

David W. Blois, Ph.D.
Vice President
Worldwide Regulatory Affairs

Merck & Co., Inc.
West Point PA 19486
Fax 610 397 2335
Tel 610 397 2304
215 652 5000

0644 00 SEP 28 08:33

September 27, 2000

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



RE: [Docket No. 00D-0186]
Draft Guidance: M4 Common Technical Document

Merck & Co., Inc. is a leading worldwide, human health product company. Merck's corporate strategy -- to discover new medicines through breakthrough research -- encourages us to spend more than \$2 Billion, annually, on worldwide Research and Development (R & D). Through a combination of the best science and state-of-the-art medicine, Merck's R & D pipeline has produced many of the important pharmaceutical products on the market, today.

Merck supports regulatory oversight of product development that is based on sound scientific principles and good medical judgment, to ensure that important therapeutic advances reach patients without unnecessary or unusual delays.

Merck has participated with health authorities from around the globe in the harmonization of regulatory standards under the auspices of the International Conference on Harmonization (ICH). The objectives of ICH have been to identify and correct unnecessary redundancies and time-consuming inefficiencies in development of pharmaceutical products caused by incompatible regulatory schemes. We continue to monitor the equitable and consistent application of these harmonized standards to product development in order to ensure that *new* or *improved* therapies reach patients as swiftly as possible.

In the course of bringing our product candidates through developmental testing and clinical trials, Merck scientists file numerous original and supplemental New Drug Applications each year, that contain documentation addressed in the Draft Guidance: M4 Common Technical Document (hereafter referred to as the CTD). For these reasons, we are very interested and well qualified to comment on this Draft Guidance.

We commend the FDA as well as all ICH participants in their pursuit of harmonized and streamlined documentation requirements for marketing applications for products for human use. Merck has a number of comments on the Draft Guidance which may clarify the current draft.

00D-0186

C8

Dockets Management Branch
RE: [Docket No. 00D-0186]
Draft Guidance: M4 Common Technical Document

General Comments

1. The amount of cross-referencing or repetition of information across the quality, safety, and efficacy modules seems excessive and may extend the length of time required to prepare the dossier, since most documents are written independently of each other. Considering the pending availability of ICH M2 [Electronic Standards for the Transfer of Regulatory Information and Data (ESTRI)], Merck recommends consideration of the advantages and the inherent functionality of electronic submissions which may enhance navigation through documents, rather than requiring mandatory cross-references throughout the dossier.
2. It is desirable to have consistency across the M4 CTD guidance document and the resulting CTD created in support of a marketing application. Standardization of outline format and nomenclature within the Draft Guidance is therefore important. Currently the presentation is at times inconsistent with respect to outline numbering and naming of subsections within the draft guidance.
3. If references are made to regional guidelines that address a particular issue, Merck recommends mentioning the guidelines available from all three regions, if applicable.

Specific Comments

QUALITY

General Comments

1. If a substance or excipient is specified according to the three monographs (USP, EP, JP), Merck recommends that the Draft Guidance be clarified so that only the monograph valid for the region is applied.
2. The Draft Guidance does not describe how references to Drug Master Files are to be addressed.
3. There is no mention regarding the placement of References within any of the Modules for example journal articles and or large bodies of data such as stability data tables for the Quality Module.

Quality Overall Summary (OOS) –Module II

1. If this Draft Guidance replaces the existing requirements for the Chemistry, Manufacturing & Controls (CMC) Summary in the U.S., the Expert Report in the EU, and Sections B and C of the Gaiyo in Japan, that should be stated within the Draft Guidance.

Dockets Management Branch
RE: [Docket No. 00D-0186]
Draft Guidance: M4 Common Technical Document

2. The first paragraph states that “The QOS cannot include information, data or justification that was not already included in the body of.....”, while paragraph two states “The QOS should include a discussion of salient and critical issues that integrates information from sections in the Quality Module and supporting information from other Modules (e.g. qualification of impurities via toxicological studies discussed under the CTD-S Module).” These appear to be contradictory. It should be reiterated that the discussions contain information already included in the body of CTD-Q and should not be opinionated or provide an assessment.
3. In the outline section (page i through iv) the following comments are provided for clarification:
 - In general, explain what is intended by the italicized entries.
 - The guidance written as “Information as provided in S# (or P#)” may be better understood if instead it specifies the need for a summary discussion.
 - S3 Characterization (spelled with an “s” or a “z”?) – In the section listed “For NCE and Biotech”, will there be a summary discussion and a tabulated summary and/or graphical representation of the data?
 - There is no indication that Section R for regional information exists or what the contents should be. Does that mean this will not be in the QOS?
 - The fact that not all of the contents are harmonized will require that “region-specific” QOSs will be required. This lends more support for continued ICH harmonization efforts, or perhaps the QOS should be positioned as a regional requirement.

