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Drug Registries and Approval of Drugs: Promises, Placebo, or a Real Success?

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ABSTRACT

Purpose: As part of the approval process, regulatory authorities often require postauthorization studies that involve patient registries; it is unknown, however, whether such registry studies are adequately completed. We investigated whether registry studies for new drugs were performed as agreed at time of approval.

Methods: This study reviewed protocols and follow-up reports for 73 registry studies that were proposed for 43 drugs approved by the Committee for Medicinal Products for Human Use in Europe in the period 2007 to 2010.

Results: The data lock point of January 1, 2016, was taken to allow a 5-year follow-up period for each drug after approval. At that time, 2 studies (3%) in registries had been finalized, 19 registries (26%) had not enrolled any patients, and 52 studies (71%) were ongoing. The median enrollment was 31% (interquartile range [IQR], 6–104) of the required number of patients for 41 registry studies that had a predefined sample size, 30% (IQR, 2–101) for nonimposed registries, and 61% (IQR, 18–144) for imposed registries.

Implications: Enrollment of patients into postapproval registries is poor, although the results for imposed registries seem better. Currently, registries only have a limited impact on resolving gaps in the knowledge of a drug's benefits and risks at time of marketing authorization. (*Clin Ther.* 2018;40:768–773) © 2018 The Authors. Published by Elsevier HS Journals, Inc.

Key words: new drugs, postapproval data, patient enrollment, registries.

INTRODUCTION

Approval is a discrete moment in the life cycle of a drug, after which the drug typically becomes widely available to the public. However, full knowledge regarding the drug's benefits and risks is not complete at this point. For some drugs, regulators and industry may agree on collecting further clinical data through additional trials or observational studies. There is a trend to expand the collection of clinical research data into more "real-life" data settings such as patient or drug registries. Registries, or registry studies, may be deemed necessary if, at the time of approval, the benefits, but especially the risks, are not completely understood. Registries may be either newly developed as a consequence of a decision by the regulatory agency (eg, European Medicines Agency [EMA]) as a "new registry" or "registry studies" can be performed in existing disease registries or other databases. Regulators may even impose a registry as a specific obligation to address a particular concern with respect to either safety or efficacy, in the framework of the marketing authorization. Moreover, the EMA has proposed in its adaptive pathways project to use registry data to generate postapproval data in more extended patient populations while giving an early license in a restricted population.[1] However, some criticism was raised with respect to this option because it is considered that industry does not always fulfill its postapproval commitments in a timely fashion.[2–4] The most recent review of postapproval studies agreed with the US Food and Drug Administration, which showed that 5 to 6 years after

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approval, 20% of these studies had not started patient inclusion, 25% were delayed or ongoing, and only 54% had been completed.[5]

Evidence is lacking from Europe whether it is realistic to expect that this kind of early approval (with "real-world" registry data being provided post-approval) is effective. Therefore, we reviewed for drugs approved between 2007 and 2010 by the Committee for Medicinal Products for Human Use in Europe. We previously reported that for 43 (37%) of 116 drugs approved in this period, 73 studies in registries had been proposed.[6] The present study investigated if the planned number of patients had been enrolled, the results are made publically available, and if the registry studies provided evidence that affected the known benefit–risk balance.

MATERIALS AND METHODS

The European Public Assessment Reports (EPAR), which are publicly available via the EMA website (http://www.ema.europa.eu/ema/), were investigated for scientific and regulatory information of the 43 drugs that had been approved in Europe by the Committee for Medicinal Products for Human Use between 2007 and 2010 and where a commitment was made to perform at least 1 study in a registry. The 2007 to 2010 time period was chosen to allow at least a 5-year follow-up for each drug after approval. This approach is in line with the time for submitting a renewal application (ie, the obligatory re-evaluation after 5 years of the risk–benefit balance of any new medicinal product after its initial approval).[7] The lead author (C.J.J.) reviewed the statistical analysis plan of the registry study protocol to determine whether target enrollment was achieved. The Mann-Whitney *U* test was used to test if enrollment differed between imposed and nonimposed registries and between disease and product registries. In addition, we evaluated what impact the data had on the drug's benefit–risk balance (ie, a change in the product label) after 5 years. To this end, EPAR updates were reviewed by using the term "registry" or the name of the registry or registry study to find evidence that these data were mentioned in the EPAR irrespective of whether they led to updates of the drug labeling. All data were systematically checked by 2 of the authors (P.G.M.M. or M.S.G.K.) to ensure accuracy of extracted information. Any discrepancies were resolved in discussion with 3 of the authors (C.J.J., M.S.G.K., and P.G.M.M.).

