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ICH Common Technical Document - Efficacy (Step 2/3)

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

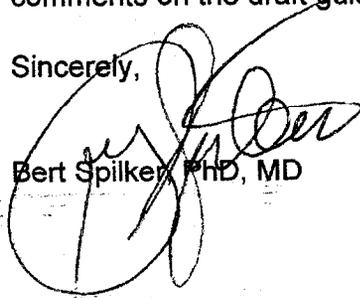
Re: Docket No. 00D-0186 - International Conference on Harmonisation; Draft Guidance on M4 Common Technical Document (65 Federal Register 51621; August 24, 2000)

Dear Sir/Madam:

Please replace the set of comments filed earlier by the Pharmaceutical Research and Manufacturers of America (PhRMA) on the "International Conference on Harmonisation; Draft Guidance on M4 Common Technical Document."

PhRMA represents the country's leading research-based pharmaceutical and biotechnology companies. PhRMA member companies are devoted to inventing medicines that allow patients to lead longer, happier, healthier, and more productive lives; our members invest over \$26 billion annually in the discovery and development of new medicines. For this reason, PhRMA and its member companies are keenly interested in all aspects of the drug development process, including the format and content of prescription drug labeling. We appreciate the opportunity to provide comments on the draft guidance.

Sincerely,


Bert Spilker, PhD, MD

00D-0186

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ICH Topic M4 - Common Technical Document Step 2
Comments from PhRMA

Pharmaceutical Research and Manufacturers of America September 2000

Overall Summary of Comments and Recommendation

The 20 July 2000 Step 2/3 draft consensus guideline for the Common Technical Document - Efficacy (CTD-E) is well on the way to becoming a milestone document for use by Industry and Regulators. PhRMA endorses continued work on the CTD-E guideline to further enhance it. However, we would strongly recommend the following two points:

- *Step 4 sign-off of the CTD* by the ICH Steering Committee should take place only after the ICH Parties agree on a clear plan for implementation;
- Regulators should require that *all Applications* meet the same standards for format and content.

We also have a number of other comments, summarized below, that detail our concerns and suggestions for improvement of the CTD-E. The comments we provide here primarily pertain to Module II.B.4 (Common Technical Document Summaries, Overall Summaries, Clinical Overall Summary), Module II.D (Common Technical Document Summaries, Clinical Written Summary), and Module V (Clinical Study Reports), although reference is made to the CTD in its entirety and to certain other Modules.

General Comments

Implementation. The objective of the M4 Topic guidelines is to present a common format for a single dossier, the CTD, to be used by Industry to prepare Applications and by Regulators to review Applications for registration of pharmaceutical products in the three ICH Regions. However, there has been no agreement amongst the ICH Parties as to how the CTD will be implemented. It is imperative that there be consistent implementation by Regulators across the Regions. Either the CTD format should be made available as a stand-alone alternative format for voluntary use in lieu of the NDA, MAA, and J-NDA formats, or the CTD format should completely supersede the currently available formats and be required for use in all Applications. In either case, the CTD must be used in its entirety. The concept of harmonizing formats will be lost if Regulators require the CTD in addition to existing requirements or if attempts are made to try to fit the CTD format around existing formats. The guideline states that it describes "a format for the CTD that will be acceptable in all three regions," but the significance of this statement is unclear. For example, it is possible that, in addition to the CTD, the EU will still require Expert Reports as Overall Summaries if the CTD Overall Summaries do not perform the critical assessment function required by the Regulatory Authorities. Likewise, the US may still require an Integrated Summary of Safety in addition to the clinical written summary. In Japan, the **GAIYO** is currently required as a Region-specific filing document; the CTD guidelines should clearly indicate whether or not, and to what extent, the CTD may substitute for documents such as these (see Regional Information, below). It is important that, if Industry submits an Application according to the CTD

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guidance as written, e.g., a CTD containing Overall Summaries (Module II.B), Nonclinical Summaries (Module II.C), Clinical Written Summary (Module II.D), Quality (Module III), Nonclinical Study Reports (Module IV), and Clinical Study Reports (Module V), the same CTD package will be acceptable to Regulators for filing in any or all of the three Regions. Regulators in all Regions should accept a CTD that is identical in format to fulfill the requirements in their Region.

Also, the guideline should confirm to what extent the format described in the guidance(s) must be followed. Early drafts of this document contained a statement at the beginning that explained that these guidelines should not be used as a template for the presentation of actual CTD submissions, and that applicants should structure and present their submissions as appropriate to their application. This statement is not in the latest version, although similar comments are made at certain points in the document. This up-front advice on presentation should be put back into the document.

