

# **M4E(R2): The CTD – Efficacy**

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

**ICH HARMONISED GUIDELINE**

**REVISION OF M4E GUIDELINE ON ENHANCING THE FORMAT AND  
STRUCTURE OF BENEFIT-RISK INFORMATION IN ICH**

**EFFICACY - M4E(R2)**

Current *Step 2* version  
dated 5 August 2015

*At Step 2 of the ICH Process, a consensus draft text or guideline, agreed by the appropriate ICH Expert Working Group, is transmitted by the ICH Steering Committee to the regulatory authorities of the ICH regions (the European Union, Japan, the USA, Health Canada and Switzerland) for internal and external consultation, according to national or regional procedures.*

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## ICH HARMONISED GUIDELINE

### REVISION OF M4E GUIDELINE ON ENHANCING THE FORMAT AND STRUCTURE OF BENEFIT-RISK INFORMATION IN ICH

#### EFFICACY - M4E(R2)

##### Draft ICH Consensus Guideline

Released for Consultation on 5 August 2015, at Step 2 of the ICH Process

#### TABLE OF CONTENTS

<b>MODULE 2 : COMMON TECHNICAL DOCUMENT SUMMARIES .....</b>	<b>1</b>
<b>2.5: CLINICAL OVERVIEW .....</b>	<b>1</b>
<b>Preamble .....</b>	<b>1</b>
<b>Table of Contents .....</b>	<b>2</b>
<b>Detailed Discussion of Content of the Clinical Overview Sections .....</b>	<b>2</b>
<b>2.5.1 Product Development Rationale .....</b>	<b>2</b>
<b>2.5.2 Overview of Biopharmaceutics .....</b>	<b>3</b>
<b>2.5.3 Overview of Clinical Pharmacology .....</b>	<b>3</b>
<b>2.5.4 Overview of Efficacy .....</b>	<b>3</b>
<b>2.5.5 Overview of Safety .....</b>	<b>4</b>
<b>2.5.6 Benefits and Risks Conclusions .....</b>	<b>5</b>
<b>2.5.7 Literature References .....</b>	<b>10</b>
<b>2.7 : CLINICAL SUMMARY .....</b>	<b>10</b>
<b>Preamble .....</b>	<b>10</b>
<b>Table of Contents .....</b>	<b>10</b>
<b>Detailed Guidance on Sections of the Clinical Summary .....</b>	<b>11</b>
<b>2.7.1 Summary of Biopharmaceutic Studies and Associated Analytical Methods .....</b>	<b>11</b>
2.7.1.1 Background and Overview .....	11
2.7.1.2 Summary of Results of Individual Studies .....	12
2.7.1.3 Comparison and Analyses of Results Across Studies .....	12
2.7.1.4 Appendix .....	13
<b>2.7.2 Summary of Clinical Pharmacology Studies .....</b>	<b>13</b>
2.7.2.1 Background and Overview .....	13
2.7.2.2 Summary of Results of Individual Studies .....	14

2.7.2.3	Comparison and Analyses of Results Across Studies.....	14
2.7.2.4	Special Studies .....	15
2.7.2.5	Appendix.....	15
<b>2.7.3</b>	<b>Summary of Clinical Efficacy .....</b>	<b>16</b>
2.7.3.1	Background and Overview of Clinical Efficacy .....	16
2.7.3.2	Summary of Results of Individual Studies.....	16
2.7.3.3	Comparison and Analyses of Results Across Studies.....	17
2.7.3.3.1	<i>Study Populations</i> .....	17
2.7.3.3.2	<i>Comparison of Efficacy Results of all Studies</i> .....	18
2.7.3.3.3	<i>Comparison of Results in Sub-populations</i> .....	18
2.7.3.4	Analysis of Clinical Information Relevant to Dosing Recommendations ..	19
2.7.3.5	Persistence of Efficacy and/or Tolerance Effects.....	19
2.7.3.6	Appendix.....	20
<b>2.7.4</b>	<b>Summary of Clinical Safety .....</b>	<b>20</b>
2.7.4.1	Exposure to the Drug .....	21
2.7.4.1.1	<i>Overall Safety Evaluation Plan and Narratives of Safety Studies</i> .....	21
2.7.4.1.2	<i>Overall Extent of Exposure</i> .....	21
2.7.4.1.3	<i>Demographic and Other Characteristics of Study Population</i> .....	22
2.7.4.2	Adverse Events .....	22
2.7.4.2.1	<i>Analysis of Adverse Events</i> .....	22
2.7.4.2.2	<i>Narratives</i> .....	26
2.7.4.3	Clinical Laboratory Evaluations .....	27
2.7.4.4	Vital Signs, Physical Findings, and Other Observations Related to Safety	27
2.7.4.5	Safety in Special Groups and Situations .....	27
2.7.4.5.1	<i>Intrinsic Factors</i> .....	27
2.7.4.5.2	<i>Extrinsic Factors</i> .....	28
2.7.4.5.3	<i>Drug Interactions</i> .....	28
2.7.4.5.4	<i>Use in Pregnancy and Lactation</i> .....	28
2.7.4.5.5	<i>Overdose</i> .....	28
2.7.4.5.6	<i>Drug Abuse</i> .....	28
2.7.4.5.7	<i>Withdrawal and Rebound</i> .....	28
2.7.4.5.8	<i>Effects on Ability to Drive or Operate Machinery or Impairment of Mental Ability</i> .....	29
2.7.4.6	Post-marketing Data.....	29
2.7.4.7	Appendix.....	29
<b>2.7.5</b>	<b>Literature References .....</b>	<b>29</b>

