AstraZeneca

Rec'd 11/7/01

Date: OCT 31 2001

Ms. Kimberly Topper
Center for Drug Evaluation and Research
Food and Drug Administration
HFD 21
5600 Fishers Lane
Rockville, MD 20857

Re: Docket # 01N-0370

Dear Ms. Topper:

Reference is made to the Meeting Notice entitled, " Preparation for ICH Meetings in Brussels, Belgium, Including Progress on Implementing of the Common Technical Document," published in the Federal Register on September 7, 2001, and subsequent cancellation of the same meeting in the Federal Register on October 1, 2001.

AstraZeneca Pharmaceuticals LP (AstraZeneca) has comments regarding the FDA's preparation for the postponed ICH Meeting. We request assurance that the numbering systems for the Quality, Safety and Efficacy Modules of the Common Technical Document (CTD) are completely harmonized in the guidances authored by the 3 ICH member regions. No differences should exist in numbering schemes. Clearly, the goal of the CTD is for efficient submission and review of marketing applications, the progress of which will be impeded unless the numbering systems are completely harmonized.

AstraZeneca has compared the guidance numbering systems published in the "Notice To Applicants" (EU), the MHLW "Notification" and the FDA "M4" Guidances. Appendix 1 of this submission contains a spreadsheet comparing the numbering systems published from these regional guidances. Differences are highlighted in color. The following discrepancies are noted:

1. The Nonclinical Summary Numbering:

The Nonclinical summary is numbered 2.6 in all guidances, but then the subsections are numbered 2.**3**.1, 2.**3**.2 etc in the Japanese document while Europe and the US continue with 2.**6**.1, 2.**6**.2 etc. Clarification is required. Our suggestion would be to harmonize the Japanese sub-section numbering with EU and US.

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2. The Nonclinical Summary-Toxicological Tabular Templates:

The EU document has a mistake in Appendix B, the Nonclinical Summary on numbering of the toxicological tabular templates. The mistake has been confirmed by the commission in contact with AstraZeneca and will be changed in the "Notice to Applicants." This mistake is pointed out as it relates to the first point, above.

3. The NonClinical Summary-Juvenile Studies:

In section 2.6.6, The Toxicology Written summary, the FDA provides for a list of studies on page 17 of the M4S Guidance. Following this, each bulleted point is assigned a sub-section beginning with 2.6.6.1, Brief Summary through 2.6.6.10, Tables and Figures. The heading 'Studies in Juvenile animals' is omitted, however, and would be section 2.6.6.7, which would make 'Local Tolerance', 2.6.6.8, 'Other Studies', 2.6.6.9, 'Discussion and Conclusions', 2.6.6.10 and 'Tables and Figures', 2.6.6.11.

Similarly, EU and Japan have not accounted for a separate section, 'Studies in Juvenile Animals.' Please clarify if this heading was omitted in error or if the intention was to summarize juvenile studies under the heading, 2.6.6.6, 'Reproductive and Developmental Toxicity.' We propose that all 3 regional guidances adopt the same approach on guidance for the summary of studies in juvenile animals.

Further to the discussion of placement of studies with juvenile animals, in the US Guidance, "M4: The CTD—Safety Appendices," it is noted on page 30 that a template for 'Studies in Juvenile Animals' is purposely omitted, but the place for the studies are held by template number 2.6.7.15. In the EU and Japan, the list of templates is numbered 2.6.7.15 for juvenile animals studies, continuing with 2.6.7.16 for 'Local Tolerance.' However, the template for local tolerance is numbered 2.6.7.15. Please clarify these differences. AstraZeneca recommends adoption of a harmonized system in all 3 regions for utilization of templates for studies with juvenile animals.

4. Nonclinical Study Reports:

Under Module 4, Nonclinical study reports, the EU and US number the' Study Reports' section as 4.2 and continue with (sub-section) 'Pharmacology' 4.2.1, while the Japanese number 'Pharmacology' with 4.2. The result is a difference in numbering of all the 'Pharmacology', 'Pharmacokinetics' and 'Toxicology' sub-sections, with the last item, 'Key Literature References' being number 4.3 in the EU and US, but number 4.5 in Japan. We propose that the Japanese harmonize these section numbers with EU and US.