Consistency of numbering and section titles. Inconsistencies in numbering and exact wording of section titles make the four Step 2/3 CTD documents confusing and difficult to navigate. Each of the guidelines should be checked for internal and cross-guideline consistency. The order and numbering of the various sections and subsections within Modules of the CTD-E should be consistent and the numbers of the sections within the CTD-E guidance should correspond to the numbers given in the "Organization of the Common Technical Document." Also, the arrangement of the Written Summary should be consistent with that of Module V. For example, the titles "1. Summary of biopharmaceutical studies and related analysis methods" (page 9) and "2. Summary of clinical pharmacology studies" (page 46) are not consistent with the titles in Module V. We would also like additional explanation provided so that the structure will be easier to understand. In addition, all pages of the guidance should be numbered.

Regional Information. The Step 2/3 CTD documents are described as "the agreed upon common format for the preparation of a well-structured Common Technical Document." However, during the development of the CTD there have been suggestions that special Regional requirements will continue. This would be counter to what we believe is the intent of the ICH Steering Committee regarding the CTD. Before there is agreement by Industry to accept the CTD, it is important that Regulators from the three Regions clearly articulate what additional Regional requirements they will impose. This has not been explicitly stated during the development of the CTD. Without explicit statements, Industry may find that they are expected to produce a significant quantity of Region-specific documentation in addition to the CTD. The CTD-Quality document has a section designated, "Part R: Regional Information." The CTD-Q "R" section would contain executed batch records, a methods validation package, comparability protocols, and the process validation protocol of the drug product, all as Regional requirements. If Regulators intend to require Region-specific components for registration purposes, we suggest that the Efficacy (and the Safety) portions of the CTD be modified to contain complete and specific information about any such Regional requirements in a corresponding "R" section. Similar statements are needed for the Safety and Efficacy components of the CTD; if Regulators do not intend to impose additional Regional requirements for the Efficacy and Safety parts of the CTD, this should be stated.

Toward a global standard. It would further the goals of international harmonization if ICH Observer countries accept the CTD as the single standard for registration requirements. Further, the CTD, perhaps with modified Quality components, should be considered as the primary registration document for marketing applications of all products in non-ICH countries. The ICH Global Coordination Group should pursue this with Regulators in these countries, with a goal of harmonizing requirements and format of registration documents for all Applicants. These countries may request the extended dossier, e.g., full reports and appendices, in addition to the standard summaries provided in the CTD. However, we believe that it is unrealistic to expect many of these countries to accept or process the full ICH dossier. The registration package could be followed, as and when appropriate, by submission of a Certificate of Pharmaceutical Product (CPP).

Maintenance of the CTD format. It is unclear whether the dossier format achieved with the CTD will require extensive maintenance and, if so, how this might be accomplished. It is expected, however, that the CTD format will need to be modified to accommodate scientific progress, particularly Module III. A process should be developed along with the Step 4 sign-off to ensure that harmonization will be maintained following an update and that implementation of an amended CTD occurs concurrently and consistently across all Regions.

Other Concerns

Genetically defined populations. Guidance on how to present data in specific, genetically defined populations should be included. This might best be incorporated in the section on special populations (4.5, page 19), which usually encompass factors of race, gender, age, renal or hepatic impairment, etc. The Benefit and Risk section should also consider genetically defined populations with reference to genetic polymorphisms that are relevant to the drug target, disease genes, and genes involved in metabolism of the drug. Guidance should be provided on other appropriate sections of the CTD to include such data.

Overall summaries (Module II.B.4.) Designation of "Overall Summaries" as a "summary" may be misleading as to its purpose. It is not actually a summary of the summary. "Overall" summary may also imply that it is a comprehensive summary of all data, which it is not. A preferred designation of the "Overall Summaries" might be "Assessment," the Clinical Overall Summary could be termed "Clinical Assessment" or, alternatively, "Clinical Benefit/Risk Assessment" to more appropriately describe this component of the CTD.

Expected authorship of the Overall Summaries is unclear (the sponsoring company or independent experts). Without a clear statement of the expectation regarding authorship, there may be divergence of opinion by Regulators as well as Companies in the three Regions.

A definition of terms should be included whenever possible (e.g., long-term studies). It would also be helpful if a glossary was included as part of the document or reference was made to existing, appropriate glossaries in other ICH Guidelines (e.g., E6).