<b>2.7.6</b>	<b>Synopses of Individual Studies .....</b>	<b>30</b>
<b>MODULE 5 : CLINICAL STUDY REPORTS .....</b>		<b>45</b>
<b>Preamble .....</b>		<b>45</b>
<b>Detailed Organisation of Clinical Study Reports and Related Information in Module 5.....</b>		<b>45</b>
<b>5.1</b>	<b>Table of Contents of Module 5 .....</b>	<b>45</b>
<b>5.2</b>	<b>Tabular Listing of All Clinical Studies .....</b>	<b>46</b>
<b>5.3</b>	<b>Clinical Study Reports.....</b>	<b>46</b>
<b>5.3.1</b>	<b>Reports of Biopharmaceutical Studies .....</b>	<b>46</b>
5.3.1.1	Bioavailability (BA) Study Reports .....	46
5.3.1.2	Comparative BA and Bioequivalence (BE) Study Reports .....	46
5.3.1.3	In Vitro – In Vivo Correlation Study Reports.....	47
5.3.1.4	Reports of Bioanalytical and Analytical Methods for Human Studies .....	47
<b>5.3.2</b>	<b>Reports of Studies Pertinent to Pharmacokinetics Using Human Biomaterials .....</b>	<b>47</b>
5.3.2.1	Plasma Protein Binding Study Reports.....	47
5.3.2.2	Reports of Hepatic Metabolism and Drug Interaction Studies .....	47
5.3.2.3	Reports of Studies Using Other Human Biomaterials .....	47
<b>5.3.3</b>	<b>Reports of Human Pharmacokinetic (PK) Studies .....</b>	<b>47</b>
5.3.3.1	Healthy Subject PK and Initial Tolerability Study Reports .....	48
5.3.3.2	Patient PK and Initial Tolerability Study Reports.....	48
5.3.3.3	Intrinsic Factor PK Study Reports .....	48
5.3.3.4	Extrinsic Factor PK Study Reports .....	48
5.3.3.5	Population PK Study Reports .....	48
<b>5.3.4</b>	<b>Reports of Human Pharmacodynamic (PD) Studies.....</b>	<b>49</b>
5.3.4.1	Healthy Subject PD and PK/PD Study Reports .....	49
5.3.4.2	Patient PD and PK/PD Study Reports.....	49
<b>5.3.5</b>	<b>Reports of Efficacy and Safety Studies .....</b>	<b>49</b>
5.3.5.1	Study Reports of Controlled Clinical Studies Pertinent to the Claimed Indication .....	50
5.3.5.2	Study Reports of Uncontrolled Clinical Studies .....	50
5.3.5.3	Reports of Analyses of Data from More than One Study .....	50
5.3.5.4	Other Study Reports.....	51
<b>5.3.6</b>	<b>Reports of Post-Marketing Experience.....</b>	<b>51</b>
<b>5.3.7</b>	<b>Case Report Forms and Individual Patient Listings.....</b>	<b>51</b>
<b>5.4</b>	<b>Literature References .....</b>	<b>51</b>



## 1                   **MODULE 2 : COMMON TECHNICAL DOCUMENT SUMMARIES**

### 2                                   **2.5: CLINICAL OVERVIEW**

#### 3   **Preamble**

4   The Clinical Overview is intended to provide a critical analysis of the clinical data in the  
5   Common Technical Document. The Clinical Overview will necessarily refer to application  
6   data provided in the comprehensive Clinical Summary, the individual clinical study reports  
7   (ICH E3), and other relevant reports; but it should primarily present the conclusions and  
8   implications of those data, and should not recapitulate them. Specifically, the Clinical  
9   Summary should provide a detailed factual summarisation of the clinical information in the  
10   CTD, and the Clinical Overview should provide a succinct discussion and interpretation of  
11   these findings together with any other relevant information (e.g., pertinent animal data or  
12   product quality issues that may have clinical implications).

13   The Clinical Overview is primarily intended for use by regulatory agencies in the review of  
14   the clinical section of a marketing application. It should also be a useful reference to the  
15   overall clinical findings for regulatory agency staff involved in the review of other sections of  
16   the marketing application. The Clinical Overview should present the strengths and limitations  
17   of the development program and study results, analyse the benefits and risks of the medicinal  
18   product in its intended use, and describe how the study results support critical parts of the  
19   prescribing information.