The number agreement between the EU and US in the Nonclinical Study Reports also deviates in the 'Local Tolerance' Section, which is numbered as 4.2.4 by the EU, as 4.2.3.6 by the US (and as 4.4.6 by Japan, stated above). The numbering continues to be inconsistent for headings 'Antigenicity', 'Immunotoxicity', 'Mechanistic Studies', 'Dependence', 'Metabolites', 'Impurities' and 'Other.' Please note that the heading, at the same "level", immediately preceding "Local Tolerance" is 'Reproductive and development Toxicity' which is numbered the same by EU and US—4.2.3.5; therefore, we suggest that the number pattern used by the FDA for 'Local Tolerance', 4.2.3.6, is the most logical.

We propose that the EU and Japan adopt the FDA numbering scheme, specifically starting with sections 4.2.3.6 through 4.3.4.7.7.

5. Reporting Several Repeat Toxicity Studies:

AstraZeneca requests clarification on how to continue the numbering when using more than one table of the same format, e.g., when reporting several repeat toxicity studies in table 2.6.7.6.

Please confirm that either one of the following numbering patterns are equally acceptable to all regions:

- 2.6.7.6.**A**, 2.6.7.6.**B**, 2.6.7.6.**C** etc.
- 2.6.7.6.**1**, 2.6.7.6.**2**, 2.6.7.6.**3** etc.

6. Reporting More Than One Indication:

The FDA guidance, M4E, states that a separate Section 2.7.3 should be provided for each indication, although closely related indications can be considered together. When more than one Section 2.7.3 is submitted, the sections should be labeled by indication (e.g., 2.7.3 **pneumonia**, 2.7.3 **URI**).

The EU and Japan handle this situation differently. A separate Section 2.7.3 should be provided for each indication, although closely related indications can be considered together. When more than one Section 2.7.3 is submitted, the sections should be labeled 2.7.3**A**, 2.7.3**B**, 2.7.3**C**.

Please confirm that either approach is acceptable in all regions.

7. Clinical Summary Appendices:

In several places, an appendix is provided for in the US Guidance which are labeled differently for EU or Japan as follows:

- Appendix for 'Summary of Biopharm Studies and Associated Analytical Methods', numbered 2.7.1.4 (designated " 2.7.1, Appendix" for EU and Japan)
- Appendix for 'Summary of Clinical Pharmacology Studies', numbered 2.7.2.5 (designated " 2.7.2, Appendix" for EU and Japan)
- Appendix for 'Summary of Clinical Efficacy', numbered 2.7.3.6 (designated "2.7.3, Appendix" for EU and Japan) and,
- Appendix for 'Summary of Clinical Safety', numbered 2.7.4.7 (designated "2.7.4, Appendix" for EU and Japan).

The FDA numbering of the appendices appears to be more straightforward and we suggest that the EU and Japan adopt the FDA labeling scheme for the appendices.

8. The Nonclinical Summary-References:

No allowance exists for the inclusion of references following the Pharmacology Written Summary, Pharmacokinetics Written Summary or the Toxicology Written Summary.

AstraZeneca suggests that the following subsections be added: 2.6.2.8, References for Pharmacology Written Summary, 2.6.4.11, References for Pharmacokinetics Written Summary, and 2.6.6.11, References for Toxicology Written Summary. Please note that this suggested numbering scheme follows the US and EU pattern, while the Japanese numbering is not harmonized in this section (addressed above).

Please refer to Appendix 1 of this submission for a spreadsheet comparing the numbering systems for the EU, US and Japan.

This submission is being provided in duplicate.

AstraZeneca claims the confidentiality of this submission, and all information contained herein, under all applicable laws and regulations. Disclosure of any such information is not authorized without the prior written authorization of AstraZeneca.

