



March 8, 2005

Division of Dockets Management  
U.S. Food and Drug Administration  
5630 Fishers Lane, Room 1061 (HFA-305)  
Rockville, MD 20852

**Re: Docket No. 2004N-0181 Critical Path Initiative; Establishment of a Docket**

Dear Sir or Madam:

Hoffmann-La Roche Inc. appreciates the opportunity to comment on the FDA's Critical Path Initiative and is supportive of the Agency's efforts to develop the new tools needed to improve the process of drug development and review. Roche is a global healthcare company with a leadership position in both pharmaceuticals and diagnostics, and as such, is committed to bringing important new medicines to patients. We support the Agency's goal of bringing innovative, safe and effective medicines and technologies to the market and establishing a closer link between advances in basic and applied sciences.

Outlined below are our specific thoughts related to the various aspects of the Critical Path. We would be pleased to discuss these in greater detail and to work with the Agency on these programs in the future.

**Enhancing Drug Development Review Practices – Need for Openness, Transparency and Alignment**

The following recommendations focus around a pivotal theme that Roche believes is necessary to enhance the availability of novel, safe medicines and are focused on enhancement and alignment of Agency review practices via the finalization of FDA's Good Review Management Practices Guidance. Specifically, Roche believes that an open, clear and transparent process must be in place to foster Sponsor/Agency strategic alignment of IND and NDA review milestones and processes such that both the Sponsors and the Agency have clearly understood expectations around the drug development process.

The primary foundation for achieving this general process alignment revolves around the need for open communications and successful meeting management throughout the entire drug development and review process. Timely and open communication is essential to the successful management of the drug development and review process. Meetings are an essential element for keeping the review on track, and we recommend the Agency maintain a posture of openness and transparency. We recommend that if a meeting request is declined, a complete rationale be provided to the Sponsor rather than a general reference to administrative procedures. We do appreciate receiving written comments in lieu of a meeting; however, there are times where we need clarification and better understanding that can only be achieved through dialogue.

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Documentation of decisions and recommendations are critical for Sponsor and Agency follow-up and accurate minutes of interactions are important in ensuring consistency during the review process. Importantly, we appreciate clear and direct feedback at the meeting which is reflected in the minutes. At times, minutes appear to reflect recommendations not communicated to the Sponsor at the meeting and/or reflect additional FDA post-meeting discussions. We recommend consistent meeting management processes that emphasize collaboration and transparent, timely, and open communication.

***Develop a Process for Strategic Alignment of IND Review Milestones and Processes***

Roche is in the fortunate position to have a drug pipeline which includes approximately 65 new molecular entities spanning a multitude of therapeutic areas and stemming from either our own innovative research or as a result of strategic alliance partnerships. As a global company, Roche wishes to continue to conduct initial human studies within the United States through the opening of US INDs as early in the development process as possible, as we view feedback from the Agency on our development programs a critical success factor for making these innovative medicines ultimately available to the patients who need them. However, at present, there appear to be inconsistent practices between each FDA Division in reviewing and assessing the risk of an initial IND (as well as subsequent clinical studies) as reflected in the divergent Division-by-Division IND clearance statistics. Similarly, it is our experience that Divisions may have different working practices around whether or not preIND meetings are granted and how requests (outside of formal meeting requests) for scientific/medical feedback are handled and processed.

The development of an FDA internal guidance focusing on IND general principles can be of tremendous assistance in standardizing FDA IND review philosophies and best practices with a focus on how FDA assesses and arrives at risk/benefit decisions for initial INDs and subsequent clinical protocols in later phases of development.

The Special Protocol Assessment process is one that if working well serves both the FDA and Sponsor by providing a mechanism for FDA input and guidance to pivotal Phase 3, carcinogenicity and stability protocols within a defined timeframe. The current process however can be problematic, onerous and time consuming if multiple rounds of clarification and responses to suggestions are pursued as a means to achieve final agreement on a protocol. We suggest that FDA define a process for defining reasonable time limits for an FDA response to a Sponsor's resubmission. Most importantly we recommend that FDA consider allowing the bundling of a Phase 3 Special Protocol Assessment with the End-of-Phase 2 meeting package such that there is an opportunity to achieve FDA input into the Phase 3 development program and pivotal protocols in parallel versus the current sequential process which adds additional timelines onto the development program.



### ***Develop a Process for Strategic Alignment of NDA Review Milestones and Processes***

For both the Sponsor and the Agency, a drug development program is a complex, time and resource intensive endeavor with the goal of ultimately bringing important safe and effective new therapies to the marketplace. By the time a New Drug Application or Biological Licensing Application is filed, a large financial and resource commitment has been made by Sponsors with the expectation that, if Agency advice has been followed and the risk/benefit analysis of the drug is favorable, important new therapies will be approved.

As result of the implementation of PDUFA, important milestones have been identified to guide the drug review process, namely the 45-day fileability milestone, the 74 -day letter milestone and establishment of action dates. Unfortunately, between the 74-day letter (assuming one is received) milestone and the action date (which is approximately 7 months for a standard application), no other review or communication milestones are mandated. Dependent upon the Division that is reviewing the application, there may be limited communication with the Sponsor until the time prior to label negotiations. We recommend that the Agency develop additional milestones which will increase the transparency and status of the review process including target timelines for the following: discipline questions, completion of primary and secondary reviews, notification for need for Advisory Committee Meeting if applicable, beginning of label negotiations, discussion of potential Phase 4 commitments, and final Division or Office sign-off on the action letter.

