A Sponsor’s View on Postmarketing Regulatory Commitments Involving Human Drug Products

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Postmarketing commitments (PMCs) are often needed to facilitate understanding of a product’s benefit-risk profile. Conduct of feasible and effective PMCs will expedite completion and reporting of the findings and thereby hasten the provision of new and important benefit-risk information for prescribers and enable safer and more effective use of the products. Herein, guiding principles with potential to improve the PMC process are outlined and discussed.

BACKGROUND

Global regulators may require postmarket studies and/or drug safety registries, hereafter collectively referred to as postmarketing commitments (PMCs) to evaluate topics not fully addressed in the original application, such as special populations, drug interactions, or clinical outcomes, or to assess potential serious risks that might be associated with the drug.¹ ² A high proportion of PMCs require the conduct of a randomized clinical trial (RCT). At any one time worldwide, Pfizer has 200–250 or more PMC clinical studies across a broad spectrum of medical specialties. An evidence base to further understand and extend the scope of the benefit-risk of therapeutic products is important and accepted. However, the availability of an approved drug makes enrollment in postmarket clinical trials more difficult, and when the situation involves a serious disease in a vulnerable population or when the potential risk is rare, conduct of an RCT may be very difficult or infeasible. The timing of health authority / sponsor discussions on PMCs can also be problematic. Discussions regarding the need for PMC clinical studies prior to drug approval is not always supported with sufficient time to thoughtfully reflect on the design and feasibility of conducting the study or consider alternative approaches to satisfy the scientific question. Sponsors often view waivers for preregistration local data requirements, acceptance into expedited review pathways, and/or product approval as being contingent on acceptance of a PMC and enter into agreements to avoid delays in product approval. In addition, PMCs are routinely negotiated on a single country/market basis and sponsors submitting applications are not always able to leverage or benefit from already agreed-upon PMC studies being conducted elsewhere. Hasty design of PMCs may contribute later on to delays in availability of important information on safety risks for regulators, prescribers, and patients. Postapproval, the process of negotiating PMC amendments and modifications and satisfying PMCs can be cumbersome and consume health authority and industry resources that could be better utilized on further research and development efforts that may provide more value and benefit to patients.

Application of modeling, simulation, and extrapolation, where applicable, along with other novel, innovative approaches should be considered when developing plans for gathering necessary data to fulfill PMCs. Both the US Food and Drug Administration (FDA)³ and the European Medicines Agency (EMA)⁴ have recommended extrapolation as a powerful scientific method to expedite pediatric drug development. Further, the International Conference on Harmonization (ICH) formed an expert working group to establish a guideline that focuses on pediatric extrapolation to harmonize methodologies and strategies in overall drug development plans.⁵ There is also an increasing focus on opportunities for real-world evidence (RWE), and novel trial designs to inform regulatory decision making.⁶ However, opportunities to leverage these sources of evidence to satisfy PMCs and PMCs are not routinely considered by regulators or applicants. Although some limitations may need to be addressed to avoid overinterpretation, novel methods can gather safety data from large numbers of people in a shorter period of time than an RCT and provide more timely information on safety risks to regulators, prescribers, and patients.

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GUIDING PRINCIPLES FOR ADVOCACY

Design of efficient, effective PMCs will lessen the burden on patients, regulators, the healthcare system, and industry, and better utilize limited resources and strained clinical research infrastructure. Regulators often propose PMCs too close to the end stages of the marketing application assessment. Thus, the applicant does not have adequate time to effectively consider study design, feasibility, and realistic timelines, nor to have a robust scientific discussion with regulators regarding the PMC. Design and feasibility assessment of such important studies, particularly in vulnerable or at-risk populations, requires time. Process improvements would facilitate more effective, feasible data collection that would better utilize industry and health authority resources. The health authority/sponsor discussions regarding new PMCs should be grounded in science, and allow sufficient time to assess feasibility and consider design options. Iterative engagement with regulators early and throughout the product lifecycle will help to address potential uncertainties or potential serious risks associated with a product. The PMC review process would be strengthened and improved by establishing a process whereby discussions and agreements concerning PMCs initiate pre-approval and continue postapproval to allow sufficient time for consideration of feasibility, study design, timelines, analytical methods, and potential for use of nontraditional data sources. There should also be an established process for periodic postapproval review of existing PMCs to address relevant new or emerging science and determine if the PMC agreements are still feasible, necessary, and relevant to the use of the approved drug. PMCs completed for other regulatory jurisdictions should be considered in this assessment.

Discussions around PMCs should be focused on the balance of benefit-risk and framed with a specific scientific question to be addressed that narrowly focuses on the remaining uncertainty. The health authority’s rationale for proposing a PMC should be data-driven, include a feasibility assessment, and consider current and evolving standards of care for the study population. The potential impact of missing information on the benefit-risk assessment should also be considered. Better understanding of the regulatory decision making process would strengthen the applicant’s ability to respond and ensure specific concerns are being addressed in proposed study designs or alternative data collection approaches.