Module	Section number as listed in M4 (step 4 November 2000)	Content	Section number as defined by CPMP	Section number as defined by FDA	Section number as defined by MHLW
1		**ADMINISTRATION INFORMATION and PRESCRIBING INFORMATION**			1
1A		**Table of contents**	**1.1**	**1.1**	1.1
1A		**Table of contents (Module 1-5)**	**1.1**	**1.1**	
1B		**Documents specific to each Region**		**1.2**	1.2
1B		**Documents specific to each Region**	**Module 1-ANNEX**		
2		**COMMON TECHNICAL DOCUMENT SUMMARIES**			2
2A		**Overall Common Technical Document Table of Contents (Module 2-5)**	**2.1**	**2.1**	2.1
2B		**Introduction**	**2.2**	**2.2**	2.2
2C		**Quality Overall Summary**	**2.3**	**2.3**	2.3
		Drug Substance	2.3S	**2.3S**	2.3S
		General Information	2.3.S.1	**2.3.S.1**	2.3.S.1
		Manufacture	2.3.S.2	**2.3.S.2**	2.3.S.2
		Characerisation	2.3.S.3	**2.3.S.3**	2.3.S.3
		Control of Drug Substance	2.3.S.4	**2.3.S.4**	2.3.S.4
		Reference Standards or Materials	2.3.S.5	**2.3.S.5**	2.3.S.5
		Container Closure System	2.3.S.6	**2.3.S.6**	2.3.S.6
		Stability	2.3.S.7	**2.3.S.7**	2.3.S.7
		Drug Product	2.3.P	**2.3.P.**	2.3.P
		Description and Composition of Drug Product	2.3.P.1	**2.3.P.1**	2.3.P.1
		Pharmaceutical Development	2.3.P.2	**2.3.P.2**	2.3.P.2
		Manufacture	2.3.P.3	**2.3.P.3**	2.3.P.3
		Control of Excipients	2.3.P.4	**2.3.P.4**	2.3.P.4
		Control of Drug Product	2.3.P.5	**2.3.P.5**	2.3.P.5
		Reference Standards or Materials	2.3.P.6	**2.3.P.6**	2.3.P.6
		Container Closure System	2.3.P.7	**2.3.P.7**	2.3.P.7
		Stability	2.3.P.8	**2.3.P.8**	2.3.P.8
		Appendices	2.3.A	**2.3.A.**	2.3.A
		Facilities and Equipment	2.3.A.1	**2.3.A.1**	2.3.A.1
		Adventitious Agents Safety Evaluation	2.3.A.2	**2.3.A.2**	2.3.A.2

		Novel Excipients	2.3.A.3	**2.3.A.3**	2.3.A.3
		Regional Information	2.3.R	**2.3.R**	2.3.R
2D	not defined	**NonClinical Overview**	**2.4**	**2.4**	2.4
	not defined	Overview of the nonclinical testing strategy	2.4.1	**2.4.1**	not defined
	not defined	Pharmacology	2.4.2	**2.4.2**	not defined
	not defined	Pharmacokinetics	2.4.3	**2.4.3**	not defined
	not defined	Toxicology	2.4.4	**2.4.4**	not defined
	not defined	Integrated overview and conclusions	2.4.5	**2.4.5**	not defined
	not defined	List of literature citations	2.4.6	**2.4.6**	not defined
2E		**Clinical Overview**	**2.5**	**2.5**	2.5
	1	Product Development Rationale	2.5.1	**2.5.1**	2.5.1
	2	Overview of Biopharmaceutics	2.5.2	**2.5.2**	2.5.2
	3	Overview of Clinical Pharmacology	2.5.3	**2.5.3**	2.5.3
	4	Overview of Efficacy	2.5.4	**2.5.4**	2.5.4
	5	Overview of Safety	2.5.5	**2.5.5**	2.5.5
	6	Benefits and Risks Conclusions	2.5.6	**2.5.6**	2.5.6
	7	References	2.5.7	**2.5.7**	2.5.7
2F		**NonClinical Summary**	**2.6**	**2.6**	2.6
	2.3.1	**Introduction**	2.6.1	**2.6.1**	2.3.1
2F1a	2.3.2	**Pharmacology Written Summary**	2.6.2	**2.6.2**	2.3.2
	2.3.2.1	Brief Summary	2.6.2.1	**2.6.2.1**	2.3.2.1
	2.3.2.2	Primary Pharmacodynamics	2.6.2.2	**2.6.2.2**	2.3.2.2
	2.3.2.3	Secondary Pharmacodynamics	2.6.2.3	**2.6.2.3**	2.3.2.3
	2.3.2.4	Safety Pharmacology	2.6.2.4	**2.6.2.4**	2.3.2.4
	2.3.2.5	Pharmacodynamic Drug Interactions	2.6.2.5	**2.6.2.5**	2.3.2.5
	2.3.2.6	Discussion and Conclusions	2.6.2.6	**2.6.2.6**	2.3.2.6
	2.3.2.7	Tables and Figures	2.6.2.7	**2.6.2.7**	2.3.2.7
2F1b	2.3.3	**Pharmacology Tabulated Summary**	2.6.3	**2.6.3**	2.3.3
	2.3.3.1	Pharmacology: Overview	2.6.3.1	**2.6.3.1**	2.3.3.1
	2.3.3.2	Primary Pharmacodynamics	2.6.3.2	**2.6.3.2**	2.3.3.2

