of

orphan drugs differ slightly between the US and the EU, which may partly explain the larger number of users of orphan drugs in the US and subsequent relatively larger number of safety warnings. Third, the lower numbers of safety-related regulatory actions in the EU may also be caused by the fact that in the EU, a number of the underlying safety issues were already included in the SPC at the time of approval, or were updated in the SPC when the safety issue became known. The latter indicates a different risk perception by the regulatory authorities, for which no urgent action was needed. Finally, these changes in the SPC (EU) or drug labels (US, except black-box warnings) have not been included in this study. The reason for this was that we were interested in the major safety-related regulatory actions issued, which are, in our opinion, covered by withdrawal of the product, a black-box warning in the US, or the dissemination of a DHPL in the US or DHPC in the EU. These additional safety warnings were therefore beyond the scope of the study.

Conclusion

This study has determined the nature and frequency of safety-related regulatory actions for orphan drugs in the US and the EU. Although we found slightly lower frequencies and probabilities of safety-related regulatory actions for orphan drugs than those presented for biologicals in one study or new molecular entities in another study, it is clear from the above that these actions issued on orphan drugs are just the tip of the iceberg. Issuing safety-related regulatory actions is based on the early detection and communication of safety issues. The lower utilization of these drugs, however, also means that the chances for detection of a safety issue are lower. The slightly lower numbers of safety-related regulatory actions reported for orphan drugs therefore do not indicate a greater safety for orphan drugs. In particular, orphan drugs approved in an accelerated procedure and orphan drugs indicated for oncological and gastrointestinal and metabolic indications have an increased risk for a safety-related regulatory action. However, these may be explained by higher utilization or monitoring and, consequently, higher chances for detection of a safety issue, of these groups of drugs. Doctors and pharmacists should therefore be vigilant with regard to the chance of occurrence of a safety-related issue for orphan drugs.

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