Nontraditional data sources, novel clinical trial designs, and historical data should be considered an efficient means of generating evidence to satisfy PMCs. Traditional data sources obtained through interventional RCTs are not always the best option to understand the safety of the product, particularly postapproval. For example, certain registries, such as pregnancy registries, are typically required and, despite tremendous efforts involved in establishing and maintaining these registries, they often fail to generate the desired data. There should be consideration for use of disease-specific registries or national product monitoring systems, for example Sentinel in the United States, and thoughtful use of composite datasets integrated from different global sources as alternatives to traditional postmarketing studies. Regulators should also expand the use of observational data sources, such as RWE, as a key resource for safety signal characterization before requiring Applicants to conduct postmarketing controlled studies. Where appropriate, evaluation of related, but not necessarily identical populations to those studied in the database provided for the initial marketing application should be considered when determining the acceptable benefit-risk of the product.

Pediatric study requirements are especially difficult to satisfy in a postmarket setting. The FDA has evaluated time from adult to pediatric approval and on average, there is an 8-year lag between initial approval and addition of pediatric-specific labeling (Figure 1) and it is becoming longer in recent time periods. Difficulties evaluating therapeutics in children result in challenges completing pediatric studies and may result in off-label utilization by healthcare providers without clear dosing recommendations or understanding of safety and efficacy in pediatric populations. Although the requirements that govern pediatric investigations may be unique, points that have been raised regarding transparency, communication, and consideration of nontraditional data sources are also essential to pediatric study agreements. Discussion regarding pediatric studies and assessments generally begins early in the product development process, and as a result, it is often difficult for sponsors to provide realistic pediatric study/investigation plans at this stage of development. However, early engagement, even with the inherent uncertainties, is desirable. Further consideration of what is feasible to assess in the pediatric populations.

Figure 1. US Food and Drug Administration (FDA) approval data from 1998–2007 and 2008–2017. The FDA has evaluated time from adult to pediatric approval and on average, there is an 8-year lag between initial approval and addition of pediatric-specific labeling.

| Year | Count of Approvals |
|------|-------------------|
| 1998-2007 | 40 |
| 2008-2017 | 60 |

| Time to Pediatric Approval (y) | Count of Approvals |
|--------------------------------|-------------------|
| 0                              | 20                |
| 5                              | 30                |
| 10                             | 40                |
| 15                             | 50                |
| 20                             | 60                |
| More                           | 70                |
Table 1 Key points

- Efficient, effective PMCs will lessen stakeholder burdens and better utilize limited resources and strained clinical research infrastructure
- Expediting reporting of PMC findings will hasten the labeling of important benefit-risk information and enable safer, more effective use of products
- The process for determining new PMCs should be predictable, grounded in science, and allow sufficient time to assess feasibility
- Non-traditional data sources, novel clinical trial designs, and historical data should be considered potential means of satisfying PMCs
- Feasibility is especially important in pediatric populations; alternative approaches to data collection, application of extrapolation is essential
- To fully realize the value of feasible and effective PMCs there will be a need for global regulatory convergence, as encouraged by ICH

ICH, International Conference on Harmonization; PMCs, postmarketing commitments.

and regulator willingness to consider alternative approaches to data collection and model-informed drug development are needed, as is more consistent consideration for extrapolation.\(^{3,4}\) The same should apply to other special populations (e.g., in geriatrics or those with organ compromise, etc.), as may be appropriate. Information to guide decision making for safe and effective use of medications in special populations is a largely unmet need that hinders optimal care of those patients and may foster empirical use when there are few other options for treatment. Conduct of feasible and effective PMCs will expedite completion and reporting of the findings and thereby hasten the timely provision of new and important information for prescribers and safer and more effective use of products.

To fully realize the value of feasible and effective PMCs there also will be a need for global regulatory convergence, as encouraged by the ICH. For example, smaller markets with more limited resources may not be as aware or open to nontraditional data sources and novel clinical trial designs. Further, local government economic and political factors leading to requirements for local data or other studies that are not grounded in science will be a business challenge in some markets; application of ICH E17 guidance on multiregional clinical trials should help offset this.\(^{12}\) Applicants and regulators should harmonize approaches to addressing the scientific question(s) across regions and maximize opportunities to improve feasibility and efficiencies in completing clinical studies. Global data should be leveraged to satisfy PMCs to the extent possible unless there is scientific or legal need for local data. Changes to regulatory and legal frameworks should also be sought, if necessary, to further drive harmonization or convergence of PMCs globally and to support the use of global data.

Key points are summarized in Table 1.

CONCLUSION

PMCs are often needed to facilitate understanding of a product’s evolving benefit-risk profile. Clear scientific questions and well-designed approaches are essential for success, but there are risks that suboptimal approaches could draw scarce resources from other, potentially more productive research and development efforts. Improving this process can help reduce the cost burden associated with drug development and approval. Design of efficient, effective PMCs will lessen the burden on patients, health authorities, and industry, and better utilize limited resources and strained clinical research infrastructure. Furthermore, conduct of feasible and effective PMCs will expedite completion and reporting of the findings and thereby hasten the provision of new and important benefit-risk information for prescribers and enable safer and more effective use of the products.

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CONFLICT OF INTEREST

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