Roche

May 29, 2003

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

Re: Docket No. 02N-0528: Draft Concept Papers: Risk Assessment and Risk Management Programs

Dear Sir or Madam:

Thank you for the opportunity to comment on FDA's concept papers relating to Risk Assessment and Risk Management Programs (Docket No. 02N-0528). We understand that the concept papers are intended to facilitate public discussion on the development, implementation, and evaluation of pharmaceutical product risk and programs to address those risks.

Roche hereby provides comments on the overall concept of risk management and specifically on the concept paper. We base our comments on the valuable experience we have gained from our risk management programs for Accutane (isotretinoin), Copegus (ribavirin), Xeloda (capecitabine), and the Antiretroviral Registry (HIVID, Fortovase, Invirase and Fuzeon.

Overall Comments to Risk Management

(1) Stakeholder Buy-In

We appreciate FDA's first step to provide draft concept papers for the public and industry. We strongly believe that where risk management requires action by healthcare providers beyond compliance with the product label, it is critical that all healthcare providers agree with the FDA plan. In particular, physicians, pharmacists, and other relevant healthcare professionals should be proactively approached by the Agency for feedback and to obtain a broad understanding of their expectations. Additionally, their concerns must be taken into account since they will have the final responsibility in ensuring that the patient receives the necessary information prior to, during, and/or after treatment. We were concerned that neither the AMA nor any other physician's group was not represented at the FDA open public workshop on April 8-10, 2003. We understand the pharmacy associations expressed initial concerns regarding consistency of programs, resource and financial burden. Based on our experience, we anticipate that physician groups would have similar as well as additional concerns.

(2) Innovator and Generic Program Consistency

From the time of product approval it is important that FDA consider how a risk management program will operate within a multi-source environment. All suppliers of the product must be required to provide the same risk management program and to achieve the same results as FDA expects from the innovator. We understand that FDA's current practice is to provide the innovator with an informal statement that FDA expects generic

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suppliers to provide and maintain the same risk management program as the innovator. However, we would expect in the future that written approval letters specifically include these expectations. To date, we have not seen these commitments contained in approval letters. Additionally, it does not appear that FDA would have statutory authority to mandate risk management programs for generics if the program is not specifically addressed in the product labeling. Therefore, inclusion of the risk management program in the product label is advised to eliminate this concern.

(3) Internal FDA Collaboration and Consistency

We believe that it is important that the various Centers within FDA have the same understanding and interpretation of a risk management program. Responsibility for review and approval of educational components of risk management should not be treated as promotional activities subject to additional, and perhaps, inconsistent review by DDMAC. It would be helpful if FDA clarifies this process and determines which group within the Agency has final responsibility for review and approval of such materials. As an example of the current process, Roche obtained fundamental agreement within the FDA Review Division regarding educational pieces only to be later told that DDMAC would review these materials as advertising and promotion. The Division may have as its goal information that is concise and easy for the patient to use and comprehend. DDMAC could then add significantly greater amounts of information because it views the educational materials of the risk management program as a "Direct to Consumer" promotion. We recommend the Division or the Office of Drug Safety have final decision making authority on educational pieces, as most are non-promotional educational documents focused on safety.

(4) Risk versus Benefit

As stated at the public workshop, 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. With respect to the pregnancy labeling initiative, we understand that the Agency does not want to unduly alarm physicians or patients with information in labels or pregnancy related programs that fail to provide a fair balance regarding the benefits of the drug. 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.

(5) Labeling Changes Based on Risk Management

The current trend by the Agency in drug labeling appears to be very conservative. Even when a signal or a finding is detected with inadequate information regarding the potential relationship between an adverse event and a drug, the event is captured in the product label. Regardless of the context within which this information is collected, the use of risk management to gather additional scientific information may or may not be recommended. We believe that where there is no scientific proof, over emphasis on adverse events that may not be associated with a product is inappropriate because patients may not receive medically appropriate and/or necessary treatments. We emphasize that when additional scientific information demonstrates a lack of adverse drug effect, the Agency should include this positive information in the label.

The Agency should also specify in the guidance documents when they anticipate or encourage Sponsor discussions of risk management programs with FDA. The assumption is that the Agency would grant type B meetings for these discussions.

General Comments on the Concept Paper

Our assumption is that the Agency plans three separate guidances organized according to the concept papers. As mentioned throughout our response, the language and the definitions used in these guidances needs to be clear and consistent. A common glossary of terms may be considered useful.

Overall, we found the risk management concept paper difficult to follow. We believe the document would be more useful if structured in a manner similar to FDA's recently issued final *Guidance for Industry on Establishing Pregnancy Exposure Registries.* Specifically, this concept paper would be easier to follow if it contained three sections:

1. Overview – This section would frame the safety issues of concern.

2. Structuring the risk management intervention – This section would explain the goals and objectives of a risk management program, the appropriate target population(s), proper communications methods, and contain timelines for rollout of a program.