Comments on Quality – Module III

1. The statement on page 1 that reads “The text following the section titles is intended to be explanatory and illustrative only. It is not all-inclusive and additional regional requirements may apply,” appears to be contradictory to the intent of a harmonized guidance. It is to be expected that ICH will take on the additional future assignment to harmonize any of the sections which are currently the most different between the regions. These may include the manufacturing process description requirements for both drug substance and drug product, the information required for container closures and the harmonizing of the differences between compendia, for example.
2. In Sections S2.3 and S2.4, the level of detail for method description and specification justification for starting materials and intermediates should be much less than that for drug substance and drug product.

Dockets Management Branch
RE: [Docket No. 00D-0186]
Draft Guidance: M4 Common Technical Document

3. In Section P2, Merck recommends deleting the sentence in the first paragraph that reads, "Additionally, this report should identify and describe the formulation and process attributes (critical parameters)..." since this information is included in other sections of the document. Is the format of this section (1., 1.1, 1.2, 2. etc) intended to be how subsections are expected to be handled in other sections of the CTD-Q? Are the attachments mentioned to be included at the end of the P2 section or at the end of the Drug Product section or at the end of the complete document after A. Appendices? Is the information typically submitted in the NDA under D. Investigational Formulations expected to be included in P2.2.1 Formulation Development? Is it intended to be as inclusive as the NDA currently requires? If so can the investigational formulations be included as an attachment or reference?
4. Regarding Section A 2 (Viral Safety Evaluation), Merck recommends that an evaluation of the presence/ absence of all adventitious agents be included, not just a status report of the presence of viruses because bacteria or virions may also be introduced during the process. Accordingly, Merck recommends that the focus of this section be expanded and re-titled to: "*Safety Evaluation*".
5. The placement of regional information in Part R could create a large subsection. Merck recommends being very specific about what the regional requirements are rather than leave the section open to interpretation. We also recommend considering the use of references for regional information as a more flexible option. Providing less detail within the summaries while including specific regional supplements is preferred over including more detail within the summaries to satisfy the needs of all three regions.
6. There should be a separate section for References or Attachments where information can be placed rather than including in the body of the text e.g., stability data tables and journal articles or container closure schematic drawings, DMF Letters of Authorization, etc.
7. A revision is needed to the FDA Electronic Submission Guidance that outlines how folders and references are to be handled.

SAFETY

Nonclinical Overall Summary – Module IIA

1. Merck supports the page limits suggested for the length of the Nonclinical Overall Summary.

2. The Draft Guidance states that the Nonclinical Executive Summary should note “any association between findings and the quality of the human pharmaceutical, the results of clinical trials, and effects seen with related products should be indicated”. Since nonclinical results are typically available much earlier than the clinical results, this requirement will make it very difficult for sponsors to finalize any documentation for a marketing application until after all results are available. Merck recommends that this position be further discussed in the context of the availability of ICH M2 [Electronic Standards for the Transfer of Regulatory Information and Data (ESTRI)]. The facilitation of electronic navigation may preclude the need to discuss this association in the Executive Summary. The issue of how this can be reconciled with the current Guidance For Industry regarding Fast Track NDA and its provision for early submission of technical section before the complete NDA must also be addressed.
3. The Draft Guidance states: “Nonclinical testing strategy should be discussed.” Does this require more or different information than what is already provided in the rationale currently included in the Pharmacology section? Merck recommends that this section and the Content and Structural Format section should be clarified if new information is required to explain nonclinical testing strategy.
4. The Draft Guidance states: “Except for biotechnology-derived products, an assessment of the impurities and degradants present ...”. It is important to Merck (and other vaccine & /or biologicals manufacturers) that this Draft Guidance be extended to traditional biologic products.. However, since it is not possible to identify, purify, characterize, and then perform preclinical studies on all potential biological by-products that may be present in trace amounts, Merck recommends that this sentence be changed to: “Except for *biologically-sourced products*, an assessment of the impurities and degradants present ...” as it was changed in the Quality Guidance.
5. Merck recommends that the term “pharmacology” be replaced with “pharmacodynamics” when discussing topics within Module II.

