



February 2, 2004

5701 W. CE - 3 2003

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

**Re: Draft Guidance for Industry: Pharmacogenomic Data Submissions  
(Docket No. 2003D-0497, 68 Federal Register, 62461-62463, November 4, 2003)**

Ladies and Gentlemen:

Roche appreciates the opportunity to comment on the above referenced draft guidance and supports the initiative FDA has taken to move forward in this area.

Roche concurs with the overriding FDA goal to facilitate scientific progress in the field of pharmacogenomics. As stated in the FDA draft guidance, Roche feels strongly that it is *"important that FDA policy facilitate, not impede, the use of pharmacogenomic tests during drug development and, to the extent possible, encourage open and public sharing of data and information on pharmacogenomic test results."* We propose that some areas of the draft guidance require clarification or revision to be most effective in achieving these goals recognizing that the existing regulations, to some extent provide a boundary and framework which must apply to the draft guidance.

**SPECIFIC COMMENTS**

**Voluntary Genomic Data Submissions**

The draft guidance introduces the option of voluntary submission to an IND, NDA or BLA of exploratory or research data (VGDS) which FDA will not use for "regulatory decision making". Roche welcomes this concept and has the following specific comments including suggestions for how the VGDS idea might be further adapted towards the FDA aim of "encouraging open and public sharing of data and information on pharmacogenomic test results":

The draft guidance emphasizes that information submitted through VGDS is not necessarily suitable for and will not be used for regulatory decision making. This is a critical concept which may be a key factor for many Companies in deciding whether to move forward with voluntary submissions and indeed in undertaking the enabling science in the first instance. **Roche believes that further elaboration of the term "regulatory decision making" is warranted so there is a clear understanding of how data submitted under VGDS can and cannot be applied in the regulatory review process and decisions with respect to product approval and labeling.**

2003D-0497

C16



Dockets Management Branch (HFA-305)  
February 2, 2004  
Page 2 of 4

Roche proposes that the draft guidance should be explicit about the possible implications for description of exploratory or research data in the product label if submitted via VGDS. **Roche proposes that the guidance clarify that FDA will not mandate inclusion of a description of exploratory data which fulfills the VGDS criteria in product labels i.e. this is encompassed by the term "regulatory decision making".**

The draft guidance requires that voluntary submissions of pharmacogenomic data should be made to the relevant IND, NDA or BLA, clearly labeled as a VGDS, or as a pre-IND submission in the case of candidate drugs. Roche is concerned that the requirement to submit VGDS submissions to the respective IND, NDA or BLA could unintentionally become a barrier to open and transparent sharing of information. We understand that the suggested mechanism for submission is in part driven by concerns around maintaining the confidential nature of proprietary data. Roche has received advice from our internal lawyers suggesting that submission to the IND, NDA or BLA is not the only mechanism to maintain the confidentiality of proprietary data and would request that FDA further investigate this aspect. **Roche recommends that if submission to the IND, NDA or BLA is not a prerequisite for maintaining the proprietary nature of VGDS submissions, then alternative submission mechanisms should be considered.**

The draft guidance states that VGDS filings will be analyzed by the Interdisciplinary Pharmacogenomic Review Group (IPRG) and the relevant review division staff. **Roche considers it important that the guidance better defines the remits and mandates of the respective bodies in this review process. In particular, the role of the IPRG relative to review Division staff should be clarified.**

**Roche proposes that opportunities for informal non-binding meetings or interactions between the sponsor and the IPRG should be possible prior to submission of a formal VGDS. Roche recommends that the sponsor can stipulate if they do not wish members of the IND/ NDA/BLA review team to be involved in such informal discussions.**

**Roche proposes that the guidance should clearly define how the FDA opinion on VGDS submissions will be communicated to the sponsor and proposes that the possibility for informal dialogue between the sponsor and FDA via a non-binding teleconference or meeting is a mechanism for such discussion. This meeting could occur outside the routine meetings specified in the regulations such as pre-IND, end of phase II etc**