20   In order to achieve these objectives the Clinical Overview should:

- 21   • describe and explain the overall approach to the clinical development of a medicinal  
22    product, including critical study design decisions.
- 23   • assess the quality of the design and performance of the studies, and include a statement  
24    regarding GCP compliance.
- 25   • provide a brief overview of the clinical findings, including important limitations (e.g., lack  
26    of comparisons with an especially relevant active comparator, or absence of information  
27    on some patient populations, on pertinent endpoints, or on use in combination therapy).
- 28   • provide an evaluation of benefits and risks based upon the conclusions of the relevant  
29    clinical studies, including interpretation of how the efficacy and safety findings support  
30    the proposed dose and target indication and an evaluation of how prescribing information  
31    and other approaches will optimise benefits and manage risks.
- 32   • address particular efficacy or safety issues encountered in development, and how they  
33    have been evaluated and resolved.
- 34   • explore unresolved issues, explain why they should not be considered as barriers to  
35    approval, and describe plans to resolve them.
- 36   • explain the basis for important or unusual aspects of the prescribing information.

37   The Clinical Overview should generally be a relatively short document (about 30 pages). The  
38   length, however, will depend on the complexity of the application. The use of graphs and  
39   concise tables in the body of the text is encouraged for brevity and to facilitate understanding.  
40   It is not intended that material presented fully elsewhere be repeated in the Clinical Overview;  
41   cross-referencing to more detailed presentations provided in the Clinical Summary or in  
42   Module 5 is encouraged.

43 **Table of Contents**

44           2.5.1       Product Development Rationale  
45           2.5.2       Overview of Biopharmaceutics  
46           2.5.3       Overview of Clinical Pharmacology  
47           2.5.4       Overview of Efficacy  
48           2.5.5       Overview of Safety  
49           2.5.6       Benefits and Risks Conclusions  
50                2.5.6.1     Therapeutic Context  
51                    2.5.6.1.1   Disease or Condition  
52                    2.5.6.1.2   Current Therapies  
53           2.5.6.2     Benefits  
54           2.5.6.3     Risks  
55           2.5.6.4     Benefit-Risk Assessment  
56           2.5.6.5     Appendix  
57           2.5.7       Literature References

58 **Detailed Discussion of Content of the Clinical Overview Sections**

59 **2.5.1       Product Development Rationale**

60 The discussion of the rationale for the development of the medicinal product should:

- 61 • identify the pharmacological class of the medicinal product.  
62 • describe the particular clinical/pathophysiological condition that the medicinal product is  
63 intended to treat, prevent, or diagnose (the targeted indication).  
64 • include a brief overview of the major therapies currently used in the intended population  
65 and how they influenced product development.  
66 • briefly summarise the scientific background that supported the investigation of the  
67 medicinal product for the indication(s) that was (were) studied.  
68 • briefly describe the clinical development programme of the medicinal product, including  
69 ongoing and planned clinical studies and the basis for the decision to submit the  
70 application at this point in the programme. Briefly describe plans for the use of foreign  
71 clinical data (ICH E5).  
72 • note and explain concordance or lack of concordance with current standard research  
73 approaches regarding the design, conduct and analysis of the studies. Pertinent published  
74 literature should be referenced. Regulatory guidance and advice (at least from the  
75 region(s) where the Clinical Overview is being submitted) should be identified, with  
76 discussion of how that advice was implemented. Formal advice documents (e.g., official  
77 meeting minutes, official guidance, letters from regulatory authorities) should be  
78 referenced, with copies included in the references section of Module 5.

79

## 80 2.5.2 Overview of Biopharmaceutics

81 The purpose of this section is to present a critical analysis of any important issues related to  
82 bioavailability that might affect efficacy and/or safety of the to-be-marketed formulation(s)  
83 (e.g., dosage form/strength proportionality, differences between the to-be-marketed  
84 formulation and the formulation(s) used in clinical trials, and influence of food on exposure).

## 85 2.5.3 Overview of Clinical Pharmacology

86 The purpose of this section is to present a critical analysis of the pharmacokinetic (PK),  
87 pharmacodynamic (PD), and related *in vitro* data in the CTD. The analysis should consider all  
88 relevant data and explain why and how the data support the conclusions drawn. It should  
89 emphasise unusual results and known or potential problems, or note the lack thereof. This  
90 section should address:

- 91 • pharmacokinetics, e.g., comparative PK in healthy subjects, patients, and special  
92 populations; PK related to intrinsic factors (e.g., age, sex, race, renal and hepatic  
93 impairment) and to extrinsic factors (e.g., smoking, concomitant drugs, diet); rate and  
94 extent of absorption; distribution, including binding with plasma proteins; specific  
95 metabolic pathways, including effects of possible genetic polymorphism and the formation  
96 of active and inactive metabolites; excretion; time-dependent changes in  
97 pharmacokinetics; stereochemistry issues; clinically relevant PK interactions with other  
98 medicinal products or other substances.
- 99 • pharmacodynamics, e.g., information on mechanism of action, such as receptor binding;  
100 onset and/or offset of action; relationship of favorable and unfavorable pharmacodynamic  
101 effects to dose or plasma concentration (i.e., PK/PD relationships); PD support for the  
102 proposed dose and dosing interval; clinically relevant PD interactions with other medicinal  
103 products or substances; and possible genetic differences in response.
- 104 • interpretation of the results and implications of immunogenicity studies, clinical  
105 microbiology studies, or other drug class specific PD studies summarised in section  
106 2.7.2.4 of the Clinical Summary.