3. Evaluating the risk management intervention – this section could explain what portions of the program FDA will evaluate, which aspects of the intervention will be considered when judging intervention performance, what standards must be reached for the intervention to be successful, what evidence will be used to indicate how the intervention has performed, what conclusions regarding intervention performance are justified by comparing the available evidence to the selected standards, how the lessons learned from the inquiry be used to improve patient safety and public health effectiveness, etc. (See MMWR, September 17, 1999, vol 48, No-RR-11).

Additionally, throughout the documents, we found the "program" versus "planning" distinction confusing. We suggest that the "program" be renamed the "intervention" and the "plan" should be designated the final "strategies." Discussions in the public workshops covered additional issues with definitions within the proposed guidance documents. We reiterate the concerns that "signal" be clearly defined and equally welcome clarity on the definitions used for "race" for demographic analyses.

The Agency should also avoid analogy between risk management program and clinical development plan. The lengthy discussions at the public workshop already emphasized the potential confusion between definitions of program and plan. It needs to be clear that a risk management program may include some clinical studies but has a different scope and objective than the clinical development plan.

Specific Comments on the Risk Management Program Concept Paper

The terminology used to define important risk management concepts (lines 16-35), should focus on not only risk management, defined by Roche as the making of decisions concerning risks and their subsequent implementation, but also on the activities from which risk management follows, i.e., risk assessment, risk estimation, and risk evaluation. Reference

should be made to the Royal Society definitions from 1992 regarding risk evaluation, estimation, and management.

The examples of objectives for achieving a goal (lines 88-97) were very helpful, and we were pleased that the examples chosen are the objectives outlined in the S.M.A.R.T. program. We believe, however, it may be useful to also present an example that focuses on the approved indication for the product. This is especially true for a product presenting significant risks that has great benefit for a specific indication. For example, "patients without condition A should not receive product B" or "patients without condition A should only receive product B under X circumstances." A more specific, highly-defined indication might also be proposed for products that are considered high risk but also of high benefit for a specific population.

In the "What Interventions or Tools Are Available for Use in Achieving RMP Goals and Objectives" section, we believe the use of both the word "tools" and "intervention" is unnecessary. (lines 129-261) The term "tool" is defined as "a process or system intended to enhance safe product use by reducing risk." This is similar to the definition of an intervention. Should you adopt our earlier suggestion and rename the "program" to be the "intervention," then the use of the word "tools" in this section would be appropriate for describing a means of effectuating the "intervention," and there would be no need to use the word "intervention" in this section. However, should you continue to use the plan/planning dichotomy, we suggest you eliminate the word "tools" from this section and refer to "intervention" as the process or system intended to enhance safe product use by reducing risk.

We strongly believe the categorization of risk management program levels (beginning on line 244) should be deleted from the document. A numbering or lettering system would apply a rigidity to the classification of compounds based on the type of intervention scheme without, necessarily, a correlation to the overall risk to patients. For instance, a low risk drug requiring (or voluntarily applying) a number or type of tools that place it with a Level 3 or 4 category would be disadvantaged with respect to a higher risk compound that may only be required to have a Level 2 designation. It is possible that the Level classification could be used in promotional activities that, contrary to regulatory intent, would disadvantage a lower risk therapy. If a classification system is deemed necessary, we suggest the following system, which is more descriptive of the actual interventions, and relates more closely to the "prescribing, dispensing and use" framework identified in line 249 without the numerical hierarchy of the proposed levels:

- Conventional: Labeling modifications based on post-marketing reporting of spontaneous events.
- Education/Outreach: Conventional plus additional education and outreach to health professionals and consumers/patients further elaborating on the safe use of the product.
- Voluntary System: Conventional, plus Education/Outreach and voluntary systems which guide the circumstances for practitioners and/or patients for prescribing, dispensing, and reception/use of a product.

- Mandatory System: Access to product requires adherence to specific program elements of Education/Outreach, Voluntary System, or a controlled distribution system.

Modifying elements of a product's risk management program should be based on an evaluation plan that assesses the overall scope and content of the program. In the section on RMP evaluation, we were uncertain what was meant by the latter part of the statement: "RMP evaluation may be directed to assess both (1) the individual tools and (2) overall RMP effectiveness in achieving their pre-specified objectives and goals." (line 310) Specifically, it is unclear if you are discussing the individual tool effectiveness or another type of RMP effectiveness. Additionally, it is unclear why two different evaluation methods for the key risk management program goals or objectives are needed. (line 326)

Finally, we believe the "What are the Desired Elements of a Risk Management Program Submission" section of the concept paper is a very important section. (lines 389-484) The plans need not be elaborate or lengthy. The applicant must, however, recognize the new product's risk profile for its target population, and submit an appropriate plan for addressing those safety issues of importance.

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

Sincerely,

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