A general statement should be made to encourage cross-referencing where possible to avoid redundant text when this will not impede agency reviews. The use of electronic links should be strongly encouraged in the electronic CTD.

According to our understanding, the electronic CTD will be developed only for the harmonized portion of the CTD (Modules II-V). Items that will be required to satisfy regional requirements will have to be linked electronically into the pre-designed CTD electronic submission. Therefore, consideration should be given to the design and organization of a Module VI to include items that are regional requirements, which will not be part of the harmonized portion of the CTD.

Specific Comments – Organization guideline

Page 1 (Objective of the Guideline) An additional stated objective of the common technical document would be to assure that agency's review times are not lengthened by implementation of the CTD.

Page 2 (Organization of the Common Technical Document) The description of the Common Technical Document summaries refers to them as the "Overall Summaries of the Quality, Nonclinical, and Clinical information." This is not consistent with the titles of the individual guidelines, which refer to them as the Overall Summaries of the Quality, Safety, and Efficacy. This text and other text throughout the document should be reviewed and revised, as needed, to terminology that is more consistent.

Specific Comments – Efficacy guideline

Anti-infective products. For anti-infective products, it may be appropriate to include reports of in vitro antimicrobial activity studies, including spectrum of activity, and animal infection model studies in the clinical section (Module V). Written guidance should be included on this point, along with instructions for placement in 2.4 (Special Studies). It is important to include reports on the spectrum of antimicrobial activity and reports on any standardized in vitro susceptibility tests (with quality control parameters) and interpretive criteria for results of testing anti-infective agents in the clinical section: this should be stated in the guidance.

Clinical Overall Summary

Many of the comments on the *Clinical Overall Summary*, below, particularly those intended to clarify information requested, especially adverse event information, and those related to CTD data presentation also apply directly to the Written Summary.

If the Clinical Overall Summary guidance is followed carefully and all requirements are addressed, it would result in a document that far exceeds 30 pages for most New Molecular Entities. This could obscure the intended messages in the Clinical Overall Summary. Further, if every point in the CTD guidance must be addressed, it could make it difficult to get both the Benefits and Risks across succinctly within 30 pages. It would

also be difficult for those Regulators who want the bottom line first, to find the key messages in the Clinical Overall Summary. It would also be helpful if the guidance made it clear that, where there is nothing of importance to report, the Clinical Overall Summary should remain silent. The data, of course, will be provided in the written summary.

The purpose of the Clinical Written Summary (Module II.D.) is not clearly stated. Guidance on the Clinical Overall Summary states that the intent is to provide a critical analysis. A similar statement is needed for the Written Summary to provide guidance to the author. Applicants should be advised that the Written summary should not contain a discussion of the data. Any issues that need discussion should be dealt with in the Clinical Overall Summary.

It would be helpful if the Clinical Overall Summary included a summary of the common elements of the proposed Prescribing Information, possibly as part of the Benefit and Risk section. Guidance should be given on the expected size of the Written Summary as has been done for the Clinical Overall Summary.

Page 2 (1. Product Development Rationale) In section 1 of the guidance on the Clinical Overall Summary, fifth bullet, there is a reference that "Pertinent regulatory guidance or advice should be identified." However, it is not clear as to the advice that should be identified in each of the three ICH Regions. Also, it is not clear whether advice from all three Regions should be included and submitted with the CTD to all Authorities. Regarding Scientific Advice from the CPMP, it is accepted that the official CPMP letter could be supplied. However, when seeking advice from many national agencies within the EU, formal minutes or other official records of the meeting that detail advice or resulting agreements are often not available.

A description should be added to 1. Product development rationale relating to the structure of "the complete clinical data package." It is necessary to clarify where the structure of "the complete clinical data package" defined in ICH E5 should be described.

A summary of the justification for concluding that bridging is possible should be included as the final bullet of the justification for product development. Stating it in this part will prevent confusion in comparisons with foreign data in other parts.

Add the text (**in bold**) to the following sentence:
"Pertinent published **literature and regulatory guidance and advice** should be identified."

Page 2 (2. Overview Analysis of Biopharmaceutics) It is beyond the scope of this document to provide actual analyses, rather it is intended to be an assessment of the analysed data. We propose that the headings throughout the document be changed to "overview assessment" instead of "overview analysis". For example:

"OVERVIEW ASSESSMENT OF BIOPHARMACEUTICS"

Also, this section may be too brief for a useful analysis. We propose that the sentence below be reworded:

"The purpose of this section is to describe and **assess** important issues related to drug formulations that might affect efficacy and/or safety of the to-be-marketed formulations
....."