## 107 2.5.4 Overview of Efficacy

108 The purpose of this section is to present a critical analysis of the clinical data pertinent to the  
109 efficacy of the medicinal product in the intended population. The analysis should consider all  
110 relevant data, whether positive or negative, and should explain why and how the data support  
111 the proposed indication and prescribing information. Those studies deemed relevant for  
112 evaluation of efficacy should be identified, and reasons that any apparently adequate and well-  
113 controlled studies are not considered relevant should be provided. Prematurely terminated  
114 studies should be noted and their impact considered.

115 The following issues should generally be considered:

- 116 • relevant features of the patient populations, including demographic features, disease stage,  
117 any other potentially important covariates, any important patient populations excluded  
118 from critical studies, and participation of children and elderly (ICH E11 and E7).  
119 Differences between the studied population(s) and the population that would be expected  
120 to receive the medicinal product after marketing should be discussed.
- 121 • implications of the study design(s), including selection of patients, duration of studies and  
122 choice of endpoints and control group(s). Particular attention should be given to endpoints

123 for which there is limited experience. Use of surrogate endpoints should be justified.  
124 Validation of any scales used should be discussed.

125 • for non-inferiority trials used to demonstrate efficacy, the evidence supporting a  
126 determination that the trial had assay sensitivity and justifying the choice of non-inferiority  
127 margin (ICH E10).

128 • statistical methods and any issues that could affect the interpretation of the study results  
129 (e.g., important modifications to the study design, including endpoint assessments and  
130 planned analyses, as they were specified in the original protocol; support for any  
131 unplanned analyses; procedures for handling missing data; and corrections for multiple  
132 endpoints).

133 • similarities and differences in results among studies, or in different patient sub-groups  
134 within studies, and their effect upon the interpretation of the efficacy data.

135 • observed relationships between efficacy, dose, and dosage regimen for each indication, in  
136 both the overall population and in the different patient subgroups (ICH E4).

137 • support for the applicability to the new region of data generated in another region, where  
138 appropriate (ICH E5).

139 • for products intended for long-term use, efficacy findings pertinent to the maintenance of  
140 long-term efficacy and the establishment of long-term dosage. Development of tolerance  
141 should be considered.

142 • data suggesting that treatment results can be improved through plasma concentration  
143 monitoring, if any, and documentation for an optimal plasma concentration range.

144 • the clinical relevance of the magnitude of the observed effects.

145 • if surrogate endpoints are relied upon, the nature and magnitude of expected clinical  
146 benefit and the basis for these expectations.

147 • efficacy in special populations. If efficacy is claimed with inadequate clinical data in the  
148 population, support should be provided for extrapolating efficacy from effects in the  
149 general population.

### 150 **2.5.5 Overview of Safety**

151 The purpose of this section is to provide a concise critical analysis of the safety data, noting  
152 how results support and justify proposed prescribing information. A critical analysis of safety  
153 should consider:

154 • adverse effects characteristic of the pharmacological class. Approaches taken to monitor  
155 for similar effects should be described.

156 • special approaches to monitoring for particular adverse events (e.g., ophthalmic, QT  
157 interval prolongation).

158 • relevant animal toxicology and product quality information. Findings that affect or could  
159 affect the evaluation of safety in clinical use should be considered.

160 • the nature of the patient population and the extent of exposure, both for test drug and  
161 control treatments. Limitations of the safety database, e.g., related to inclusion/exclusion  
162 criteria and study subject demographics, should be considered, and the implications of  
163 such limitations with respect to predicting the safety of the product in the marketplace  
164 should be explicitly discussed.

- 165 • common and non-serious adverse events, with reference to the tabular presentations of  
166 events with the test drug and with control agents in the Clinical Summary. The discussion  
167 should be brief, focusing on events of relatively high frequency, those with an incidence  
168 higher than placebo, and those that are known to occur in active controls or other members  
169 of the therapeutic class. Events that are substantially more or less common or problematic  
170 (considering the duration and degree of the observed events) with the test drug than with  
171 active controls are of particular interest.
- 172 • serious adverse events (relevant tabulations should be cross-referenced from the Clinical  
173 Summary). This section should discuss the absolute number and frequency of serious  
174 adverse events, including deaths, and other significant adverse events (e.g., events leading  
175 to discontinuation or dose modification), and should discuss the results obtained for test  
176 drug versus control treatments. Any conclusions regarding causal relationship (or lack of  
177 this) to the product should be provided. Laboratory findings reflecting actual or possible  
178 serious medical effects should be considered.
- 179 • similarities and differences in results among studies, and their effect upon the  
180 interpretation of the safety data.
- 181 • any differences in rates of adverse events in population subgroups, such as those defined  
182 by demographic factors, weight, concomitant illness, concomitant therapy, or polymorphic  
183 metabolism.
- 184 • relation of adverse events to dose, dose regimen, and treatment duration.
- 185 • long-term safety (E1a).
- 186 • methods to prevent, mitigate, or manage adverse events.
- 187 • reactions due to overdose; the potential for dependence, rebound phenomena and abuse, or  
188 lack of data on these issues.
- 189 • world-wide marketing experience. The following should be briefly discussed:  
190 - the extent of the world-wide experience,  
191 - any new or different safety issues identified,  
192 - any regulatory actions related to safety.
- 193 • support for the applicability to the new region of data generated in another region, where  
194 appropriate (ICH E5).