Nonclinical Written Summaries - Module IIB1

1. In Section 2.1, the proposed order of dosage groups is not consistent with the order currently used for human trials. Merck recommends that the Draft Guidance not mandate the order of the groups.
2. The Draft Guidance should clarify whether reference citations are to the Tabulated Summaries and Study/Report number (Table X.X, Study/Report Number) or to a reference number.
3. The Draft Guidance requests cross-referencing to data contained in other sections of the application.. As stated under General Comments above, this complicates preparation of a dossier and may be awkward and time-consuming to implement into current practice.
4. In the table titled, “Model-independent pharmacokinetic parameters....” in Section 3.6, a $t_{1/2}$ is missing and should be included.

5. Generally, in most of the tables and figures in the Draft Guidance, symbols were not used systematically as recommended in writing guides (e.g., *AMA Manual of Style*). Merck recommends using a standard approach for use of symbols that is commonly accepted in industry practice.

Nonclinical Tabulated Summaries - Module IIB2

1. The Draft Guidance states that the statistical significance of the actual data and not of the percent differences, be used in the Carcinogenicity tabulations. Merck recommends that the rationale for this request be provided .

Table of Contents: Organization of Nonclinical Data - Module IV

1. Merck recommends that the phrase "where appropriate" be added to Local Tolerance in Section B 3.6.

EFFICACY

Clinical Overall Summary – Module IIC1

Merck has no comments on this section.

Written Summary of Clinical Studies and Experience – Module IIC2

1. One needs to understand the pharmacokinetics of a compound before one can follow the ramifications of Bioavailability (BA), Bioequivalence (BE), and other biopharmaceutics studies. The proposed manner of discussing biopharmaceutics, first in section 1, then followed by clinical pharmacology in section 2, breaks up any kind of flow intended for an integrated summary. Also, some studies that have both biopharmaceutics and clinical pharmacology aspects will need to be discussed in both sections. Merck recommends merging these two sections into one, resulting in one table of studies instead of two.
2. In the Appendix to Section 3, the statement, "Tabular presentations.....pertinent to the evaluation of efficacy (including studies that were terminated or are not yet completed,...." may be misinterpreted. Merck would supply information on results of ongoing studies relevant to the indication *only* if there was a planned interim analysis and data/results were available. Other sponsors may interpret this requirement differently.
3. Reference is made to the regional requirement for a more extensive integrated safety discussion. It is unclear where this should be located in the dossier. It is Merck's interpretation that this would be included in section 5.3 of Module V but this should be more clearly stated.
4. It appears that many of the table and figure examples have been removed. Although each program has unique attributes, Merck recommends providing suggestions for at least some of the basic safety tables that rarely change from program to program.

5. Merck recommends that the language in the Draft Guidance regarding pooling data from studies to analyze efficacy and safety be minimized. There are very specific criteria that must be met in order for valid analyses to be conducted on pooled data. It may be more useful for applicants, if the Draft Guidance were to outline some examples of what might be considered valid, rather than discuss the uses of pooled data. In general, pooling of data is very difficult to accomplish with any meaningful result unless the data that are pooled are from studies identical in design and conduct, and there is an *a priori* plan to pool data.
6. Currently sponsors report adverse experiences alphabetically within each body system. Order of decreasing frequency may or may not be commonly used. Merck recommends that the alphabetical system be maintained in order to enhance reviewability.
7. The display and discussion of clinical and laboratory adverse experiences in a combined fashion is similar to that in ICH E3. Merck experience indicates that it may be more beneficial to discuss clinical and laboratory adverse experiences separately, since it helps keep the discussion focused and is more consistent with how the adverse experiences are displayed in the product labeling.
8. There is no provision for sets of declarative statements that can be termed "conclusions" in the efficacy or safety sections. Merck recommends including a subheading to capture these statements, as they are often used in product labeling.

Clinical Study Reports - Module V

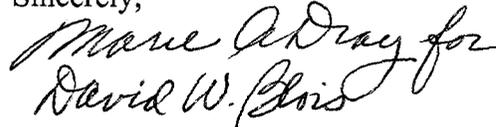
1. In Section A (Table of Contents) - For supplements or variations, the Draft Guidance states that the Table of Contents should indicate either "not applicable" or "no study conducted". There will be many situations where that would apply to all but 2 or 3 of the sections which could make the dossier appear deficient. Merck recommends that, for clarity and simplicity, if an entire category is not applicable, then only one statement be indicated on the Table of Contents at the top level and not repeated for every subsection (e.g. 3.1, 3.2, 3.3, etc.).
2. Merck recommends including the U.S.-required document entitled "Table of All Investigators" as part of Module V to be placed with the Tabular Listing of All Clinical Studies. This would facilitate the compilation of the dossier and may be useful information for all three regions.
3. Merck recommends that this requirement to include reports on studies investigating related indications and indications other than those proposed would add unnecessarily to the volume of and to the time required to prepare the application; it should be simplified or omitted.
4. It is unclear whether the report for post-marketing experience is to be based on published and/or unpublished information.