PubMed was searched to determine if the protocols or findings of the registry or registry studies had been published in a peer-reviewed journal to investigate if translation of knowledge had occurred from registry owners and industry to health care professionals and the scientific community. Search terms included the generic name of the drug and the term "registry" or the name of the registry or study as recorded in the EPAR. The status of the registry with respect to statistical analysis plan and enrollment was retrieved from the study reports submitted to the Dutch Medicines Evaluation Board; the data lock point was January 1, 2016.

RESULTS

Of the 73 identified registry studies, 9 (12%) were imposed by the regulatory authority as a specific postapproval obligation.[6] The remaining 64 registries were proposed voluntarily by companies and agreed with by the regulatory authority. At the data lock point of January 1, 2016, two registry studies (3%) had been finalized,[8] and 52 studies (71%) were ongoing. In 19 registries (26%), no patients were enrolled. Reasons for not enrolling any patients were as follows: withdrawal of the drug from the market (4 [of which 2 registry studies had been imposed]), the drug was not reimbursed (1), the data were collected through other pharmacovigilance activities (2), and there was no (recorded) use of the drug in the at risk population (pregnant women) (3). For 9 registries, the reason could not be retrieved from the data submitted to the agency.

The planned number of patients to be included was described in the statistical analysis plan of 41 registry studies (56%); for the imposed registry studies, this factor was known for 7 (78%) of 9 registry studies. The Figure shows the percentage of patients enrolled in registry studies with a predefined number of patients to-be-enrolled in the statistical analysis plan. The median enrollment in these 41 registry studies was 31% (interquartile range [IQR], 6–104) of the required sample size, 30% (IQR, 2–101) for nonimposed registries, and 61% (IQR, 18–144) for imposed registries ($P = 0.46$). The median enrollment in product registries was 50% (IQR, 1–119) and 28% (IQR, 11–93) in disease registries ($P = 0.74$).

