INTERNATIONAL CONFERENCE ON HARMONISATION OF TECHNICAL
REQUIREMENTS FOR REGISTRATION OF PHARMACEUTICALS FOR HUMAN USE

M4E Implementation Working Group
Questions & Answers (R4)

Current version
dated June 10, 2004

ICH Secretariat, c/o IFPMA,15, chemin Louis-Dunant, P.O. Box 195, 1211 Geneva 20, Switzerland
Telephone: +41 (22) 338 32 06 *Telefax:* +41 (22) 338 32 30
E-mail : admin@ich.org Web site : *http://www.ich.org*

In order to facilitate the implementation of the CTD Efficacy (M4E) guideline, the ICH Experts have developed a series of Q&As:

M4E Q&As
Document History

First Codification	History	Date	New Codification **November 2005**
M4E Q&As	Approval by the Steering Committee.	11 February 2002	M4E Q&As
M4E Q&As	Approval by the Steering Committee of the newly added questions.	12 September 2002	M4E Q&As (R1)
M4E Q&As	Approval by the Steering Committee of the newly added questions.	6 February 2003	M4E Q&As (R2)
M4E Q&As	Approval by the Steering Committee of the newly added questions.	11 November 2003	M4E Q&As (R3)

Current M4E Questions & Answers posted on the web site

M4E Q&As	Approval by the Steering Committee of the newly added questions.	10 June 2004	M4E Q&As (R4)

In November 2005, the ICH Steering Committee adopted a new codification system for ICH Guidelines. The purpose of this new codification is to ensure that the numbering / coding of ICH Guidelines is more logical, consistent and clearer. Because the new system applies to existing as well as new ICH Guidelines a history box has been added to the beginning of all Guidelines to explain how the Guideline was developed and what is the latest version.

With the new codification revisions to an ICH Guideline are shown as (R1), (R2), (R3) depending on the number of revisions. Annexes or Addenda to Guidelines have now been incorporated into the core Guidelines and are indicated as revisions to the core Guideline (e.g., R1).

For better comprehension of the M4E references within the text, please see below the document change history for M4E guideline.

M4E Document History

First Codification	History	Date	New Codification **November 2005**
M4E	Approval by the Steering Committee under *Step 2* and release for public consultation.	20 July 2000	M4E
M4E	Approval by the Steering Committee under *Step 4* and recommendation for adoption to the three ICH regulatory bodies.	8 November 2000	M4E

Current *Step 4* version

M4E	Approval by the Steering Committee of Numbering and Section Headers changes for consistency directly under Step 4 without further public consultation.	12 September 2002	M4E(R1)

CTD Efficacy (M4E) Questions and Answers (R4)

Date of Approval		Questions	Answers
1	**Feb 2002**	Clinical study reports contained in Module 5 are cited in the Clinical Overview and/or the Clinical Summary in Module 2. Each clinical study report may be given a unique short name when cited. **Does the method of citing and naming have to be uniform throughout all modules?**	We recommend that each study have a unique short identifier that is used consistently throughout the application. The applicant can select the identifier. The full title of the study is provided in the Tabular Listing of All Clinical Studies (Section 5.2).
2	**Sept 2002**	**Definitions/Terminology** What is the definition of 'Common Adverse Events' as used in the CTD?	Guidance is provided by ICH E3 Guideline.
3	**Sept 2002**	**Section Numbering/Title (in Module 5)** In the module 5 of the CTD, is it necessary to have a section number for each clinical study report in a certain section, or is it enough just to mention the title: 5.3.5 Reports of Efficacy... 5.3.5.1 Study Reports.... 5.3.5.1.1 Placebo Controlled.... Study XXX	See ICH Granularity document.
4	**Feb 2002**	**How many pages should a Clinical Summary be for an application that contains multiple indications? (Section 2.7)**	The estimated size of this document is 50-400 pages, assuming one indication. Applications that include multiple indications will be larger, reflecting the submission of multiple efficacy sections.