	2.3.3.3	Secondary Pharmacodynamics	2.6.3.3	**2.6.3.3**	2.3.3.3
	2.3.3.4	Safety Pharmacology	2.6.3.4	**2.6.3.4**	2.3.3.4
	2.3.3.5	Pharmacodynamic Drug Interactions	2.6.3.5	**2.6.3.5**	2.3.3.5
2F2a	2.3.4	**Pharmacokinetics Written Summary**	2.6.4	**2.6.4**	2.3.4
	2.3.4.1	Brief Summary	2.6.4.1	**2.6.4.1**	2.3.4.1
	2.3.4.2	Methods of Analysis	2.6.4.2	**2.6.4.2**	2.3.4.2
	2.3.4.3	Absorption	2.6.4.3	**2.6.4.3**	2.3.4.3
	2.3.4.4	Distribution	2.6.4.4	**2.6.4.4**	2.3.4.4
	2.3.4.5	Metabolism (Inter-species Comparison)	2.6.4.5	**2.6.4.5**	2.3.4.5
	2.3.4.6	Excretion	2.6.4.6	**2.6.4.6**	2.3.4.6
	2.3.4.7	Pharmacokinetic Drug Interactions	2.6.4.7	**2.6.4.7**	2.3.4.7
	2.3.4.8	Other Pharmacokinetic Studies	2.6.4.8	**2.6.4.8**	2.3.4.8
	2.3.4.9	Discussion and Conclusions	2.6.4.9	**2.6.4.9**	2.3.4.9
	2.3.4.10	Tables and Figures	2.6.4.10	**2.6.4.10**	2.3.4.10
2F2b	2.3.5	**Pharmacokinetic Tabulated Summary**	2.6.5	**2.6.5**	2.3.5
	2.3.5.1	Pharmacokinetics: Overview	2.6.5.1	**2.6.5.1**	2.3.5.1
	2.3.5.2	Analytical Methods and Validation Reports	2.6.5.2	**2.6.5.2**	2.3.5.2
	2.3.5.3	Pharmacokinetics: Absorption after a Single Dose	2.6.5.3	**2.6.5.3**	2.3.5.3
	2.3.5.4	Pharmacokinetics: Absorption after a Repeated Dose	2.6.5.4	**2.6.5.4**	2.3.5.4
	2.3.5.5	Pharmacokinetics: Organ Distribution	2.6.5.5	**2.6.5.5**	2.3.5.5
	2.3.5.6	Pharmacokinetics: Plasma Protein Binding	2.6.5.6	**2.6.5.6**	2.3.5.6
	2.3.5.7	Pharmacokinetics: Study in Pregnant or Nursing Animals	2.6.5.7	**2.6.5.7**	2.3.5.7
	2.3.5.8	Pharmacokinetics: Other Distribution Study	2.6.5.8	**2.6.5.8**	2.3.5.8
	2.3.5.9	Pharmacokinetics: Metabolism in Vivo	2.6.5.9	**2.6.5.9**	2.3.5.9
	2.3.5.10	Pharmacokinetics: Metabolism in Vitro	2.6.5.10	**2.6.5.10**	2.3.5.10
	2.3.5.11	Pharmacokinetics: Possible Metabolic Pathways	2.6.5.11	**2.6.5.11**	2.3.5.11
	2.3.5.12	Pharmacokinetics: Induction/Inhibition of Drug-Metabolising Enzymes	2.6.5.12	**2.6.5.12**	2.3.5.12
	2.3.5.13	Pharmacokinetics: Excretion	2.6.5.13	**2.6.5.13**	2.3.5.13
	2.3.5.14	Pharmacokinetics: Excretion into Bile	2.6.5.14	**2.6.5.14**	2.3.5.14
	2.3.5.15	Pharmacokinetics: Drug-Drug Interactions	2.6.5.15	**2.6.5.15**	2.3.5.15
	2.3.5.16	Pharmacokinetics: Other	2.6.5.16	**2.6.5.16**	2.3.5.16
2F3a	2.3.6	**Toxicology Written Summary**	2.6.6	**2.6.6**	2.3.6
	2.3.6.1	Brief Summary	2.6.6.1	**2.6.6.1**	2.3.6.1
	2.3.6.2	Single-Dose Toxicity	2.6.6.2	**2.6.6.2**	2.3.6.2
	2.3.6.3	Repeat-Dose Toxicity (Including Supportive Toxicokinetics Evaluations)	2.6.6.3	**2.6.6.3**	2.3.6.3
	2.3.6.4	Genotoxicity	2.6.6.4	**2.6.6.4**	2.3.6.4