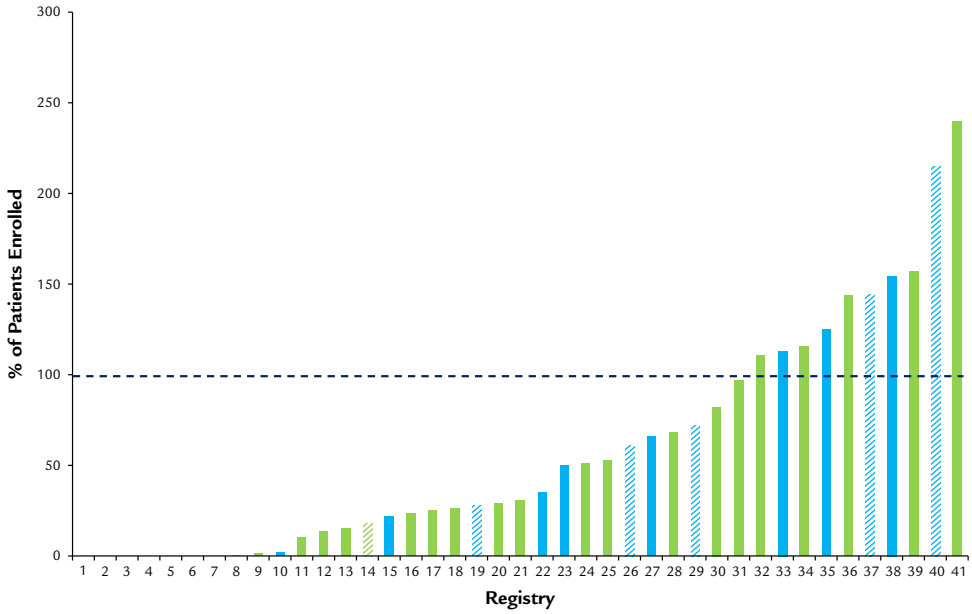

Figure. Percentage of patients enrolled in registry studies with a predefined number of patients to-be-enrolled in the statistical analysis plan. The bars indicate the percentage of patients enrolled from those planned to-be-enrolled in registry studies (data lock point is January 1, 2016). The green bars indicate the disease registries, the blue bars the product registries, and the striped bars the registries that were imposed. Note that for 32 registries, the percentage could not be calculated due to missing numbers.

For 6 drugs, data from the registry studies were published in a follow-up EPAR published on the EMA website.[9–14] In addition, for 2 products, these data led to changes in the Summary of Product Characteristics (ie, the drug label). The first drug is eculizumab; at the time of approval, a single pivotal study supported the benefit–risk of eculizumab in patients with paroxysmal nocturnal hemoglobinuria but only in patients who had undergone transfusion previously.[9] The registry study data then confirmed that a positive benefit–risk applied to all patients with paroxysmal nocturnal hemoglobinuria irrespective whether they had a previous transfusion. The second drug that led to a label change was the influenza A (H1N1) pandemic vaccine, for which the results of the registry study conducted in pregnant women (an important hitherto not studied population) showed that the vaccine was not associated with an increased risk of adverse pregnancy outcomes.[10] The 4 other registry studies reported in EPARs complemented the limited datasets at time of approval confirming the benefit–risk balance at this time point, thus not requiring any label changes. Two registries—Psoriasis Longitudinal Assessment Registry and the Icatibant Outcome Survey) for ustekinumab and icatibant, respectively—provided reassurance that no new safety signals emerged.[11,12] Registry data indicated that longer treatment of romiplostim did not lead to unexpected immunogencity.[13] Finally, the US Cystic Fibrosis Foundation Patient Registry provided controlled long-term effectiveness data for aztreonam lysine; it reported a better outcome of aztreonam-treated patients with respect to hospitalization.[14]

Data from 11 registry studies (15%) were published in peer-reviewed journals.[8,15–24] For 4 registry studies, these data were only published for the baseline characteristics of the patients enrolled[15,16] and/or the enrollment process was described.[17,18] Five articles published baseline data and interim data after 1 year[19] or after ≥1 years of treatment.[20–23] Publications with data generated in a registry of pregnant women receiving the pandemic vaccine provided evidence on absence of risk, which (as described earlier) is also reflected in the Summary of Product Characteristics.[8] Data from pregnant women with Gaucher disease suggest that continuing treatment during pregnancy may be appropriate.[24]

DISCUSSION

The present study, including 73 postapproval studies in registries imposed or agreed on by the Committee for Medicinal Products for Human Use, showed that 5 years after approval, only 2 registry studies (3%) had been finalized[8] and that 19 registries (26%) had not enrolled any patients. Of the 41 registry studies with predefined sample sizes, enrollment was poor (median inclusion of 31% for all registry studies), albeit that inclusion for imposed registry studies seemed better (61% vs 30% enrollment for nonimposed registry studies).