## 195 **2.5.6 Benefits and Risks Conclusions**

### 196 **Preamble**

197 The purpose of this section is to provide a succinct, integrated, and clearly explained benefit-  
198 risk assessment of the medicinal product for its intended use. This assessment should include  
199 any important strengths, limitations, and uncertainties in the available data. Some of the  
200 expected information in Section 2.5.6 as described below may be adequately addressed in  
201 other parts of the application and should not be reiterated here in detail. In such cases, the  
202 applicant should use cross-references to more detailed presentations provided elsewhere in the  
203 application. The content of each subsection should provide the applicant's conclusions with a  
204 clear explanation of the reasoning behind the analysis and the thought process that led to the  
205 conclusions.

206 Section 2.5.6 represents the first benefit-risk assessment of a medicinal product in the  
207 proposed indication submitted to a regulatory authority. This assessment is based on a  
208 weighing of the key benefits and key risks of the medicinal product—those that contribute  
209 importantly to the benefit-risk assessment—and do not necessarily include all benefits and  
210 risks. The identification of the key benefits and key risks of a product requires a critical  
211 review of the entirety of the efficacy and safety information relevant for the application.  
212 Subsequent benefit-risk assessments of approved products are the subject of the ICH E2C(R2)  
213 (Periodic Benefit-Risk Evaluation Report: PBRER) guideline, which similarly uses the  
214 concepts of key benefits and key risks.

215

216 The following additional points should be considered when completing this section:

217

- 218 • Multiple indications: If multiple indications are proposed for the medicinal product,  
219 each indication may be supported by a separate section heading where appropriate.  
220 For example, it may be sensible to separate the discussion of therapeutic context,  
221 benefit, and the benefit-risk assessment for different indications, whereas the  
222 discussion of risk may be combined. Where indications are discussed separately, a  
223 separate section should be provided for each indication using headings, e.g., 2.5.6.1  
224 Pneumonia and 2.5.6.1 Upper Respiratory Infection. When indications are closely  
225 related, the applicant may consider discussing them together in the appropriate  
226 sections.
- 227 • In some cases, a certain characteristic of the medicinal product may reasonably be  
228 described under benefits or risks. For example, the medicinal product may exhibit an  
229 improved safety profile over existing treatment, a reduced risk (e.g., fractures in  
230 osteoporosis), or may show reduced efficacy over time. Whether such considerations  
231 are discussed as benefits or as risks is a decision for the applicant, but they should not  
232 be discussed as both.
- 233 • Available information about the patient perspective<sup>1</sup> may be considered when  
234 completing Section 2.5.6.
- 235 • Tables or figures may be included in Section 2.5.6 to support or provide greater clarity  
236 to key points or conclusions.

### 237 **2.5.6.1 Therapeutic Context**

238 This section should briefly discuss the therapeutic context for the purpose of describing the  
239 medical need for a new medicinal product. The therapeutic context includes the disease or  
240 condition and the benefits and risks of current therapies that are most relevant to the  
241 evaluation of the medicinal product in the intended population. Significant limitations or  
242 uncertainties in the understanding of the condition or therapies should be discussed.  
243 Information about disease severity in subpopulations should be provided as it relates to  
244 differences in how the therapeutic context may be considered in the benefit-risk assessment  
245 for those populations. The discussion may be brief if the condition and treatment options are  
246 well understood. This section should not include information on the benefits and risks of the  
247 applicant's medicinal product; this information should be discussed in Sections 2.5.6.2 and  
248 2.5.6.3.

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<sup>1</sup> Patient perspective information encompasses descriptive information of patient attitudes regarding aspects covered in this section, as well as information obtained from methodologies intended to elicit the patient perspective (e.g., patient preference studies). If such studies are submitted, the detailed study reports may be submitted to Module 5.

#### 250 2.5.6.1.1 *Disease or Condition*

251 This section provides a description of aspects of the disease or condition that are most relevant  
252 to, or have the greatest impact on, the intended population (e.g., incidence, duration,  
253 morbidity, mortality, health-related quality of life) across the spectrum of disease severity.  
254 The discussion may begin from a broad perspective of the disease and then should focus on  
255 the aspects of the disease that would be covered by the proposed indication for the medicinal  
256 product. Societal or public health implications of the condition (e.g., impact of poor control  
257 and prevention of an infectious disease) should also be addressed where relevant.

#### 258 2.5.6.1.2 *Current Therapies*<sup>2</sup>

259 This section provides a description of the major therapies in the intended population (i.e.,  
260 those therapies used most frequently and/or recommended in clinical guidelines) and the  
261 medical need for a new therapy in terms of efficacy, safety, tolerability, convenience, or  
262 preference, if applicable. For disease areas that are treated by different pharmacologic classes  
263 of therapies, this analysis may be simplified by grouping and providing commentary by drug  
264 class. Other interventions used for the intended population may also be discussed when their  
265 use is supported by established clinical practice. Such interventions could include medical  
266 and surgical procedures, drugs used off-label, and other non-drug interventions (e.g., diet  
267 modifications, physical therapy). Major differences in current therapies between regions may  
268 be noted. If no therapies are currently available to treat the indication, this should be stated.