The following text should be deleted from the list of examples; it would better serve as an example in the Quality document rather than as an example in the Efficacy document for biopharmaceutics:

"...lot-to-lot variability)."

Page 3 (4. Overview analysis of efficacy) The statement, "support for the applicability to the new region of data generated in another region" in the CTD section described under 1. Product Development Rationale (page 2) should be clarified and a similar description should be placed in 3. Overview Analysis of Clinical Pharmacology (page 2) and in 5. Overview Analysis of Safety, as well. As in ICH E5, a general investigation of the potential to extrapolate from foreign data includes not only efficacy, but safety as well.

Page 4 (5. Overview of Analysis of Safety) "Common" adverse events might be better understood as "frequent" and this terminology should be consistent throughout the document. As an example, we note that paragraph (bullet) 5 discusses adverse events of "high frequency" which is certainly clearer than "high commonality".

The fifth bullet refers to "incidence higher than." It is not clear whether this incidence should be expressed as a percentage or absolute number. Clarity is needed.

This document recognizes an opportunity to harmonize the way adverse events are reflected in product labeling in the three ICH Regions. We recommend that this document provide specific guidance in Section 4.2 as to a preferred approach, which would be acceptable in all Regions, for presentation of adverse event data. We recommend that the safety data be presented as:

- **All adverse events and**
- **Causally-related adverse events (i.e., adverse reactions).**

This recommendation for presentation of **adverse reactions** data should be considered in light of other sections of the guidance that refer to "new adverse events" and treatment emergent signs and symptoms (TESS). The terminology should be reconciled throughout the guidance.

A common format for product labels in the three Regions would enhance the ability of Industry and Regulators to make reference(s) to the product label in a single CTD. We suggest that consideration be given to harmonizing the format and content of the data sheet/Package Insert/Summary of Product Characteristics, according to the internationally promulgated proposed standard described in the recent CIOMS III/V document. Regardless of whether harmonization of the data sheet is achieved, we strongly recommend that **REACTIONS** be the focus of all labels; this would affect the terminology used throughout the guidance (e.g., in most, but not all, instances "reactions" would be substituted for "events," etc):

Page 5 (6. Benefits and Risks) – The information related to safety should read as follows:

“significant safety findings, including common adverse **reactions** (bold) and serious adverse **reactions** associated with use of the pharmaceutical, and any measures that may enhance safety.”

To be consistent, similar wording should be used in the safety section of the CTD. In addition, it would seem that "frequent" would be a more appropriate term to use than "common" as mentioned above.

Pages 5-6 Section numbering should be checked, as Section 6 (Benefits and Risks) is followed by Section 9 (references).

Page 6 (9. References) The purpose of this section should be further clarified to avoid any confusion. It is unclear whether or not to reference documents not contained in the dossier.

Written Summary of Clinical Studies and Experience

Biopharmaceutics and Clinical Pharmacology The organization of Section 1 and 2 are problematic with reference to human pharmacokinetic data. One needs to understand the pharmacokinetics of a compound before one could follow the ramifications of BA, BE, and other biopharmaceutics studies. The proposed manner of discussing biopharmaceutics first in section 1 (Summary of Biopharmaceutics Studies and Associated Analytical Methods), then followed by Summary of Clinical Pharmacology Studies 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. We would rather see one section instead of two.

If we combine both sections, then we just need one table of studies, instead of having Tables 1.1 and 2.1 separately.

Background and Overview sections (1.1, 2.1 and 3.1). The text should make it clear that these sections provide an overview and rationale for the program of studies in these categories, not more narratives of individual trials.

Page 3/4 (2.2 Summary of Results of Individual Studies). These sections note expectations that the narrative for each study is to be abstracted from the ICH E3 Study Report Synopsis. We see no value in repeating the synopsis text since this information can be accessed as a direct electronic link to the synopsis. Written summaries should be reference documents, and do not need to be written in such a way that they must be read from beginning to end. The current structure requires that individual trials are summarized in at least four different places.

If the intention of the section-specific synopsis is to give the reviewer a more detailed discussion of the pharmacokinetic data than one would do in the Study Report synopsis, then this should be stated clearly. For example, the guidance could state that "The pharmacokinetic data should be discussed thoroughly with minimum reference to other considerations to emphasize the purpose of the particular pharmacokinetic study conducted. This is in contrast to the Study Report synopsis that considers -safety and efficacy as well as pharmacokinetics. Detailed synopses need not be prepared for every pharmacokinetic study, but only for those that support essential disposition or support the product label. Similar text substituting "efficacy" for "pharmacokinetic" should be inserted in Section 3.2 for the Summary of Individual Clinical Efficacy Studies.