	2.3.6.5	Carcinogenicity (Including Supportive Toxicokinetics Evaluations)	2.6.6.5	**2.6.6.5**	2.3.6.5
	2.3.6.6	Reproductive and Developmental Toxicity (Including Range-finding Studies and Supportive Toxicokinetics Evaluations)	2.6.6.6	**2.6.6.6**	2.3.6.6
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	2.3.6.8	Other Toxicity Studies	2.6.6.8	**2.6.6.8**	2.3.6.8
	2.3.6.9	Discussion and Conclusions	2.6.6.9	**2.6.6.9**	2.3.6.9
	2.3.6.10	Tables and Figures	2.6.6.10	**2.6.6.10**	2.3.6.10
2F3b	2.3.7	**Toxicity Tabulated Summary**	2.6.7	**2.6.7**	2.3.7
	2.3.7.1	Toxicology: Overview	2.6.7.1	**2.6.7.1**	2.3.7.1
	2.3.7.2	Toxicokinetics: Overview of Toxicokinetics Studies	2.6.7.2	**2.6.7.2**	2.3.7.2
	2.3.7.3	Toxicokinetics: Overview of Toxicokinetics Data	2.6.7.3	**2.6.7.3**	2.3.7.3
	2.3.7.4	Toxicology: Drug Substance	2.6.7.4	**2.6.7.4**	2.3.7.4
	2.3.7.5	Single-Dose Toxicity	2.6.7.5	**2.6.7.5**	2.3.7.5
	2.3.7.6	Repeat-Dose Toxicity: Non-Pivotal Studies	2.6.7.6	**2.6.7.6**	2.3.7.6
	2.3.7.7	Repeat-Dose Toxicity: Pivotal Studies	2.6.7.7	**2.6.7.7**	2.3.7.7
	2.3.7.8	Genotoxicity: In Vitro	2.6.7.8	**2.6.7.8**	2.3.7.8
	2.3.7.9	Genotoxicity: In Vivo	2.6.7.9	**2.6.7.9**	2.3.7.9
	2.3.7.10	Carcinogenicity	2.6.7.10	**2.6.7.10**	2.3.7.10
	2.3.7.11	Reproductive and Developmental Toxicity: Non-Pivotal Studies	2.6.7.11	**2.6.7.11**	2.3.7.11
	2.3.7.12	Reproductive and Developmental Toxicity: Fertility and Early Embryonic Development to Implantation (Pivotal)	2.6.7.12	**2.6.7.12**	2.3.7.12
	2.3.7.13	Reproductive and Developmental Toxicity: Effects on Embryo-Foetal Development (Pivotal)	2.6.7.13	**2.6.7.13**	2.3.7.13
	2.3.7.14	Reproductive and Developmental Toxicity: Effects on Pre- and Post-Natal Development, Including Maternal Function (Pivotal)	2.6.7.14	**2.6.7.14**	2.3.7.14
	2.3.7.15	Studies in Juvenile Animals	2.6.7.15	**2.6.7.15**	2.3.7.15
	2.3.7.16	Local Tolerance	2.6.7.16	**2.6.7.16**	2.3.7.16
	2.3.7.17	Other Toxicity Studies	2.6.7.17	**2.6.7.17**	2.3.7.17
2G	not defined	**Clinical Summary**	2.7	**2.7**	not defined
2G1	1	**Summary of Biopharmaceutic Studies and Associated Analytical Methods**	2.7.1	**2.7.1**	2.7.1
	1.1	Background and Overview	2.7.1.1	**2.7.1.1**	2.7.1.1
	1.2	Summary of Results of Individual Studies	2.7.1.2	**2.7.1.2**	2.7.1.2
	1.3	Comparison and Analyses of Results Across Studies	2.7.1.3	**2.7.1.3**	2.7.1.3

