



May 19, 2004

Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane
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RE: Docket No. 2004D-0117: International Conference on Harmonisation; Draft Guidance on E2E Pharmacovigilance Planning

Merck & Co., Inc. is a leading worldwide human health product company. Merck Research Laboratories (MRL), Merck's research division, is one of the leading U.S. biomedical research organizations.

Merck has participated with health authorities from around the globe in the harmonization of regulatory standards under the auspices of the International Conference on Harmonization (ICH). The objectives of ICH have been to identify and correct unnecessary redundancies and time-consuming inefficiencies in development of pharmaceutical products caused by incompatible regulatory schemes.

We continue to monitor the equitable and consistent application of these harmonized standards to product development, including post-marketing pharmacovigilance activities. In our global market place, it is essential to ensure that *new* or *improved* therapies reach patients as swiftly as possible and that a favorable balance between benefits and risks is maintained after approval. This goal is advanced by harmonizing requirements to the greatest extent possible to assure that scarce resources are wisely used in the advancement of knowledge and not to satisfy regional deviations that differ in detail but not substance.

For these reasons, we are both interested and qualified to comment on draft version 4.1 of the guidance, "ICH E2E: Pharmacovigilance Planning (PvP)" dated November 11, 2003 and announced in the Federal Register of March 30, 2004.¹

Comments

1. We are pleased that the document recognizes that a PvP may be no more complex than a proposal to follow routine pharmacovigilance activities for products for which no particular

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concerns are identified during the pre-market development and review. We recommend that this point be emphasized in the final guidance.

2. Section 1.3 (Scope) states that the guideline “...*could be most useful for new chemical entities and biotechnology-derived products, as well as for significant changes in established products...and for established products that are to be introduced to new populations or in significant new indications.*” In general, the term “biotechnology-derived products” is understood to refer to products manufactured from rDNA technology. We recommend that the document specifically address whether it is also applicable to vaccines (conventional and biotechnology derived).

3. We recommend including language to encourage the international understanding that the requirement for a pharmacovigilance plan (PvP) for a new product by a regulatory agency in one region, including the details of such a plan, will be considered suitable to satisfy requirements across all regions unless additional, region-specific requirements are scientifically or medically justified.

4. Section 2.1, “Elements of the specification,” states:

A. *“The elements of the Pharmacovigilance Specification that are included are only a guide. The Pharmacovigilance Specification can include additional elements, depending on the nature of the product and its development program. Conversely, for products already on the market with emerging new safety concerns, only a subset of the elements might be relevant.”*

Because the last sentence implies that a subset of the elements may be relevant only in the specific case of emerging new safety concerns for marketed products, the implication is that for new products, all the elements are always relevant (see also comment below). Just as there may be *no* special concerns for many new products, there may be new products for which only a subset of the elements are pertinent. The language should be revised to reflect this possibility.

B. *“The focus of the Pharmacovigilance Specification should be on the identified risks, important potential risks, and important missing information. The following elements should be considered for inclusion.”*

This paragraph is followed by the extensive list of elements. We recommend including language to clarify that the PV Specification is intended to be limited to relevant issues for the product under consideration. This would avoid the potential for misconstruing the guideline as requiring written justification for the irrelevance of those elements that don’t apply.

5. Section 2.1.1 (Non-clinical) states, *“Within the Specification, this section should present non-clinical safety concerns that have not been resolved by clinical data....”* We believe that use of the term “non-clinical safety concerns” may convey the impression that the sponsor has failed to fully and responsibly evaluate the safety of the product and create unintended liability exposure. Because the purpose of non-clinical studies is to evaluate safety, we recommend consideration of alternative language, such as “non-clinical findings,” to avoid this negative connotation.

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6. Section 2.1.2(a) (Clinical – Limitations of the human safety database) says that “*Particular reference should be made to populations likely to be exposed in medical practice.*” Sponsors propose labeling to describe the population in whom the products they develop are intended to be used. We believe that it is unreasonable to expect sponsors to speculate about misuse, unintended use, or off-label use except in those situation in which data have demonstrated that a subpopulation exists for whom the drug would be particularly unsafe or ineffective, a situation that would, no doubt, be reflected in the proposed labeling. We recommend that, absent clarification, this recommendation should be deleted.

7. Section 2.1.2(b) and 2.1.2(e) both recommend consideration of patients of different “ethnic” origin. Ethnicity is term more suited to social/political purposes and is, in general, not one based on science. Race may be a better term although it, too, is imprecise.

8. Section 2.1.2(c) (Adverse events (AEs)/Adverse drug reactions (ADRs) states: “*More detailed information should be included on the most important identified ADRs, which would include those that are serious or frequent and that also might have an impact on the balance of benefits and risks of the product. This information should include evidence bearing on a causal relationship, severity, seriousness, frequency, and at-risk groups, if available. Risk factors and potential mechanisms should be discussed. These ADRs should usually call for further evaluation as part of the Pharmacovigilance Plan (e.g., frequency in normal conditions of use, severity, outcome, at-risk groups, etc.)*”

Every drug is likely to be associated with certain ADRs that are more frequent than others and ADRs that are more serious than others. For every drug, the “most important” ADRs can be identified. Further, all ADRs have an impact, at some level, on the balance of benefits and risks of the product. Therefore, the need for further evaluation should be predicated on a presumption that additional information may identify risk factors that pre-dispose certain patients to higher risk and, therefore, improve the benefit-risk ratio for the product. The language in this section should be revised to more clearly bring into focus the purpose of further evaluation under a PvP.

9. Section 3.1 discusses the purpose of the Pharmacovigilance Plan. It includes the following paragraph:

“*For products for which no special concerns have arisen, routine pharmacovigilance might be considered sufficient for post-approval safety monitoring, without the need for additional actions (e.g., safety studies). However, for products with important identified risks, important potential risks, or important missing information, additional actions designed to address these concerns should be considered.*”

The statement that routine pharmacovigilance “might be” considered sufficient for products for which no special concerns have arisen suggests that, even for such products, a PvP “might be” necessary. We recommend that this statement be revised to more clearly indicate that, in the absence of special concerns, routine PV is sufficient for post-approval safety monitoring.

Conclusion

PvP is increasingly recognized as an essential part of drug development. Global harmonization of principles of effective PvP is important to assure effective resource utilization in the generation of the information necessary to optimize benefit-risk balance. This guideline, when finalized, will be an important reference for sponsors and regulatory agencies alike.

We welcome the opportunity to comment on this ICH Guideline and, if appropriate, to meet with you to discuss these issues.

Sincerely,



for Donald M. Black, MD, MBA
Vice President
Global Regulatory Policy