Page 4 (2.3 Comparison and Analyses of Results Across Studies) The paragraph in 4) states that information should be discussed in Section 3.3.4; should this be Section 3.4?

Page 5 (2.4 Special Studies) The reference to "special studies" is not clear since studies of extrinsic and intrinsic factors affecting drug disposition are often referred to as "special studies." These studies usually are categorized within the scope of clinical pharmacology studies. Clearer guidance on the distinction between the types of studies to be included in Section 2.3 and in Section 2.4 would be helpful.

Page 6 (3.1 Background/Overview of Clinical Efficacy) – Add the following text (**in bold**):

"This section describes the program of controlled studies and other pertinent studies in the application that evaluated efficacy **specific to the indication(s) sought.**"

Page 7 (3.2 Summary of Individual Clinical Efficacy Studies) – See comments on Summary of Individual Studies (Section 2.2).

Page 7 (3.3 Comparison and analyses of results across studies) Along with section 2.3, we would like a clarification of the items that should be described individually; alternatively, since this chapter contains subsections, we would like shown either the cautions of section 3.3 or a synopsis summarizing section 3.3.

Page 8 (3.3.1 Study Populations) – It should be made clear that this section is describing the "efficacy patient population", it would be useful to provide a flow chart showing how the total population is sub-divided into other categories, e.g., per protocol, ITT, etc.

The baseline characteristics needed should be specified.

The term "adequacy" in the following text is confusing and inappropriate for defining the study population that withdrew from the study at any time. The follow-up period is typically considered part of the study. Text should be changed to (**in bold**):

"the-an assessment adequacy of follow-up and the number of patients who dropped out of the study, time of withdrawal (a defined study day or day during treatment or follow-up period), and reasons for discontinuation."

Page 9 (3.4 Analysis of clinical information relevant to dosing recommendations)
Incorporate "3.4.1 Evidence of long-term efficacy and/or tolerance effects" into section 3.4 without invoking a new section. It seems unnatural to create a section just for long-term efficacy.

Page 10 (3.4.1 Evidence of Long Term Efficacy and/or Tolerance Effects) The definition of long term efficacy should be provided. This is usually defined by ICH as trials of 6 months or longer in duration.

Page 10 (3.4.1 Evidence of Long Term Efficacy and/or Tolerance Effects) The following text should be added (**in bold**):

"The effect of switching to other therapies upon assessment of long-term efficacy during the clinical trials should be discussed, **if applicable.**"

This is not necessary in the development of all compounds and should be qualified so as not to appear to be creating additional development requirements.

Page 11 (4. Summary of Clinical Safety). Consistent with our comments, above, we recommend that the safety data be presented as: all adverse events, and causally-related adverse events (i.e., adverse, reactions). This should be stated in this section. See also comments on the overall summary above.

Page 11 (4. Summary of clinical safety) "This section is a summary of data...and other relevant reports, e.g., the integrated analyses of safety that are routinely submitted in some regions." If the ISS is included in the application, what is the value of providing a summary of the document? This requires extra work for applicants with no apparent value.

The initial Japanese translation contains expressions that could create misunderstandings. Current draft: "This section . . . is a summary of the safety-related data in the target patient population." Proposed revision: "This section . . . is a summary of the data relevant to safety in the target patient population."

This section should include data on healthy persons as well, but the current passage can be interpreted as indicating only the safety data from the patient population.

Page 13 (4.1.4 Description of Safety Studies Not Presented Elsewhere) This would be the best place to put postmarketing experience. The text could be changed to read (**in bold**):

"For example, **postmarketing experience and** narrative descriptions of controlled studies to evaluate particular adverse events (sedation, sexual function, effects on driving, absence of a class adverse effect) **would be appropriately described in this section. This section could also serve** or to assess safety in particular demographic subsets. ~~and~~ Narrative descriptions of uncontrolled safety trials would often not be included in Section 3 and could also be presented here."

NB: It must be clarified whether the intention is to limit this section to clinical trial data or whether it also should include additional clinical safety data, such as spontaneous case reports or analyses/studies conducted for pharmacovigilance purposes.