#### 269 2.5.6.2 *Benefits*

270 This section summarizes the key benefits that will be discussed in the benefit-risk assessment  
271 of the medicinal product. Benefits can be thought of as the favorable effects of the medicinal  
272 product. Typically, a benefit is described by the primary efficacy endpoint. In some cases, a  
273 benefit may be described by a combination of individual study endpoints, e.g., the benefit of  
274 improved asthma control described by the frequency of exacerbations and hospitalizations and  
275 the number of asthma-related deaths. Benefits may also include important characteristics of  
276 the medicinal product, including its convenience (e.g., a more convenient dosing regimen or  
277 route of administration) that may lead to improved patient compliance or benefits that affect  
278 those other than the patient (e.g., population benefits of a vaccine due to herd immunity).

279 The following characteristics may be considered when identifying the key benefits of the  
280 medicinal product:

- 281 • nature of benefit (e.g., life-prolonging, curative, disease-modifying, symptomatic  
282 relief, improved patient compliance, functional or quality of life improvement,  
283 preventive, or diagnostic);
- 284 • clinical importance of the benefit (e.g., less frequent hospitalization, prevention of  
285 disease progression);
- 286 • absolute difference in effect versus comparator; in some cases, also expressing the  
287 difference in relative terms can inform the assessment of benefit

288 In addition to the points above, the following considerations may also be discussed when  
289 describing each key benefit:

- 290 • time course of the key benefit (e.g., time to onset, continued effect of the medicinal  
291 product over time);

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<sup>2</sup> For purposes of this section, the term “therapy” encompasses both pharmacologic and non-pharmacologic interventions, as well as preventive measures and diagnostics. In addition, the terms “therapy” and “treatment” are used interchangeably.

- 292       • variability of the key benefit across the study population, particularly in important  
293       subpopulations (e.g., those defined by age, sex, ethnicity, organ function, disease  
294       severity, genetic polymorphism)

295 This section should also include an analysis of the strengths, limitations, and uncertainties of  
296 the evidence related to each key benefit and the implications of this information. The  
297 following points may be considered, as applicable:

- 298       • study design considerations (e.g., superiority or non-inferiority comparison to active  
299       control, superiority comparison to placebo, blinding, absence of comparator);  
300       • data analysis considerations (e.g., patient retention, missing data);  
301       • number of clinical studies and consistency of results across studies;  
302       • relationship between dose or exposure (e.g., drug levels in the blood) and benefit;  
303       • generalizability of the clinical study data to clinical practice (e.g., clinically important  
304       differences between the study population and the intended population);  
305       • confidence that surrogate endpoints, if used, predict that the intended population will  
306       receive the benefits.

### 307 **2.5.6.3 Risks**

308 This section summarizes the key risks that will be discussed in the benefit-risk assessment of  
309 the medicinal product. Risk is sometimes used to refer to a particular adverse effect (e.g., an  
310 adverse drug reaction) that can be caused by a medicinal product. However, the term is used  
311 here to refer to the frequency and severity of an unfavorable effect associated with the  
312 medicinal product, including the seriousness of the outcomes of the risk and its potential  
313 impact on public health. The key risks described in this section may not include all important  
314 risks that are described elsewhere in the application (e.g., risk management plan). For  
315 important risks that are not identified as key risks, the applicant should explain these  
316 selections.

317 This section should also consider important adverse drug reactions that affect certain  
318 subpopulations, drug interactions, unique risks compared to existing therapies, risks identified  
319 in the non-clinical data, risks to those other than the patient (e.g., fetus, those administering  
320 the medicinal product), and expected risks based on pharmacologic class or current  
321 knowledge of the product's safety if previously approved. Factors that may increase risk, such  
322 as misuse or abuse of the product, should also be considered.

323 The following characteristics of adverse drug reactions may be considered when identifying  
324 the key risks of the medicinal product:

- 325       • seriousness and/or severity of the adverse drug reaction;  
326       • frequency of the adverse drug reaction in the study population versus the  
327       comparator(s) and/or the background rate in the patient population;  
328       • reversibility of the adverse drug reaction;  
329       • tolerability of the adverse drug reaction, e.g., whether they lead to discontinuation of  
330       therapy.

331 In addition to the points above, the following considerations may also be discussed when  
332 describing each key risk:

- 333       • ability to predict, prevent, monitor, or manage the adverse drug reaction;  
334       • time course of the adverse drug reaction in the study population (i.e., time to onset,  
335       whether the frequency of the event is highest when initiating the drug and

336 subsequently decreases, is relatively constant with time, or increases with cumulative  
337 exposure).