CTD Efficacy (M4E) Questions and Answers (R4)

Date of Approval		Questions	Answers
5	Feb 2002	**Section "2.7.3.3" Comparisons and Analyses of Results Across Studies** The Guideline provides "This section should also cross-reference important evidence from Section 2, such as data that supports the dosage and administration section of the labeling." However, this Guideline also provides a Section, "2.7.3.4. Analysis of Clinical Information Relevant to Recommended Dose." Please specify how to differentiate the two sections "2.7.3.3" and "2.7.3.4".	Section 2.7.3.3 summarizes the data across all studies that characterize efficacy of the drug; Section 2.7.3.4 provides an integrated summary of the dose-response or blood concentration-response relationships of effectiveness. In both cases, supportive data from Section 2.7.2 can also be incorporated.
6	Feb 2002	**Overall Extent of Exposure (Section 2.7)** In the Guideline, a table is required to be generated to present the overall extent of drug exposure in all phases of the clinical development. Should the table include "patients alone" or "patients and healthy subjects"?	The table should refer to all subjects exposed to at least one dose of the drug product. Appropriate subsets of subjects relevant to the proposed indications should also be identified and considered.
7	Feb 2002	**Summary of Clinical Safety (Section 2.7)** Where should information be described concerning the validity of extrapolation of foreign clinical safety data to a new region?	Summaries of any bridging studies using clinical endpoints (i.e., certain studies intended to evaluate the ability to extrapolate certain types of foreign clinical data to the new region (see ICH E5)) should be included in Section 2.7.3.2. Where appropriate, such information should also be described in the summarization of safety data as related to intrinsic and extrinsic ethnic factors (ICH E5), in Sections 2.7.4.5.1 and 2.7.4.5.2. Finally, some applications might include in Section 5.3.5.3 a detailed analysis of bridging, considering formal bridging studies, other relevant clinical studies, and other appropriate information. Such information should be included in that detailed analysis of bridging.

CTD Efficacy (M4E) Questions and Answers (R4)

Date of Approval		Questions	Answers
8	**Sept 2002**	**Bioavailability/Bioequivalence Study Data (Module 5)** Where should the information on bioequivalence studies for a generic application be included?	Bioavailability study reports should be included in Module 5 (Clinical documentation), under section 5.3.1 "Reports of Biopharmaceutical Studies". More specifically, reports of comparative Bioavailability/Bioequivalence studies should go under section 5.3.1.2.
9	**Sept 2002**	**Tabular Listing of Clinical Studies in Paper CTD** In module 5, 5.2 is denoted as the 'Tabular Listing of all Clinical Studies'. Is this section for a summary listing of all clinical studies in the submission, or it is for the listings of the individual study reports? In other words, should the listings from the appendices of the individual study reports be included here, rather than as an appendix to the CSR, or are these only listings that summarize all studies?	The tabular listing described in section 5.2 is a listing of all clinical studies in the submission. An example of such a listing is given in Table 5.1.
10	**Feb 2003**	**ISS/ISE** Does the CTD section on safety in Module 2 replace the section under 21 CFR 314.50(d)(5)(v, vi) calling for integrated summary of safety and effectiveness (ISS/ISE)?	The ISS/ISE are critical components of the safety and effectiveness submission and are expected to be submitted in the application in accordance with the regulation. FDA's Guideline for the Format and Content of Clinical and Statistical Sections of Application gives advice on how to construct these summaries. Note that, despite the name, these are integrated analyses of all relevant data, not summaries. The Clinical Safety sections of the CTD follow approximately the outline of the sections of the ISS/ISE, although they are somewhat modified by experience with ICH E-3 (Structure and Content of Clinical Study Reports). The CTD Clinical Overview and Summary in Module 2 will not usually contain the

CTD Efficacy (M4E) Questions and Answers (R4)

	Date of Approval	Questions	Answers
			level of detail expected for an ISS. It may contain the level of detail needed for an ISE, but this would need to be determined on a case-by-case basis. If, the requirements of 21 CFR 314.50 can be met for a particular application by what is in the CTD Module 2 summary, then the CTD Module 2 section would fulfill the need for an ISS/ISE. In some cases it will be convenient to write much of what is needed in the CTD Module 2 with appropriate appendices in Module 5. In other cases, the ISS/ISE would be summarized in Module 2, with detailed reports in Module 5. Any questions about these matters can be raised with the reviewing division.
11	**Nov. 2003**	**Microbiology data** The microbiology data will include both in vitro and in vivo studies. Where should the microbiology summary, overview and study reports be included?	The Microbiology data from both in vitro and in vivo studies should be included with the Efficacy information. The summary information should be provided in the appropriate section 2.7 Clinical Summary and the reports should be filed in section 5.3.5.4 Other Study Reports. In addition, the microbiology information can be described in the Nonclinical sections as appropriate.
12	**Nov. 2003**	**Clinical variation** For a clinical variation application, is it mandatory to submit a clinical overview and a clinical summary, or is it acceptable to submit either only an overview or only a summary? What are the parameters/conditions to be taken into account for choosing one or the other approach?	Since variation is a term from the EU regulations, the answer should be provided by the EMEA.

