



July 8, 2005

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

**Re: Docket No. 2004N-0279: Comments on FDA's Draft Drug-Diagnostic Co-Development Concept Paper**

Dear Sir or Madam:

The following comments regarding the FDA preliminary Concept Paper represent the combined input from the drug and diagnostic arms of the Roche Group: Hoffmann-La Roche, Inc. and Roche Molecular Systems, Inc. We recognize our unique opportunity to provide integrated comments from both the therapeutic and diagnostic industry perspectives and accordingly we will term our combined input, below, as from Roche. As we are aware that this Concept Paper will be used to generate a draft guidance document on drug-diagnostic co-development, we have kept our comments quite general, focusing on key issues for FDA to consider in this guidance development.

**Key Points**

***Timeline Considerations***

A basic concern from Roche is that the co-development model presented and discussed in the Concept Paper is largely based on an unrealistic model (presented in Figure 1) of parallel timelines of drug and device development. The situation in which the marker is identified very early in the drug development cycle and is available for test validation and use in clinical trials prior to Phase 3 is rare. It is much more likely that an appropriate biomarker for IVD development will be identified in Phase 2 or even Phase 3 studies and these situations need to be considered in the proposed model. Additionally, the presented model does not accurately reflect the significant differences in normal development timelines between therapeutic and diagnostic products. While a therapeutic product often takes many years from first in man studies to marketing approval, the timeline for IVD development (to optimize for manufacture and analytical validation) is generally 1 to 2 years. We advise that FDA acknowledge these differences in the draft guidance and revise Figure 1, making it more realistic and flexible.



### ***Scope of the Concept Paper***

The scope of the Concept Paper is too narrow and doesn't reflect the realities of timing or the current practice in diagnostic test development. There is very rarely a case where the diagnostic test is developed *de novo* in complete parallel with a therapeutic. Exceptions may include assays developed for research use that may provide some information from clinical research programs and later used in the IVD development process, but this strategy is likely to begin late in development.

The scope of the Concept Paper further indicates that the concept of "co-development" is intended to address development of a single test with a single drug. There is a high likelihood that multiple tests could be developed in parallel with a drug product and that additional biomarkers could be added at a later date. In the case of Herceptin®, for example, where multiple diagnostic tests have been approved for use with the therapeutic, would only the first (earliest of these) fit into the co-development scheme? There should not be any hurdles put in the way of adding an improved diagnostic test to a drug label, which might be assumed under the one drug/one test definition provided in the Concept Paper.

### ***Demonstration of Clinical Utility***

An approved Premarket Approval Application (PMA) is currently required for all medical devices with claims of clinical utility. If establishing clinical utility is necessary for a co-development program, this requirement presents a major burden for the diagnostic partner, who otherwise might be able to develop their IVD through a less burdensome pathway (510(k), or *de novo* 510(k)). We suggest FDA consider that the *de novo* 510(k) route as an option for the co-development pathway.

The discussion of the need to establish clinical utility (Section 6, page 22) suggests that two confirmatory clinical trials might be needed to support the approval of the diagnostic under this co-development process. Although this is a normal expectation for establishing clinical efficacy of a new therapeutic agent, this is not a requirement for a PMA and this is an excessive request in terms of the Least Burdensome Provisions of FDAMA (§205). Additional studies, beyond those described in the original PMA, are commonly considered as post approval requirements. Roche suggests that FDA's expectations in this regard need to be clarified in the upcoming guidance.

### ***Considerations for Global Development Strategies***

As most critical development programs for new therapies are being carried out on a global level, it is concerning to Roche that the Concept Paper does not address how the co-development process will interact with these global strategies. For example, if a diagnostic is developed, and placed on the market in Europe prior to partnering with a therapeutic agent for Rx Dx co-development, we suggest that the experience gained with the IVD ex-US should be allowed to be referenced in the Rx Dx co-development NDA. As there is high potential for a very complicated global development process, we feel such considerations should be addressed in the upcoming guidance.



***Interaction with VGDS***

In the recently finalized Genomic Data Submission Guidance (March 2005), FDA has established clear guidelines for early development situations where the critical regulatory interactions between the sponsor and FDA are voluntary, with the IPRG (Interdisciplinary Pharmacogenomics Review Group), and do not impact FDA drug development decisions. The Concept Paper lacks adequate reference to the process by which a transition from discussions with FDA under the Voluntary Genomic Data Submission process can transition into the proposed RxDx co-development pathway. As described in Figure 1, the co-development process begins so early as to preclude useful VGDS discussions. Leaving this important opportunity for FDA industry interaction out of a parallel co-development process does not seem either appropriate or fruitful.

***Labeling Implications***

The implications for cross-labeling for drug and device are totally absent from the Concept Paper. As the labeling implications for co-development products are critical to the sponsor (both from the drug and diagnostic companies), Roche considers it critical that expectations be discussed and some guidance on cross-labeling, label changes, supplements and revisions should be provided.

Roche is pleased for the opportunity to provide this input at the early stages of the development of the co-development concept and we understand that there will be further opportunity for detailed comments when the draft guidance is issued later this year. We hope these points will help FDA in the preparing the upcoming draft co-development guidance and we look forward to working with the Agency on it in the near future.

Respectfully submitted,

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