Dockets Management Branch
RE: [Docket No. 00D-0186]
Draft Guidance: M4 Common Technical Document

5. Human Pharmacokinetic/Pharmacodynamic (PK/PD) study reports should not be separated into predefined structured categories since some studies fulfill multiple objectives. The reports should simply serve as references to the summary of PK/PD. Since electronic submissions (in PDF file format) will allow indexing, so the reviewer could easily navigate from the integrated summary to the specific reference. ICH M2 [Electronic Standards for the Transfer of Regulatory Information and Data (ESTRI)] may also provide guidance in this area when it becomes available.
6. Regarding Section C.7 on Case Report Tabulations and Case Report Forms (CRTs and CRFs), organizing the CRTs by sections consistent with the Study Reports is acceptable current practice in industry. However, it is not an appropriate system for the CRFs. Merck recommends that CRFs be organized by category (Death, Discontinued, etc.) and then in study order within each category.

We welcome the opportunity to comment on this Draft Guidance and, if appropriate, to meet with you to discuss these issues.

Sincerely,

A handwritten signature in cursive script that reads "David W. Blois". The signature is written in dark ink and is positioned above the printed name and title.

David W. Blois, Ph.D.
Vice President
Worldwide Regulatory Affairs

FedEx USA Airbill

FedEx Tracking Number **818884439959**

Form ID No.

0215

Recipients Copy

RECIPIENT: PEEL HERE

1 From This portion can be removed for Recipient's records.

Date **9-27-00** FedEx Tracking Number **818884439959**

Sender's Name **David W. Blois** Phone **301 941-1400**

Company **MERCK RESEARCH LABS**

Address **2 BETHESDA METRO CTR STE 700** Dept./Floor/Suite/Room

City **BETHESDA** State **MD** ZIP **20814-5378**

2 Your Internal Billing Reference

00D-0186

3 To

Recipient's Name **Dockets Management Branch** Phone **301 827-6860**

Company **Food and Drug Administration**

Address **5630 Fishers Lane HFA-305, Room 1061** Dept./Floor/Suite/Room

We cannot deliver to P.O. boxes or P.O. ZIP codes.

To "HOLD" at FedEx location, print FedEx address here.

City **Rockville** State **MD** ZIP **20852**



0144115358

4a Express Package Service

FedEx Priority Overnight Next business morning

FedEx Standard Overnight Next business afternoon

FedEx First Overnight† Earliest next business morning delivery to select locations

FedEx 2Day* Second business day

FedEx Express Saver*† Third business day

* FedEx Letter Rate not available
† FedEx Packet Rate not available
Minimum weight may apply

4b Express Freight Service

FedEx 1Day Freight* Next business day

FedEx 2Day Freight Second business day

FedEx 3Day Freight Third business day

* Call for Confirmation. † Declared value limit \$

5 Packaging

FedEx Letter*

FedEx Packet* Limited availability

FedEx Pak*

Other Pkg. Includes FedEx Box, Ft Tube, and customer kit

6 Special Handling

Saturday Delivery Available for FedEx Priority Overnight and FedEx 2Day to select ZIP codes

Sunday Delivery Available for FedEx Priority Overnight to select ZIP codes

HOLD Weekday at FedEx Location Not available with FedEx First Overnight

HOLD Saturday at FedEx Local Available for FedEx First Overnight and FedEx to select locations

Does this shipment contain dangerous goods? One box must be checked.

No Yes As per attached Shipper's Declaration Yes Shipper's Declaration Not required

Dangerous Goods cannot be shipped in FedEx packaging.

Dry Ice Dry Ice, 9, UN 1845 x

Cargo Aircraft Only

7 Payment Bill to:

Enter FedEx Acct. No. or Credit Card No. below.

Sender Acct. No. in Section will be billed.

Recipient Third Party Credit Card Cash/C

Obtain Recip. Acct. No.

Total Packages **1** Total Weight **5**

Total Charges **36.00**

Credit Card

*Our liability is limited to \$100 unless you declare a higher value. See the FedEx Service Guide for details.

8 Release Signature

Sign to authorize delivery without obtaining signature.

By signing you authorize us to deliver this shipment without obtaining a signature and agree to indemnify and hold us harmless from any resulting claims.

Questions? Call 1-800-Go-FedEx (800-463-3339)

Visit our Web site at www.fedex.com

Rev. Date 12/89 Part #154820G ©1994-98 FedEx-PRINTED IN U.S.A. GBFE 10/98

36.00