CTD Efficacy (M4E) Questions and Answers (R4)

Date of Approval		Questions	Answers
13	**Nov. 2003**	**Integrated analysis of efficacy (ISE) - Section 2.7 Clinical Summary – Statistical Listings** What approach should applicants take for the formatting and presentation of their integrated analyses when they have large amounts of statistical output to present (several thousands of pages)?	As stated in section Reports of Analyses From More Than One Study 5.3.5.3, where the details of the analysis are too extensive to be reported in a summary document, for example, section Clinical Summary 2.7, they should be presented in a separate report. Such report should be placed in section 5.3.5.3.
14	**Nov. 2003**	**Cross references / Cross Strings (in Paper Submissions)** It is stated in the CTD that the section should be indicated in cross strings. What is meant here: The section number, or the section number and section name? (The section name is in many cases too long to indicate in a cross string.)	Providing the section header in addition to the section number improves the clarity of the reference, particularly for the uninitiated reader. To reduce the length of the cross string while maintaining the ease of use, it is recommended to include only the section number in the cross string and write the text so the reader will also know the section content. For example, "…as seen in the population PK study 101 (5.3.3.5)" helps the reader to find the referenced study report under the Population PK Study Reports section. The text "…no safety problems were noted in the uncontrolled pneumonia study 101A (5.3.5.2)" helps the reader find the referenced study report under the section Study Reports of Uncontrolled Clinical Studies for the Pneumonia indication.
15	**Nov. 2003**	**Limitations of the Safety Database and Potential Implications** Section 2.5 Clinical Overview and section 2.5.5 Overview of Safety both refer to an assessment of the limitations of the safety database but give few details on how to describe them. How should these limitations be described? In addition, there is no specific reference to any postmarketing steps the applicant can take to remedy those limitations. Where should a discussion of any postmarketing pharmacovigilance and other postmarketing study plans go?	A fuller discussion of how to describe in the CTD the limitations of the safety database and the potential implications for the safety of the drug when marketed is as follows: • Nonclinical toxicology and safety pharmacology concerns, such as those arising from reproductive / developmental toxicity, carcinogenicity, hepatic injury, central nervous system injury, or effects on cardiac repolarization that are not fully resolved by available human data, or that arise from

CTD Efficacy (M4E) Questions and Answers (R4)

Date of Approval		Questions	Answers
			incomplete testing. • Limitations of human safety database, such as: o Patient selection criteria that excluded people who are likely to be candidates for treatment in medical practice. o Evaluations that were deficient for certain purposes (e.g., many drugs with sedative properties are not evaluated for effects on cognitive function in the elderly). o Limited exposure of demographic or other subgroups, such as children, women, the elderly, or patients with abnormal hepatic or renal function. • Identified adverse events and potential adverse events that require further characterization or evaluation with respect to frequency and/or seriousness in the general population or in specific subgroups. • Important potential risks (e.g., known risks of pharmacologically related drugs) that require further evaluation. • Drug-drug interactions that have not been assessed adequately. Such information should be described and discussed in section 2.5.5 Overview of Safety, with appropriate cross references to section 2.7.4 Summary of Clinical Safety and any other relevant sections. A discussion of any planned postmarketing activity or study to address the limitations of the premarketing safety database, should also be included in section 2.5.5 Overview of Safety, with any protocols for specific studies provided in section

CTD Efficacy (M4E) Questions and Answers (R4)

