



July 6, 2004

Dockets Management Branch (HFA-305)  
Food and Drug Administration  
5630 Fishers Lane, rm. 1061  
Rockville, MD 20852

Re: Draft Guidance for Industry: Development and Use of Risk Minimization Action Plans, Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment, and Premarketing Risk Assessment

Dear Sir or Madam:

Thank you for the opportunity to comment on FDA's draft guidance for industry relating to Risk Management Activities -- Risk Assessment, Pharmacoepidemiologic Assessment, and Risk Minimization Plans. We understand that the draft guidances are FDA's current thinking on these topics, and are intended as recommendations on the development, implementation, and evaluation of pharmaceutical product risk and programs to address those risks.

We appreciate that FDA took into consideration a majority of comments provided to the Agency by Roche (submitted, May 29, 2003). However, we continue to believe that it is important that the philosophy of the Agency with regard to risk management is actually "risk/benefit management". A focus on the possible signals or on real but rare safety issues may give the public and healthcare professionals the perception that the drug should not be used. This emphasis on adverse events may not be beneficial for the patient. We strongly recommend that all FDA guidances and communications contain information concerning the benefits of a drug, as well as the risks in order to provide a well balanced view of the product.

Roche hereby provides comments on the three new Risk Management draft guidance documents. We base our comments on the valuable experience we have gained from our post-marketing risk management programs for Accutane (isotretinoin), Copegus (ribavirin), Xeloda (capecitabine), and the Antiretroviral Registry (HIVID, Fortovase, Invirase and Fuzeon) and on our experience conducting pharmacoepidemiologic studies and risk assessments in both a pre- and post-marketing environment.

#### Overall Comments

We agree with FDA on the need for Risk Management activities throughout the product's lifecycle. While each of the guidance documents focuses on a different aspect of risk management, Roche believes that the language and the definitions used in these documents need to be clear and consistent. A common glossary of terms may be considered useful.

We further agree with the Agency that in most cases product labeling is sufficient, and in rare cases, a more comprehensive program is necessary to ensure the safe use of a product.

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However, it would be useful for the Agency to provide further guidance or criteria on when a RiskMAP may be indicated. Developing and implementing RiskMAPs for safety issues that can be tracked and managed in other ways will lead to the proliferation of complex programs. If these programs become too burdensome for patients and providers, they may compromise patient access to important therapies or drive patients to seek alternative sourcing to obtain needed medications, thus defeating the reason for developing RiskMAPs. In particular, the potential for alternative sourcing could fundamentally compromise the success of RiskMAP implementation. For example, recent reviews by FDA and the General Accounting Office have documented significant availability on the Internet of products that are (1) wholly banned from electronic prescribing; (2) entirely lacking in cautionary labeling (or labeling in English); (3) in unapproved strengths or dosage forms; and (4) counterfeit.

The patient access and alternative sourcing problems inherent in unduly restrictive RiskMAPs cannot be approached in an *ad hoc* manner. Rather, FDA should consider commissioning research to determine the aspects of RiskMAPs that may drive patient decisions to decline treatment or to seek risk managed products from the Internet or other unauthorized sources. The potential inclusion of such tools in RiskMAPs should involve careful consideration of the likely overall impact on patient health, either from non-treatment decisions or product sourcing from outside of the risk management program.

#### **Specific Comments to the Development and Use of Risk Minimization Action Plans**

Roche appreciates the further clarification provided on the design of a RiskMAP evaluation plan (Lines 440-626). The development of metrics to assess the effectiveness of a program can be challenging. A performance measure that is based on an individual patient's behavior, such as obtaining a zero pregnancy rate, is not realistic. While "reducing fetal exposures" may be more realistic, translating this goal into a meaningful and measurable health outcome can be difficult. If the objective is to continually improve a RiskMAP in order to better manage risk, the evaluation and outcomes measures chosen are extremely important. Roche, therefore, seeks further guidance from FDA regarding the development of meaningful and acceptable RiskMAP evaluation metrics.

