Barriers and Opportunities for Use of Patient Registries in Medicines Regulation

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The European Medicines Agency (EMA) established the Patient Registry Initiative to explore ways of supporting the use of patient registries in generating high-quality data for regulatory decision making and to enable a systematic approach to their use. We review barriers and opportunities for using patient registries in medicines regulation. A key aspect is that early discussions between all parties may often help address concerns including heterogeneity of data collection, data quality, data sharing, or questions on safety reporting.

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335 products centrally authorized between 2005 and 2013 found that a registry was requested of marketing authorization holders (MAHs) by EMA’s Committee for Medicinal Products for Human Use (CHMP) as a condition of the marketing authorization for 30 products (9%). These were mainly products approved under exceptional circumstances, where a registry was imposed for 14 of 21 (67%) products and for orphan medicinal products (20 of 70, 29%). Another review of 116 new products authorized between 2007 and 2010 found that at least one registry was included in the risk management plan of 43 (37%) and was imposed as an obligation for 9 (21%) products.

The role of registries in regulatory decision making is illustrated in Table S1, which provides recent examples where patient registries were proposed to be used to confirm a response rate in a single-arm trial and monitor the product safety (axicabtagene ciloleucel (Yescarta), tisagenlecleucel (Kymriah)), to provide an external control arm for an on-going phase III trial (genetically modified allogeneic T cells (Zalmoxis)), to monitor long-term safety and efficacy postauthorization (nusinersen (Spinraza)), or to provide data supporting an extension of indication (eculizumab (Soliris)).

In 2015, EMA established the Patient Registry Initiative 1 to explore ways of expanding the use of patient registries by supporting a systematic and standardized approach to their contribution to the benefit–risk evaluation of medicines. During 2017 and 2018, EMA organized four disease-specific workshops on cystic fibrosis, multiple sclerosis, CAR T-cell therapy, and hemophilia registries. Based on that experience, this commentary reviews barriers to the use of patient registries in medicines regulation as well as the opportunities they provide.

DISCUSSION ON REGISTRIES EARLY IN THE PRODUCT LIFE CYCLE

Initiation of a registry-based study by a MAH may require a considerable amount of time, involving a large number of steps, including identification of potentially suitable patient registries, feasibility analysis, writing of a study proposal, negotiation and decision making within the registry governance structure, development of the study protocol, and contractual agreement.

It is therefore important that MAHs consider the need to use patient registry data early in their drug development programs. Figure 1 sketches the multiple opportunities during the product life cycle process for early proactive consideration on the use of a patient registry. MAHs are encouraged to initiate discussions with EMA in business pipeline meetings where companies discuss their future marketing applications, in scientific advice, and in presubmission meetings. Such discussions facilitate identification of the data collected by registries and the data needed by regulators, especially for postauthorization product evaluation. They may also assist early consideration of data likely to be needed for health technology assessment or reimbursement decisions. Involving registry holders in early discussions permits assessment of whether they can participate in a proposed postauthorization registry study in terms of data availability and required quality standards.

COMMON CORE DATA ELEMENTS

Heterogeneity in the data collected by different registries in the same disease area is an important barrier for multicenter
studies. Use of a common data set, data format, and terminologies can facilitate implementation of a common data quality system (automated data entry control, checks for data consistency, routine statistical screening), data exchange, common data analysis on a large number of patients, and interpretation of results from different registries. Lack of harmonization across registries requires a mapping of data elements. As the mapping process may be time-consuming, and resource intensive, common core data elements and formats should be preferably implemented at the design or amendment stages of registries. Examples of lists of core data elements agreed for patient registries have been published in the reports of the cystic fibrosis, multiple sclerosis, CAR T-cell therapy, and hemophilia registry workshops.1

DATA QUALITY
Uncertainties about the quality of the data collected in registries and the level of quality management applied have often been barriers to the use of patient registries by regulators and MAHs, as these uncertainties undermine confidence in the validity and reliability of the evidence generated. Concerns about data quality are particularly important in the context of postauthorization registry studies imposed on MAHs by regulators as a condition of the marketing authorization, where the legal responsibility to conduct the study and provide valid and reliable results lies with the MAHs. This legal context has often stimulated MAHs to create their own product registry providing them full control of the data collection.2 Data quality assurance has therefore been a key component of the recommendations issued from the disease-specific patient registry workshops. In addition to quality checks and audit, benchmarking of the actual registry population in comparison with another data source covering the same population (e.g., electronic health care records) can help assess the representativeness of the registry in terms of characteristics of included patients.