338 This section should also include an analysis of the strengths, limitations, and uncertainties  
339 regarding the relevant safety information. The following points may be considered, as  
340 applicable:

- 341 • adequacy of assessment of risk (e.g., number of patients, number and design of trials,  
342 duration of exposure, frequency of monitoring, or the conduct of special studies to  
343 assess risk such as QTc effect studies);
- 344 • duration and completeness of follow-up;
- 345 • number of patients in relevant subpopulations treated at the intended dose;
- 346 • mechanism of action for the adverse drug reaction, if known, including non-clinical  
347 information or class effects;
- 348 • completeness of information on relevant risk factors associated with observed adverse  
349 events in trial subjects (e.g., baseline smoking history, concomitant medication use);
- 350 • consistency of results across studies;
- 351 • relationship between dose or exposure (e.g., drug levels in the blood) and risk;
- 352 • limitations on the ability to generalize clinical study data to clinical practice (e.g.,  
353 clinically important differences between the study population and the intended  
354 population).

355 The proposed approach to managing each key risk should also be discussed, including an  
356 explanation of why the approach provides reasonable assurance that the risk can be  
357 appropriately managed. Repetition of details from the Risk Management Plan is not  
358 necessary. In certain cases, a discussion of the overall approach to risk management may be  
359 sufficient and may be included after all key risks have been identified and described.

#### 360 **2.5.6.4 Benefit-Risk Assessment**

361 This section should provide the applicant's conclusion on the benefit-risk assessment,  
362 including a succinct explanation of the reasoning and clinical judgment used in assessing and  
363 weighing the key benefits and key risks. In addition, the applicant should explain how any  
364 uncertainties affect the interpretation of the evidence and the conclusion. Although previous  
365 parts of Section 2.5.6 focus on factual descriptions of the data, the benefit-risk assessment  
366 should focus on interpretation of the data.

367 There are many approaches available for conducting the benefit-risk assessment. A  
368 descriptive approach that explicitly communicates the interpretation of the data and the  
369 benefit-risk assessment will generally be adequate. Beyond this, the guideline does not  
370 prescribe a specific methodology. However, an applicant may choose to use methodologies  
371 that quantitatively express the underlying judgments and uncertainties in the assessment.  
372 Before using such methodology, the applicant should consider its utility, complexity, the  
373 extent to which the methodology is established, and the ease of interpretation of the results. In  
374 this situation, a written summary and explanation of the conclusions should still be provided  
375 in this section. The detailed presentation of the methodology should be appended in Section  
376 2.5.6.5.

377 Applicants may, at their discretion, use summary tables or graphical displays to communicate  
378 the clinical importance of the key benefits and key risks, as well as the resulting benefit-risk  
379 assessment.

380

381 The following aspects should generally be considered when describing the benefit-risk  
382 assessment:

- 383 • The impact of the therapeutic context on the assessment, including how the severity of  
384 disease and expected benefit influence the acceptance of the risks of the therapy and  
385 how the medicinal product is expected to fit with current treatment options. This  
386 discussion may be supported by available information about patient perspectives;
- 387 • The ability of the patient or healthcare provider to determine if the drug is having the  
388 intended effect, allowing for appropriate risk mitigation by discontinuing treatment in  
389 non-responders;
- 390 • Key aspects of the proposed labeling and risk management activities that are important  
391 in reaching a favorable benefit-risk assessment

#### 392 **2.5.6.5 Appendix**

393 Lengthy reports of a benefit-risk assessment that are summarized in Section 2.5.6.4 can be  
394 provided in this section.

#### 395 **2.5.7 Literature References**

396 A list of references used, stated in accordance with the current edition of the *Uniform*  
397 *Requirements for Manuscripts Submitted to Biomedical Journals*, International Committee of  
398 Medical Journal Editors (ICMJE) <sup>3</sup> or the system used in “Chemical Abstracts”, should be  
399 provided. Copies of all references cited in the Clinical Overview should be provided in  
400 Section 5.4 of Module 5.

### 401 **2.7 : CLINICAL SUMMARY**

#### 402 **Preamble**

403 The Clinical Summary is intended to provide a detailed, factual summarisation of all of the  
404 clinical information in the Common Technical Document. This includes information  
405 provided in ICH E3 clinical study reports; information obtained from any meta-analyses or  
406 other cross-study analyses for which full reports have been included in Module 5; and post-  
407 marketing data for products that have been marketed in other regions. The comparisons and  
408 analyses of results across studies provided in this document should focus on factual  
409 observations. In contrast, the CTD Clinical Overview document should provide critical  
410 analysis of the clinical study program and its results, including discussion and interpretation of  
411 the clinical findings and discussion of the place of the test drug in the armamentarium.

412 The length of the Clinical Summary will vary substantially according to the information to be  
413 conveyed, but it is anticipated that (excluding attached tables) the Clinical Summary will  
414 usually be in the range of 50 to 400 pages.

#### 415 **Table of Contents**

#### 416 **2.7.1 Summary of Biopharmaceutical Studies and Associated Analytical Methods**

417 2.7.1.1 Background and Overview

418 2.7.1.2 Summary of Results of Individual Studies

419 2.7.1.3 Comparison and Analyses of Results Across Studies

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<sup>3</sup> The first edition of the *Uniform Requirements for Manuscripts Submitted to Biomedical Journals* was conceived by the Vancouver Group and was published in 1979.

