

To: Ginny Butler  
Agency: FDA, HHS; Dockets Management Branch (HFA-305)  
Docket No.: 00D-0186  
Topic: ICH M4 Common Technical Document  
Action: Comments on initial components on or before March 13, 2000  
Date: 3/13/2000

This document has been released for public consultation (step 3 of harmonization effort). In this regard please find enclosed comments that are either general or specific to drug safety aspects from the Drug Regulatory Affairs Department of Sanofi-Synthelabo Research Division, 9 Great Valley Parkway, Malvern, PA 19355.

## GENERAL COMMENTS

### 1. Comment re: Structure of CTD

The ICH Expert Working Groups may consider adding a brief description of the CTD, emphasizing objectives to be met by such a structure and aspects of the process which previously were carried out differently by one or more of the three regions (USA, Europe, Japan). For example, a description of which modules are intended for assessment by all regulatory reviewers, OR the quality, clinical, or non-clinical reviewer, should be included, along with the intended exclusion of raw data, e.g., individual patient case report forms or individual animal data records.

It is also suggested that the ICH Groups comment on the use of in-text vs full-length tables that follow the main body of text.

### 2. Comment re: Executive Summaries

It is suggested that the ICH Working Groups include the proposed 'strategic' focus of these summaries, e.g., to assess critical aspects of the sequential development of the product, rather than drawbacks of the product, itself so that all relevant data elucidating certain effects or phenomena are brought together in a logical order. This represents a departure from the philosophy of the European expert reports.

In addition, the Working Groups are urged to elaborate on the role of the Executive Summary, i.e., integration, critical assessment, and interpretation of findings across studies and disciplines (pharmacodynamics, pharmacokinetics, toxicology, and clinical development) to support the proposed clinical dose under the stated conditions of use and justify other sponsor positions made in the label re: mechanism of action, reproduction, toxicology, carcinogenicity, the over risk: benefit assessment, etc.

Also important is the inclusion of justification for the choice of pharmacologic models and analytical methods.

### 3. Comment re: Written summaries

It is recommended that the ICH Working Groups clearly state their desire that these summaries represent a comprehensive review in only 100-150 pages of non-clinical studies with less detail that which is contained in individual study reports.

4. General Principles: p 5 - Maybe we could standardize page size?
5. Content and Structural Format: p 6 - Add to list: Qualification of Impurities/Degradants
6. Content and Structural Format: p 7 - Move 3<sup>rd</sup> paragraph (The evaluation....) ahead of 2<sup>nd</sup> paragraph (The onset...); it makes the text flow better.
7. Nonclinical Tabulated Summaries: p 27  
The tabulated summaries should include a paragraph with additional information including the very important short conclusion or comment on the study.

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**COMMENTS RE: TOXICOLOGY**

1. 3.4 Toxicology Written Summary: p 15 - Where would neonatal (juvenile) toxicology studies be placed, Repeat-Dose, Reproduction Toxicity, Other Toxicity ?
2. Tabulated Non-clinical Summaries: Templates p 28 - Why separate non-pivotal studies from definitive studies? It is better to group non-pivotal studies with the definitive studies that they support, where applicable.
3. Tabulated Non-clinical Summaries: Templates p 28 - Where would neonatal (juvenile) toxicology studies be placed?
4. Overview: p 51 - Where would neonatal (juvenile) toxicology studies be placed?
5. Repeat-Dose Toxicity: p 54 - ICH needs to define NOEL, NOAEL, and LOAEL. If NOAEL is not available, can NOEL or LOAEL be substituted and defined?
6. Repeat-Dose Toxicity: p 55 - Should clinical observations of moribund animals be presented separate from non-moribund animals?
7. Repeat-Dose Toxicity: p 56 - Where should recovery data be listed? This table has the potential to be very bulky and busy.
8. Repeat-Dose Toxicity: p 57 - In regards to Note 11, is the same format to be used for animals killed early? Also, a definition for 'sacrificed early' is needed. Would this include scheduled interim sacrifices as well as animals killed moribund?
9. Carcinogenicity: p 60 - Need to state how the following will be handled: hematology data, multiple control groups, diet restriction (if necessary).
10. Reproduction Toxicity: p 64 - If the study design (ICH 4.1.1, 4.1.2, 4.1.3) differs from that specified by ICH, the differences should be clearly specified (somewhere) on the table.
11. Reproduction Toxicity: p 64 - The **Date of First Dose** needs to be separated for males and females since they are not started on the same day.
12. Reproduction Toxicity: p 64 - **Day of Mating** needs to be changed to **Day of Confirmed Mating** (Insemination). As presently stated, implies day of cohabitation. This needs to be changed for ICH 4.1.1, 4.1.2, 4.1.3.
13. Reproduction Toxicity: p 64 - NOAEL should be footnoted to include LOAEL also. This needs to be changed for ICH 4.1.1, 4.1.2, 4.1.3.
14. Reproduction Toxicity (Males) : p 64 - Change **Mean No. Days Prior to Mating** to **Pre-Coital Interval (days)**. Also change for Females (p 65), F1 males (p 70), and F1 females (p 71).
15. Reproduction Toxicity (Females): p 65 - Need to include Females with Copulatory Plugs with Females Sperm-Positive.
16. Reproduction Toxicity: p 66 - Note 8 should be modified to read: Day of mating confirmation (insemination) should be indicated.
17. Reproduction Toxicity: p 68 - many of the parameters need to be expressed as mean and Number X / Litter. Add, Mean and No. Dead Fetuses/Litter and Mean Affected Fetuses/Litter.
18. Reproduction Toxicity: p 70 - For consistency, use (Pup) Body Weight Change for F1 Litters, F1 Males and Females and F2 litters
19. Reproduction Toxicity: p 70 - Add **Mean Age of Preputial Separation**.

**Comments Re: Metabolism and Pharmacokinetics**

1. 3.3.4, p 14, Tissue Distribution: - Include: **Placental transfer/excretion into milk** studies
2. p 14, Metabolism (inter-species comparison):  
Please specify if data in human have to be added in this part (in vitro and in vivo) for comparison.  
Are in vitro data on human material to be reported in this section ?
3. 3.4, p16, Pharmacokinetic Written Summary, Toxicology Written Summary:  
Please note that the toxicokinetic part is requested for section 3.4, and not 3.3, and discussed with the toxicology. But the tables are only in the pharmacokinetics section. Shouldn't the toxicokinetic part also be discussed in the pharmacokinetics section?

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