Regulatory Impact of Post Marketing Safety Registries Submitted to FDA to Fulfill a Post Marketing Safety Requirement

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Abstract

Background One of the U.S. Food and Drug Administration (FDA)'s missions is to ensure that drugs already marketed remain safe for as long as the drugs remain on the U.S. market.

FDA uses several postmarketing surveillance tools for drug product safety signal detection including Postmarketing Requirements (PMRs) and Postmarketing Commitments (PMCs).

The main goals of requesting PMR and PMC safety studies are to assess the known and unknown risks, or adverse events, associated with the use of the drug product in routine clinical practice. The evaluation of final study reports helps the FDA to make regulatory decisions such as updating the labeling to inform providers and patients about potential risks associated with the product use.

Purpose To assess the regulatory impact of long-term postmarketing safety studies on drug product labeling update.

Methodology Postmarketing safety studies were identified in internal record repositories for the Center for Drug Evaluation and Research (CDER). The assessment included long-term (at least 2 years) postmarketing safety registries conducted for drug products used to treat inflammatory or autoimmune conditions, approved by Divisions of Dermatology, Rheumatology, and Gastroenterology.

Results This paper analyzed 10 safety (non-pregnancy) registries and 4 pregnancy registries (n=14). Most of these registries (5 safety registries and 4 pregnancy registries) addressed the safety of Tumor Necrosis Factor Alpha (TNF-α) inhibitors, and malignancies were the most common (8 studies) safety outcomes of interest in safety registries. Two of the 8 safety registries with pre-specified enrollment targets and 2 of the 4 pregnancy registries did not reach their pre-specified enrollment targets. Ten registries lasted for at least 5 years, but only 4 (safety) registries reached their targets for person-years (PYs) of follow-up time or drug exposure. While all 4 pregnancy registries resulted in labeling updates, none of the 10 safety registries had a regulatory impact in terms of safety labeling update due to various study limitations. However, these safety registries were successful in producing final study reports that fulfilled their PMRs or PMCs.

Conclusions None of the 10 non-pregnancy registry studies produced safety results considered sufficiently robust to warrant specific regulatory action including safety-related labeling updates.

Introduction

- ❑ The U.S. Food and Drug Administration (FDA)'s mission is to ensure that safe and effective new drugs are available as quickly as possible and remain safe for as long as the drugs remain on the U.S. market.[1]
- ❑ Before approval, FDA reviews data submitted by drug manufacturers with New Drug Applications (NDA) or Biologic License Application (BLA) to ensure medical products are effective and safe.
- ❑ After approval, FDA uses several postmarketing surveillance tools for drug product safety signal detection including Postmarketing Requirements (PMRs) and Postmarketing Commitments (PMCs).[2,3]
- ❑ PMRs and PMCs are observational studies or clinical trials that are conducted by the drug manufacturers after the FDA has approved or licensed a product for marketing,[4] and aim to answer particular questions about a product's safety or efficacy.[5] One type of drug safety studies conducted under PMRs and PMCs are registries, including pregnancy registries.
- ❑ The main goals of requesting PMR and PMC safety studies are to assess the known and unknown risks, or adverse events, associated with the use of the drug product in a routine clinical practice setting. The evaluation of final study reports helps the FDA to make regulatory decisions such as updating the labeling to inform providers and patients about potential risks associated with the product use.
- ❑ The current study assesses the regulatory impact of long-term (at least 2 years) PMR and PMC safety studies on safety labeling update for drug products, used to treat inflammatory or autoimmune conditions, approved by Divisions of Dermatology, Rheumatology, and Gastroenterology.

Materials and Methods

- ❑ **We identified:**
  - 1,125 PMRs and PMCs by conducting a database search in the Center for Drug Evaluation and Research (CDER)'s Document Archiving, Reporting and Regulatory Tracking System (DARRTS).
  - 522 completed PMR and PMC safety studies and trials by separate database search conducted by the CDER's Analytics and Data Services Staff (ADSS).
- ❑ **Inclusion criteria:**
  - Biologic product, used for inflammatory or autoimmune condition, approved by Divisions of Dermatology, Rheumatology, or Gastroenterology or a non-biologic product of special interest.
  - Registry with a final study report reviewed by the FDA.
  - Registry with patients enrolled prospectively.

