

Evaluation of Post-Authorization Safety Studies in the First Cohort of EU Risk Management Plans at Time of Regulatory Approval

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Abstract

Background: Since November 2005, an EU Risk Management Plan (EU-RMP) has had to be submitted as part of a marketing application for all new chemical entities in the EU. In the EU-RMP, the safety profile of the medicine has to be described and pharmacovigilance activities should be proposed to study further safety concerns during use of the drug in the real-world setting. These activities include, for example, collection of spontaneously reported adverse events and post-authorization safety studies (PASS). Since the submission of an EU-RMP is a relatively new requirement, there is limited knowledge on the quality and completeness of the study protocols of PASS at the time of approval and there are no data on the influence of certain drug characteristics on the proposed pharmacovigilance activities.

Objective: To examine the types of proposed pharmacovigilance activities in a sample of EU-RMPs, describe and evaluate the methodology of PASS, identify problems and propose remedies, and compare characteristics between biologicals and small molecules.

Methods: Eighteen EU-RMPs (nine for biologicals, nine for small molecules) given a positive decision regarding the marketing application by the Committee for Medicinal Products for Human Use between November 2005 and May 2007 were included in this descriptive cohort study. The EU-RMPs were selected over time and different therapeutic areas. Classification of the safety concerns ('important identified risks', 'important potential risks', 'important missing information' within the EU-RMP was studied. For PASS, data source (registry,

population-based database, sponsor-owned clinical trial database), source of study population to be included in PASS and comprehensiveness of study protocol (full protocol, limited protocol, study synopsis, short description, commitment without further information) were studied.

Results: Compared to small molecules, safety concerns for biologicals were less frequently classified as important identified risks (relative risk [RR] 0.6; 95% CI 0.3, 1.0) and more frequently as important missing information (RR 1.6; 95% CI 1.0, 2.7).

Forty-seven PASS were proposed; 31 for biologicals and 16 for small molecules. Compared with studies proposed in population-based databases (4 for biologicals, 8 for small molecules), studies in registries (18 for biologicals, 4 for small molecules) were more frequently proposed for biologicals than for small molecules (RR 2.5; 95% CI 1.1, 5.7). About 60% of the proposed PASS will include EU inhabitants. No full study protocols were submitted; 26% involved a limited study protocol, 33% a study synopsis, 37% a short description and 4% a commitment without further information.

Conclusion: Approximately 40% of the study proposals for PASS were classified as a short description or a commitment to perform a study without further information, precluding an adequate scientific assessment. Studying non-EU populations may give rise to difficulties with generalizability of the results to the EU due to differences in patient characteristics, differences in the indication for the medicine and different healthcare systems. This study emphasizes the need for more complete study proposals to be submitted earlier on in the evaluation period and for the inclusion of EU inhabitants in PASS. In addition, differences in the characteristics between biologicals and small molecules, e.g. in the data source proposed, support the need for individualized tailored PASS depending on the type of drug.

Background

The first spontaneous reports suggesting an association between the use of tumour necrosis factor antagonists and the occurrence of tuberculosis occurred during use of the drug in the postmarketing setting; the occurrence of tuberculosis had not been identified in pre-approval randomized clinical trials.^[1,2] A recent study has shown that approximately one of four biologicals approved in the US and/or the EU required a safety-related regulatory action, defined as written communications to healthcare professionals and 'black-box' warnings, after approval

of the drug by the regulatory authorities.^[3] This illustrates the need for safety data to be gathered throughout the life cycle of a medicine due to the known limitations of clinical trials in predicting safety in 'real-world' use.^[4] Therefore, postmarketing data offer a valuable and necessary complement to pre-registration studies in continuously evaluating the benefit-risk balance of marketed drugs, especially with respect to safety.^[5] A more proactive approach towards the identification and quantification of safety concerns after marketing was aimed for in the International Conference on Harmonisation (ICH) guideline on pharmacovigilance planning, which