The FDA decisions on Post Approval Commitments are consistently communicated very late in the review process and do not allow for the Sponsor to understand rationale nor commit to realistic timelines to conduct and submit additional trials. We would recommend that at the pre-NDA meeting, FDA communicate at least their thoughts on additional work that may be needed if the application were approved. Guidance documents that specifically address best practices for labeling discussions and postapproval commitments should be developed to ensure that these issues are addressed early enough in the review process so that they are driven by science rather than by review timelines at the end of the approval process. This documentation is also necessary to ensure that there is consistency among review divisions.

### ***Finalize Good Review Management Practices Guidance***

We recommend finalization of the guidance document on Good Review Management Practices with attention to the points above.

### **Develop or Update Guidance Documents in Key Therapeutic Areas**

In pursuit of the goal to achieve greater transparency and strategic alignment during the drug development and review process, we strongly urge the Agency to proactively



develop and update Guidances for key therapeutic areas, including a schedule to update them on a regular basis. The development of these guidances, such as those in the areas of diabetes, dyslipidemia, asthma, to name a few, should be geared toward providing the Sponsors a framework for building a development program that will meet the necessary regulatory requirements. These guidances will also provide the foundation for more productive interactions with the Agency. In the absence of these guidances, the Sponsors are left to assess and interpret the most recent approvals in that therapeutic area as a benchmark for the proposed design of a development program. Also, as Sponsors develop global development programs to meet the needs of worldwide regulatory authorities, any effort to synchronize the development of US guidances with those that have been recently created by the EMEA, will allow for improvements in the design of registration programs that will meet the needs of multiple Health Authorities.

### **Develop Guidance for Regulatory Decisionmaking Based upon Biomarkers/Surrogate Endpoints**

We support FDA activities to articulate standards for biomarker development and the integration of biomarker development into the overall drug development process. We believe that through a consensus building process this will identify what should be contained within a biomarker research plan. We encourage FDA, in collaboration with its stakeholders, to continue developing specific guidance documents related to the various stages of development and various development cases. The issues of risk, biomarker selection, testing, method validation, qualification, and variability should be addressed. The guidance documents should outline the continuum for overall evaluation of a biomarker and link it to expectations for the various stages of development. We believe the FDA can accomplish the work most effectively by integrating programs within its existing structures and using the existing advisory committee process rather than by creating additional review groups or new layers of regulatory review.

### **Establish a Working Group for Pharmacogenetics/Pharmacogenomics within the ICH Program**

We believe that there is a need for global harmonization on conducting pharmacogenetic research. Early efforts to harmonize fundamental concepts and processes at an international level, between the regulators and industry, will facilitate the integration of these promising technologies in the global drug development process. It will be time-consuming and challenging to harmonize in this area once regional guidances are in place. The ICH process offers an existing framework for undertaking this work which should focus initially on the following: 1) standardizing terminology and definitions; 2) reviewing the regulatory framework for the review and approval of pharmacogenetics research sampling protocols by health authorities/central ethics committees; and 3) developing recommendations on the conditions for the collection, storage and future use of pharmacogenetics/pharmacogenomics samples collected in industry-sponsored clinical studies.



**Develop Guidance on Pharmacokinetically-Guided Starting Dose**

During the drug development process dose decisions are key milestones that need to integrate the available knowledge of a compound in order to optimize the benefit/risk of the population to be exposed. Roche has established a global network of pre-clinical and clinical modeling and simulation specialists that use state-of-the art techniques to provide model-based simulations for drug development decisions.

One of the recent focus areas has been the development of Physiologically-based Pharmacokinetic (PBPK) models to support extrapolating pharmacokinetics from animal to humans. We conducted a retrospective analysis and compared various methods of starting dose selection for EIH studies and came to the conclusion that the pharmacokinetically-guided starting dose using PBPK has advantages over the more traditional alternatives such as allometric scaling or BSA adjustments. In the spirit of an improved collaboration between the Agency and Sponsor, we are willing to share our internal experience and collaborate with the Agency on the development of a Guidance for a Pharmacokinetically-Guided Starting Dose.

The starting dose for EIH studies based on PBPK models is just one example of a Pharmacokinetically-Guided Starting Dose. We currently have work in progress to use this technique to bridge from adults to children and use a PBPK guided starting dose for pediatric studies. The basic model has been established and we could envision working with the Agency to validate the model and derive appropriate guidances.

In conclusion, Roche appreciates the opportunity to comment on the Agency's Critical Path Initiative and believes that this program is necessary to ensure that new tools are developed which will advance science in the area of drug development and review. We would be pleased to discuss in greater detail the comments contained in this submission and look forward to working with FDA on this important program. If you have specific questions about the content of this proposal, please contact the undersigned.

Respectfully submitted,

A handwritten signature in black ink, appearing to read "Cynthia H. Dinella".

Cynthia H. Dinella  
Vice President  
Drug Regulatory Affairs

cc: Dr. Lisa Rovin  
Dr. Janet Woodcock

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