Date of Approval		Questions	Answers
			5.3.5.4 Other Clinical Study Reports or other sections as appropriate (e.g., module 4 if the study is a nonclinical study). An ICH guideline (E2E Pharmacovigilance Planning) is being developed to further address the question of how to describe the safety data and its limitations and how to describe planned postmarketing activities and studies.
16	**Nov. 2003**	**Multiple Indications** When submitting one dossier for multiple indications, how should the applicant present them in the clinical part of the registration dossier, for example sections 2.5 Clinical Overview, 2.7.3 Summary of Clinical Efficacy and 5.3.5 Reports of Efficacy and Safety Studies?	One section 2.5 Clinical Overview is recommended for multiple indications to be registered along with development rationale and cross-referencing to the corresponding 2.7.3 and 5.3.5 sections; the "benefit/risk" conclusions should support corresponding claimed indications. For section 2.7.3 Summary of Clinical Efficacy, in the case of more than one indication, the following organization is recommended as applicable. The current CTD numbering should be retained with identification of the indication, for example: 2.7.3.UTI Summary of Clinical Efficacy 2.7.3.1.UTI Background 2.7.3.2. UTI Summary of Results of individual studies 2.7.3.3. UTI comparison and analysis 2.7.3.3.1. UTI study population 2.7.3.3.2. UTI Comparison of efficacy results 2.7.3. Pneumonia Summary of Clinical Efficacy 2.7.3.1. Pneumonia Background Other sections follow the same organization where applicable. For section 5.3.5 Reports of Efficacy and Safety Studies, in case of more than one indication, the following organization is recommended as applicable. The current CTD numbering should

CTD Efficacy (M4E) Questions and Answers (R4)

Date of Approval		Questions	Answers
			be retained with identification of the indications, for example: 5.3.5.UTI 5.3.5.1. UTI Controlled studies 5.3.5.2. UTI Uncontrolled studies 5.3.5. Pneumonia 5.3.5.1. Pneumonia Controlled studies 5.3.5.2. Pneumonia Uncontrolled studies Other sections follow the same organization, where applicable.
17	**Nov. 2003**	**Narrative descriptions** The CTD guidance for Section Overall Safety Evaluation Plan and Narratives of Safety Studies 2.7.4.1.1 states that narrative descriptions for studies that contributed both efficacy and safety should be included in Section Summary of Results of Individual Studies 2.7.3.2 and only referenced in the safety section. Please clarify whether the narrative to be included in 2.7.3.2 should include the safety results as well as "enough detail to allow the reviewer to understand the exposure… and how safety data were collected" or whether the results should be included in Section 2.7.4.1.1.	In general, safety results should be described in section 2.7.4.1.1, because section Summary of Clinical Efficacy 2.7.3 is devoted to efficacy. To avoid the need to describe the same study twice, section 2.7.3.2 asks for a reasonably complete description of studies pertinent to both safety and efficacy, including, in study narratives, information about the extent of exposure of study subjects to the test drug and how safety data were collected. This approach is confirmed in section 2.7.4.1.1, which notes that narratives for studies contributing both safety and efficacy data should be included in section 2.7.3.2. As noted in section Background and Overview of Clinical Efficacy 2.7.3.1, however, any results of these studies that are pertinent to evaluation of safety should be discussed in section Summary of Clinical Safety 2.7.4.

CTD Efficacy (M4E) Questions and Answers (R4)

Date of Approval		Questions	Answers
18	**June 2004**	According to ICH E3 Structure and Content of Clinical Study Reports, the case report forms should be located in Appendix 16.3, the individual patient data listings in Appendix 16.4 and the publications and literature references in Appendices 16.1.11 and 16.1.12 respectively. The CTD organization provides locations for case report forms and individual patient data listings in Module 5.3.7 and for literature references in Module 5.4. Can clarity be provided as to where these items should actually be placed in CTD and the eCTD submissions?	For paper submissions, case report forms and individual patient data listings should be located in Module 5.3.7, identified by study. For eCTD, PDF files for case report forms and individual patient data listings should be organised by study in the folder for Module 5.3.7. However, in the *index.xml* file the leaf elements for the case report forms and individual patient data listings should be included under the same heading as other study report files with additional information included with any accompanying study tagging file. In addition, a repeat of the leaf element can be placed under the heading 5.3.7 Case Report Forms and Individual Patient Data Listings. Datasets, if required by the region, should be organised according to regional guidance. For paper submissions publications and literature references should be located in Module 5.4. For eCTD, the files for publications and literature references should be located in the folder for Module 5.4. However, in the *index.xml* file the leaf elements for the publications and literature references should be included under the same heading as other study report files with additional information included with any accompanying study tagging file. In addition, a repeat of the leaf element should be placed under the heading for 5.4 Literature References.