In 2012, pharmacovigilance legislation was implemented to enable regulators to protect the public from emerging safety issues not only at the time of approval of a drug but throughout a drug's life cycle. The impact on industry is that a clear legal framework for postauthorization monitoring has been established. Regulators can now take action if industry does not complete its postapproval studies.[25] Our study was performed on drugs approved before the new pharmacovigilance legislation came into force. This approach was taken to allow registries to mature, considering among others the delay in "real-world" use of a drug after approval due to sometimes protracted reimbursement negotiations. Obviously, we cannot dismiss the possibility that the new pharmacovigilance regulation may have had an impact on the performance of registries. Two studies focusing on more recent imposed registry studies (albeit with inherently shorter follow-up periods than our study and one being a study from the United States) however, found similar results of slow recruitment.[26,27] What we add is that even with longer follow-up periods, recruitment in registries remains poor and that imposed registry studies (a regulatory tool that is likely to have been used more frequently since the new pharmacovigilance legislation) may perform better than nonimposed ones. The exact reasons for poor recruitment were not easily identifiable in our study. For 9 registries, no reason was provided for the lack of or poor enrollment. To improve enrollment for the future, more attention is needed on the feasibility to conduct a registry; for example, whether an existing registry is available. It is important that this factor has been explored by both industry and the regulatory authority beforehand.[28]

Finally, EMA promotes making use of existing disease registries.[28] These registries have the advantage of having already shown the ability to recruit and follow up patients. These registries usually have extensive track records of generated valuable health care knowledge beyond specific effects of a drug of interest, and they may provide historical or contemporaneous control data. Product registries, conversely, may have the advantage that industry sponsors pay data monitors to ensure quality and validity of data entered into the registry. In contrast, disease registries are often created by academic investigators, where quality control may be limited due to limited resources. These differences may affect accrual rates and success of the studies performed in registries. Interestingly, data from our study suggested, however, that product registries achieved higher enrollment rates.

Our study also showed that for a few drugs only, the data generated from registries were published on the EMA website or in peer-reviewed journals. Only 8 of the 73 registry studies reviewed in the present study were published in the European Union electronic Register of Post-Authorisation Studies, but it should be kept in mind that this register was launched in November 2010, whereas our study period was 2006 to 2010.

Once a drug is approved, it will usually be used by much larger numbers of patients than studied preapproval. Safety and/or efficacy data generated in the registry or real-world setting can only translate into knowledge for prescribers and other health care professionals if such data are made publicly available. Although it is challenging to study the exact impact of registry data on the knowledge of benefits and risks of any drug, the knowledge obtained thus far through registries seems limited. Results of 6 registries were mentioned in EPAR updates only, of which 2 (eculizumab and influenza A [H1N1] pandemic vaccine) resulted in changes in the label. A small proportion of the registry studies were published in the peer review literature. Our results on poor performance of registry studies ties in with the work of Vermeer et al,[29] who found that only one fifth of all uncertainties described in Risk Management Plans were resolved 5 years after marketing authorization. Importantly, Hoekman et al[30] showed that most postmarketing obligations were eventually completed but often with substantial delay. We appreciate the work done so far by regulators to be more transparent[31] and to swiftly publish information on their developing knowledge of the benefits and risks of drugs. Our results

suggest, however, that more effort is needed from all stakeholders.

Poor performance of postapproval registry studies challenges the real-world evaluation of, for example, rare cancer drugs that require further data to complement the knowledge on drug benefits and harms after approval. To improve the knowledge of new drugs, the value of registries depends not only on recruitment but also on quality and completeness of the data collected; some articles suggest that improvements need to be made in this context as well.[32,33] Although postapproval registries are, however, just one part of the real-world evaluation, the poor performance of studies in these registries challenges the authorization of drugs. This situation can only be improved if regulators are explicit about data that are needed and what the consequences will be if data are not timely delivered.

CONCLUSIONS

Five years after approval, only 2 (3%) of 73 registry studies had been finalized, 19 registries (26%) had not enrolled any patients, and 52 (71%) were ongoing. Enrollment for imposed registries seemed better, but the overall inclusion rate was poor. Registries have had only a limited impact on resolving gaps in the knowledge of a drug's benefits and risks at the time of marketing authorization. It is important to be careful with broadening the use of postmarketing studies as a means of resolving uncertainties about benefits and risks after marketing authorization.[30]

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CONFLICTS OF INTEREST

The authors have indicated that they have no conflicts of interest regarding the content of this article.

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