14 final registry reports conducted as either a PMR or PMC, met the criteria for inclusion.

- ❑ **We abstracted and summarized** the following information from study reports, protocols, statistical analysis plans, product labeling, and related internal and external communications:
  - Study objectives, outcomes, and design.
  - Patient enrollment, drug exposure, and patient follow-up.
  - Study findings and conclusions.
  - FDA assessment of the study findings, strengths or limitations, as well as recommendations for safety labeling update.

Results and Discussion

- ❑ **Distribution of Registries and Safety Outcomes of Interest**
  - 10 of the 14 registries are safety (non-pregnancy) registries and 4 are pregnancy registries.
  - 9 of the 14 registries (5 safety and 4 pregnancy) addressed the safety of Tumor Necrosis Factor Alpha (TNF-α) Inhibitors.
  - The most common safety outcomes of interest in safety registries were malignancies (8 studies), followed by infection (7 studies), cardiovascular events (4 studies), and autoimmune diseases (4 studies).
- ❑ **Study Enrollment**
  - Study enrollment goals were pre-specified in 8 of the 10 safety registries and all 4 pregnancy registries.
  - 4 registries (2 safety and 2 pregnancy) with pre-specified enrollment goals did not reach their targets due to challenges with enrollment.
- ❑ **Study Follow-up**
  - 10 registries (6 safety and 4 pregnancy) lasted for at least 5 years.
  - However, only 4 safety registries reached their targets for person-years (PYs) of follow-up time or drug exposure. These 4 studies also reached their targets for patient enrollment.
  - They were either multi-center, multinational studies (2 studies) or studies using participants from a health insurance or health maintenance organization (2 studies).
- ❑ **Regulatory Impact in Terms of Safety Labeling Update**
  - Final reports from 14 registry studies fulfilled FDA's PMRs and PMCs.
  - However, none of the 10 safety registries led to safety-related labeling update. FDA assessed these safety registries results as too limited for any specific regulatory action.
  - All 4 pregnancy registries resulted in labeling update, as required by the Pregnancy and Lactation Labeling Rule (PLLR) guidance: "when a registry is closed or there are changes to the contact information of an existing registry, the labeling must be updated"[6].
  - Some significant limitations in both registries included the inability to recruit and/or retain a sufficient number of relevant subjects.
  - Other deficiencies may preclude these registries from providing robust data including: absence or inadequacy of control groups, frequent treatment switching and use of concomitant treatments, exposure or outcome misclassification, confounding, and selection bias.
  - 4 safety registries were inconclusive regarding malignancy risks. These safety registries contributed little to the overall understanding of malignancy risks from use of drugs or biologics of interest.
- ❑ **Strengths and Limitations of the Current Study**
  - The strengths of the current study include the use of information from study reports, protocols, statistical analysis plans, product labeling, in addition to related communications.
  - The limitations include the relatively small sample (n=14).
  - The current paper assessed safety registries conducted for drug products used for inflammatory or autoimmune conditions, approved by Divisions of Dermatology, Rheumatology, and Gastroenterology; therefore, the findings from this study may not be generalizable to registries requested for different indications.

Conclusion

- ❑ All 4 pregnancy registry studies resulted in safety labeling update, as required by the Pregnancy and Lactation Labeling Rule (PLLR) guidance.
- ❑ None of the 10 non-pregnancy registry studies produced safety results considered sufficiently robust to warrant specific regulatory action including safety-related labeling updates.
- ❑ Multi-center multinational registry studies and registries using participants from a health insurance or health maintenance organization may have greater chance for reaching their targets for both patient enrollment and patient follow-up and/or drug exposure.
- ❑ However, besides recruiting and retaining a sufficient number of relevant subjects, other postmarketing safety registries challenges need to be dealt with are to: include an adequate control group; account for frequent treatment switching, concomitant treatments, and confounding; and minimize exposure and outcome misclassification.

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Disclaimer

The information in these materials is not a formal dissemination of information by FDA and does not represent agency position or policy.

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