Through its scientific advice procedure, the CHMP may issue a qualification opinion on the acceptability of a specific use of a method, such as the use of a novel methodology in the context of research and development. A CHMP opinion is based on the evaluation of a scientific rationale submitted to EMA by the requester and recommendations from the Scientific Advice Working Party, which includes experts from national regulatory agencies (see www.ema.europa.eu). EMA has recently provided scientific advice to support qualification opinions on two platforms of EU-wide patient registries regarding their suitability for pharmacoepidemiology studies.6,7 In both cases, the opinions describe the context of use for which the registry data are considered suitable by CHMP and address key aspects such as the choice of the target population, core data elements to be collected on outcomes of interest, safety reporting and data quality, completeness, and timelines.

The possibility for registries to obtain a qualification opinion may help assure stakeholders that qualified registries are satisfactory for specified regulatory studies. MAHs may also seek scientific advice on appropriate methodologies to be applied in studies using registries as a source of data.

In terms of data quality, linkage of a patient registry to other registries or existing databases could also enrich the data collected with, for example, information from cancer registries, prescription databases, or mortality records. It may also improve long-term follow-up data collection in situations where patients are lost from a registry, such as may arise when they move to another region.

SAFETY REPORTING
Although patient registries are generally not suitable for a rapid statistical analysis of new safety signals, as they do not systematically collect adverse event information, they may be useful for monitoring and characterizing known or suspected adverse reactions to different therapies and for product comparisons. However, as many registries have been established for clinical evaluation and academic research purposes, some do not have processes in place to allow use of the data for other purposes, such as to support monitoring of the safety or utilization of medicinal products. Some have limited flexibility for providing individual patient-level or aggregated data to external organizations. This may conflict with the legal obligations for reporting safety data applicable to MAHs using a patient registry for a postauthorization study (PAS). While patient registries conducted by organizations such as academia or medical research associations should follow the national requirements for the management of safety data, any active data collection system put in place in a registry by a MAH to collect and record suspected adverse reactions to one of its medicinal products must follow the regulatory framework for PASs applicable in the European Union8 and may therefore conflict with the registry holders’ priorities. Effective collaboration between all parties is needed to make best use of registry data in the patients’ interest.

From the discussion above, it follows that regulatory obligations for PASs apply to product registries established by MAHs where entry is defined by exposure to a defined medicinal product. In this respect, the term “product registry” is considered misleading and should be replaced by what it really is, i.e., a postauthorization safety and/or efficacy study, for which the regulatory framework provides clarity on legal requirements.

DATA SHARING AND DATA PROTECTION
Data from patient registries are of value for regulators and MAHs, as they may help to understand the disease, allow monitoring of the safety and effectiveness of medicinal products, especially during the longer term in the context of usual clinical care, and inform appropriate decisions to protect patients’ health. Aggregated data (supported by statistical analysis if needed) are generally sufficient. Like other regulatory agencies, EU regulators will rarely request patient-level data or analytical datasets, and requests for patient-level data would be based on important public health reasons. EMA lessons learned from the workshops helped to understand data-sharing problems faced by registry holders when more detailed patient data is requested. It is the responsibility of the treating center to ensure that patients have consented to the recording and use of their data. Patients need to be aware of why data is collected, what is collected, how it will be used, by whom and with whom it will be shared,
and at what level of detail. In addition, some patient registries have been expanded to include additional data such as genetic profiling and other biochemical analyses. This information may be sensitive, and it is important that patients have a good understanding of the data that could be provided to external organizations. Principles of informed consent should be applied in accordance with the General Data Protection Regulation.9

CONCLUSION

Since the start of the EMA patient registries initiative in 2015, there is a paradigm shift from establishing individual product registries owned by a single MAH to collaborations between one or several MAHs and patient registries for long-term follow-up of therapies. While concerns about data quality of existing patient registries persist, the workshops revealed interest from MAHs and registry holders to collaborate and improve on this aspect. Tools put in place by EMA also support improvements, for example, the inventory of registries hosted at the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) resources database10 and the Qualification procedure, used already by two registry platforms.6,7

SUPPORTING INFORMATION

Supplementary information accompanies this paper on the Clinical Pharmacology & Therapeutics website (www.cpt-journal.com).

Table S1. Recent regulatory examples in which patient registries have been proposed to support regulatory decisions.

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