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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;▮:▮▮▮–▮▮▮) © 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 ($P = 0.74$).