FDA indicated that they plan to make available general information received from sponsors and others about the effectiveness of particular RiskMAP programs/tools in achieving minimization objectives. This serves two purposes. First it allows interested parties to track the progress of various RiskMAP activities. Second, it allows a forum for sponsors to choose tools that have been successful in meeting their objectives. However, the Agency should consider the confidentiality issues surrounding the disclosure of information, since patient confidentiality is at the heart of most RiskMAP activities. It would be useful for the Agency to provide guidance on how neutral or negative program evaluation results will be used in such a way as to not cause unnecessary alarm or concern by physicians and patients.

The Agency and Advisory Committees have encouraged or suggested that sponsors adopt other sponsors' specific tools or entire RiskMAP programs. However, the Agency must consider the fact that a sponsor may assert an intellectual property right to a tool or program thereby erecting a barrier to the adoption or use of the same or similar tools or programs by other sponsors. In particular, such alleged intellectual property rights may compromise the ability of companies to maintain patient access to risk managed pharmaceutical products, particularly in a multi-source product environment. FDA should carefully consider whether

to deemphasize risk minimization tools that may implicate such allegedly proprietary elements, or ensure sufficient flexibility in RiskMAPs to enable use of completely non-proprietary risk minimization tools.

Finally, FDA indicates that “focused or limited promotional techniques such as product sampling or direct-to-consumer advertising” is a tool in the targeted education and outreach category (Lines 284-285). As FDA has recognized in the consideration of its direct-to-consumer advertising policies, such promotional activities can play an important role in providing critical health information. Thus, it may be useful for FDA to provide further clarification as to the potential uses of such activities as RiskMAP tools.

#### **Specific Comments to the Premarketing Risk Assessment Guidance**

The Premarketing Risk Assessment draft guidance document provided useful recommendations and clarity with regard to FDA’s expectations regarding risk assessment activities during product development. Roche agrees with the Agency that assessment of drug-related QTc prolongation, liver toxicity, nephrotoxicity, bone marrow toxicity, drug-drug interaction, and polymorphic metabolism are extremely important (Lines 524-529). Roche would appreciate FDA’s expanding on what would be considered an appropriate assessment of these potential safety issues.

Roche notes that there does not appear to be alignment between this draft guidance and the ICH E14 draft specifying proper clinical assessment of QTc prolongation. While drug-related QTc prolongation is listed as a potential serious adverse effect that should be addressed during product development (Line 524), there is no indication that FDA expects that a formal QTc study to be routinely conducted in every development program. Moreover, Lines 363-366 might lead the reader to believe that such a study would only be necessary for compounds associated with known problematic classes like antihistamines. As drug-induced QTc prolongation has been the leading cause of postmarketing drug withdrawal in the US, we seek further elaboration from FDA on this topic.

#### **Specific Comments to the Good Pharmacovigilance Practices and Pharmacoepidemiology Assessment Guidance**

Roche found this draft guidance to be less specific than the other two. It would be helpful for FDA to provide more detailed recommendations and structure around this “assessment” phase of risk management. A model that can be used is the ICH E2E draft document on Pharmacovigilance Planning (November 2003).

FDA should provide more clarity on data mining, specifically noting that data mining is not an appropriate tool for drawing causal attributions between products and adverse events (Lines 309-353). Computer-based data mining of thousands of spontaneous reports cannot, in and of itself, be used to establish causality. While this tool can point to areas that may require further study, this technique must be used in conjunction with well-established traditional methods for determining causality. Since there is no “gold standard” to use when performing data mining, it is not possible to apply such terms as sensitivity and specificity (as well as false positive, false negative, predictive value) to this situation. These terms have well accepted definitions, for example in medical screening and diagnostics, where “gold standards” exist.



Finally, Roche seeks clarification regarding the calculation of reporting and incidence rates (Lines 386-444). In this section, FDA indicates that both the estimated number of cases of adverse events reported and the total number of patients exposed are unreliable. If so, then it is hard to understand why FDA recommends calculating crude event reporting rates. Given the deficiencies of the numerator and denominator, there appears to be little value of such a calculation. It is possible that the result of this calculation could be regarded as a number with meaning. If a reporting rate is large enough to warrant further investigation, then it is worth undertaking a serious investigation using other databases and methodologies to provide a credible estimate of the incidence or absolute risk of the adverse event.

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Thank you for your consideration of these comments. Please do not hesitate to contact me should you have any questions.

Regards,

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