The guidance states that if additional information becomes available after submission of a VGDS that renders the results required to be submitted under 312, 314 or 601, the sponsor must submit the data to the IND, NDA or BLA respectively and follow the appropriate algorithm. **Roche considers that this proposal is problematic and can currently only reasonably apply if the**



Dockets Management Branch (HFA-305)  
February 2, 2004  
Page 3 of 4

**“additional information” that becomes available is also generated from the same sponsor. It is important that this point is clarified as currently it is not clear how sponsor Companies might become aware of information from other Companies in sufficient detail to allow them to make a decision as to whether formal submission of data is now required.**

Roche agrees with the need for FDA to develop expertise and understanding of the field of pharmacogenomics to ensure that their policies are based on the best science. It would be helpful to understand the mechanism for this information sharing and education within the FDA. **Importantly, there should be a transparent defined process to communicate back to industry what FDA has learned from review of multiple VGDS submissions to sponsors. This could take place in part via one –on –one discussions with individual sponsors in relation to their own data and via a public process when general leanings based on data from multiple sponsors are communicated.**

#### **Format and Content of A VGDS**

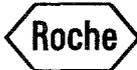
Roche supports the concept of maintaining flexibility in the format for presentation of VGDS submissions. **In order to facilitate availability of sufficient information to allow FDA to achieve the goals of the VGDS process and to simultaneously minimize the burden on sponsors of VGDS submissions, Roche proposes that options such as integration of VGDS submissions into primary study reports are open to sponsors.**

**Roche proposes that should a sponsor choose to submit a VGDS submission as a full submission, the sponsor could request a description of the exploratory data in the product label although as noted earlier, this could not be mandated by FDA if the submission was VGDS**

The Agency intends to develop an aggregate genomic knowledge database from multiple VGDSs. What level of data does FDA plan on entering into the database? Will it contain raw genotype or Affymetrix data or only aggregate results (eg compound class, p values, n). Who will be able to access the database?

#### **Biomarkers**

The draft guidance proposes definitions for “known valid” and “probable valid” biomarkers and outlines the regulatory implications for submission requirements for each entity. **Due to the variance in submission requirements and regulatory implications for the sponsor, it is very important that the guidance delineate a process for how biomarker status will transition from “probable valid” to “known valid”. The guidance should also define how sponsors are to become aware of this transition as well as define a period of time which sponsors will**



Dockets Management Branch (HFA-305)  
February 2, 2004  
Page 4 of 4

**have to comply with submission requirements in the event that a biomarker is newly elevated to the status of "known valid"**

**It is recommended that FDA prospectively establish publicly available timings for when they will review and revise a list of "known valid biomarkers"**

The draft guidance states that a probable valid biomarker may not have reached the status of a known valid biomarker because, for example, *"the data elucidating its significance may have been generated within a single Company and may not be available for public scientific scrutiny"* **This definition is troubling for the purposes of progression of drug development because of the possible implication that a probable valid biomarker may not necessarily be considered appropriate for "regulatory decision making" unless data is generated from more than one source. The guidance needs to clarify the implication of probable biomarker status for regulatory decision making.**

#### **Compliance with 21 CFR Part 58**

The proposed requirements for GLPs under 21 CFR part 58 and their application to non-clinical studies are currently unrealistic with regard to technologies such as the Affymetrix platform at this time. **Roche proposes that additional flexibility must be considered for pharmacogenomic analytical techniques with respect to 21 CFR Part 58.**

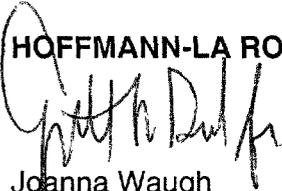
#### **Other Comments**

Roche strongly believes that there is a need to ensure global communication and exchange of information on the topic of pharmacogenetics. This is imperative to avoid disharmonious national approaches that will impede progress for global companies. One avenue to further these discussions is via an informal discussion topic as part of the ICH process.

Roche welcomes the opportunity to provide comment on this draft guidance and looks forward to availability of an updated draft guidance in the future.

Sincerely,

**HOFFMANN-LA ROCHE INC**

  
Joanna Waugh  
Regulatory Group Director  
Phone 973 562 2566  
Fax 973 562 3700

JW/gb

HLR No. 2004-305