		Appendix	2.7.1 Appendix	**2.7.1.4**	2.7.1 Appendix
2G2	2	**Summary of Clinical Pharmacology Studies**	2.7.2	**2.7.2**	2.7.2
	2.1	Background and Overview	2.7.2.1	**2.7.2.1**	2.7.2.1
	2.2	Summary of Results of Individual Studies	2.7.2.2	**2.7.2.2**	2.7.2.2
	2.3	Comparison and Analyses of Results Across Studies	2.7.2.3	**2.7.2.3**	2.7.2.3
	2.4	Special Studies	2.7.2.4	**2.7.2.4**	2.7.2.4
		Appendix	2.7.2 Appendix	**2.7.2.5**	2.7.2 Appendix
2G3	3	**Summary of Clinical Efficacy**	2.7.3	**2.7.3**	2.7.3
	3.1	Background and Overview of Clinical Efficacy	2.7.3.1	**2.7.3.1**	2.7.3.1
	3.2	Summary of Results of Individual Studies	2.7.3.2	**2.7.3.2**	2.7.3.2
	3.3	Comparison and Analyses of Results Across Studies	2.7.3.3	**2.7.3.3**	2.7.3.3
	3.4	Analysis of Clinical Information Relevant to Dosing Recommendations	2.7.3.4	**2.7.3.4**	2.7.3.4
	3.5	Persistance of Efficacy and/or Tolerance Effects	2.7.3.5	**2.7.3.5**	2.7.3.5
		Appendix	2.7.3 Appendix	**2.7.3.6**	2.7.3 Appendix
2G4	4	**Summary of Clinical Safety**	2.7.4	**2.7.4**	2.7.4
	4.1	Exposure to the Drug	2.7.4.1	**2.7.4.1**	2.7.4.1
	4.2	Adverse Events	2.7.4.2	**2.7.4.2**	2.7.4.2
	4.3	Clinical Laboratory Evaluations	2.7.4.3	**2.7.4.3**	2.7.4.3
	4.4	Vital Signs, Physical Findings, and Other Observations Related to Safety	2.7.4.4	**2.7.4.4**	2.7.4.4
	4.5	Safety in Special Groups and Situations	2.7.4.5	**2.7.4.5**	2.7.4.5
	4.6	Post-Marketing Data	2.7.4.6	**2.7.4.6**	2.7.4.6
		Appendix	2.7.4 Appendix	**2.7.4.7**	2.7.4 Appendix
2G5	5	**References**	2.7.5	**2.7.5**	2.7.5
	6	**Synopses of Individual Studies**	2.7.6	**2.7.6**	2.7.6
3		**QUALITY**	**3**	**3**	
3A		**Table of Contents**	3.1	**3.1**	3.1
3B		**Body of Data**	3.2	**3.2.**	3.2 (Data or report)
	S	**Drug Substance**	3.2.S	**3.2.S**	3.2.S
	S1	General Information	3.2.S.1	**3.2.S.1**	3.2.S.1
	S1.1	Nomenclature	3.2.S.1.1	**3.2.S.1.1**	3.2.S.1.1
	S1.2	Structure	3.2.S.1.2	**3.2.S.1.2**	3.2.S.1.2

	S1.3	General properties	3.2.S.1.3	**3.2.S.1.3**	3.2.S.1.3
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