Page 13 (4.2.1 Frequency of Adverse Events) It is not clear what the difference is between "new adverse events" and "TESS"; "TESS" is better, although see comments regarding "reactions," above. Clarify the difference between "new adverse events" and "TESS". Perhaps an explanation should be provided only for "TESS"; the expression "new adverse events" could be deleted. The term "adverse reactions" is preferred.

Page 14 (4.2.2.1.1 General Considerations) Add "control group" to the examples. Caution is required when combining (active drug control only or placebo control only).

Page 14 (4.2.2.1.1 General Considerations and 4.2.2.1.2 Methodology) We would like to confirm whether "4.2.2.1.1 General Considerations" and "4.2.2.1.2 Methodology" are titles of included sections or simply stand-alone sections.

Page 14 (4.2.2.1.2 Methodology) The text states "if the objective of the combined analysis is to increase the power for the difference between 2 treatment groups, such as the product vs. placebo, then a nonhomogeneity assay is probably useful," but it is not clear what this means. In order to study the validity of the combination, a nonhomogeneity assay would ordinarily be conducted first.

Page 16/17 (4.2.2.5 Other significant adverse events) This section should include additional information relating to the safety profile, such as information on severity of adverse reactions and discontinuations. The relative importance of the adverse reactions observed will differ, depending on the characteristics of the disease under study. For example, a determination of whether or not a specific adverse event required that administration be discontinued may vary depending on the disease under study.

Tables from Written Summary

Table 1.1 (page 22) Replace Clearance (CL) with bioavailability (F) under Mean parameters. It is more appropriate to present the bioavailability (F) than Clearance (CL) for both bioavailability and bioequivalency studies.

Table 1.2 (page 23) Since the mean is reported for each timepoint, the range for the individual units should be included.

Table 3.1 (page 25) As large studies may have hundreds of principal investigators, this table may become onerous for even one efficacy study. A "coordinating" investigator, as defined in ICH E6, is not used in all studies. Instead of "investigator" and "location" in this column, we would suggest only "study location (s)," typically defined by countries and the number of investigators in each country.

Add median to the age range in the "Gender M/F" column.

The endpoints column(s) should distinguish primary from secondary endpoints, or perhaps just be labeled "primary endpoints."

Add a comments column to table.

The enrollment target should also be included in this table.

Table 3.2 (page 26) Include the population that is being analyzed – Intention To Treat (ITT), treated, etc.

Add "primary endpoints" above column that contains that data and change "other endpoints" column to read "Secondary Endpoints." Also, where statistics are involved, the statistical test should be identified.

The "Enrolled/Completed #" column is redundant since table 3.1 contains this information.

Table 4.1 (page 27) The percent column should be defined. Patient population included in this table should be described, e.g., safety population, ITT, etc.

Table 4.2 (page 28) Add "median" under age row.

The table needs to allow for the possibility of development programs, which have utilized multiple active control agents.

While we realize this table is an example, the 40 to 64 age group is potentially confusing and could be read as a "standard." While this grouping may be appropriate for some types of therapies, it is not logical for most adult subgroup assessments, and its elimination would probably result in a better "standard model."

"Other" should be added to "Ethnicity", and perhaps a footnote to the table should recognize that the number of racial categories might be expanded.

4.2 Tables (page 28) The ethnicity section of the tables -- can this be taken to mean that Japanese are included in "Asians"? We would like to confirm that Japanese are included in the "Asians" group in the studies done in the West.

Table 4.3 (page 29) The term "the largest trials" is very troubling. The TESS incidence should be tabulated for all appropriately integrated studies, and should include all patients who received relevant doses and exposures. Safety data that are logically integrated may or may not come only from the "largest" studies, or even only pivotal studies. Because there can be no set "rule" for integration of safety data, we would be very concerned with a table that limited TESS to the largest or only pivotal studies.

Table 4.4 (page 30) The withdrawal data may be more meaningful if they were listed by dose level and drug rather than by just drug.

The intended content of the "N" columns should be clarified; the method used to calculate percentages should be described.

Although controlled and uncontrolled trials will usually be discussed separately in marketing applications (most often for efficacy discussions) -- safety data will still be logically integrated across controlled and uncontrolled trials -- depending on the study designs. Therefore, we cannot understand an a priori rationale for limiting withdrawals due to AE's to controlled trials only.

Table 4.5 (page 31) Add the location of the narrative or CRF. This table concerns us greatly. As noted in the "source" column, it combines deaths from clinical trials and post-marketing experience (where oftentimes information is limited and more complex than in clinical trials). It is also important that the table specifically include "relationship to study drug" and "cause of death." Postmarketing deaths should be addressed separately.