420	2.7.1.4	Appendix
421	<b>2.7.2</b>	<b>Summary of Clinical Pharmacology Studies</b>
422	2.7.2.1	Background and Overview
423	2.7.2.2	Summary of Results of Individual Studies
424	2.7.2.3	Comparison and Analyses of Results Across Studies
425	2.7.2.4	Special Studies
426	2.7.2.5	Appendix
427	<b>2.7.3</b>	<b>Summary of Clinical Efficacy</b>
428	2.7.3.1	Background and Overview of Clinical Efficacy
429	2.7.3.2	Summary of Results of Individual Studies
430	2.7.3.3	Comparison and Analyses of Results Across Studies
431	2.7.3.4	Analysis of Clinical Information Relevant to Dosing Recommendations
432	2.7.3.5	Persistence of Efficacy and/or Tolerance Effects
433	2.7.3.6	Appendix
434	<b>2.7.4</b>	<b>Summary of Clinical Safety</b>
435	2.7.4.1	Exposure to the Drug
436	2.7.4.2	Adverse Events
437	2.7.4.3	Clinical Laboratory Evaluations
438	2.7.4.4	Vital Signs, Physical Findings, and Other Observations Related to
439	Safety	
440	2.7.4.5	Safety in Special Groups and Situations
441	2.7.4.6	Post-marketing Data
442	2.7.4.7	Appendix
443	<b>2.7.5</b>	<b>Literature References</b>
444	<b>2.7.6</b>	<b>Synopses of Individual Studies</b>
445		
446		<b>Detailed Guidance on Sections of the Clinical Summary</b>
447	<b>2.7.1</b>	<b>Summary of Biopharmaceutic Studies and Associated Analytical Methods</b>
448	<b>2.7.1.1</b>	<b>Background and Overview</b>
449		This section should provide the reviewer with an overall view of the formulation development
450		process, the <i>in vitro</i> and <i>in vivo</i> dosage form performance, and the general approach and
451		rationale used in developing the bioavailability (BA), comparative BA, bioequivalence (BE),

452 and *in vitro* dissolution profile database. Reference should be made to any guidelines or  
453 literature used in planning and conducting the studies. This section should also provide the  
454 reviewer with an overview of the analytical methods used, with emphasis on the performance  
455 characteristics of assay validation (e.g., linearity range, sensitivity, specificity) and quality  
456 control (e.g., accuracy and precision). This section should not include detailed information  
457 about individual studies.

#### 458 **2.7.1.2 Summary of Results of Individual Studies**

459 A tabular listing of all biopharmaceutical studies should generally be provided (see 2.7.1.4  
460 Appendix), together with narrative descriptions of relevant features and outcomes of each of  
461 the individual studies that provided important *in vitro* or *in vivo* data and information relevant  
462 to BA and BE. The narrative descriptions should be brief, e.g., similar to an abstract for a  
463 journal article, and should describe critical design features and critical results. Similar studies  
464 may be described together, noting the individual study results and any important differences  
465 among the studies. These narratives may be abstracted from the ICH E3 synopsis. References  
466 or electronic links to the full report of each study should be included in the narratives.

#### 467 **2.7.1.3 Comparison and Analyses of Results Across Studies**

468 This section should provide a factual summary of all *in vitro* dissolution, BA, and  
469 comparative BA studies carried out with the drug substance or drug product, with particular  
470 attention to differences in results across studies. This overview should typically summarise the  
471 findings in text and tables (see 2.7.1.4 Appendix) and should consider the following:

- 472 • evidence of the effects of formulation and manufacturing changes on *in vitro* dissolution  
473 and BA and conclusions regarding BE. When manufacturing or formulation changes are  
474 made for products containing complex drug substances (e.g., a protein), pharmacokinetic  
475 (PK) studies comparing the product before and after the changes may be performed to  
476 ensure that the PK characteristics have not changed as a result of product changes.  
477 Although such studies are sometimes referred to as BE studies, they generally do not focus  
478 on assessing release of drug substance from drug product. Nonetheless, such studies  
479 should be reported in this section. Note also that PK studies alone may not be sufficient to  
480 assure similarity between such drug products. In many situations, pharmacodynamic (PD)  
481 studies or clinical trials may be necessary. Additionally, depending on the circumstances,  
482 antigenicity data may also be needed. Results of these other types of studies, when they  
483 are needed, should be reported in the appropriate places in the dossier.
- 484 • evidence of the extent of food effects on BA and conclusions regarding BE with respect to  
485 meal type or timing of the meal (where appropriate).
- 486 • evidence of correlations between *in vitro* dissolution and BA, including the effects of pH  
487 on dissolution, and conclusions regarding dissolution specifications.
- 488 • comparative bioavailability, including BE conclusions, for different dosage form  
489 strengths.
- 490 • comparative BA of the clinical study formulations (for clinical studies providing  
491 substantial evidence of efficacy) and the formulations to be marketed.
- 492 • the source and magnitude of observed inter- and intrasubject variability for each  
493 formulation in a comparative BA study.

494

495 **2.7.1.4 Appendix**

496 Tables and figures should be embedded in the text of the appropriate sections when they  
497 enhance the readability of the document. Lengthy tables can be provided in the appendix at  
498 the end of the Section.

499 Tables 2.7.1.1 and 2.7.1.2 are provided as examples of tabular formats for reporting  
500 information and results related to bioavailability and *in vitro* dissolution studies respectively.  
501 These examples give results as well as identifying the type and design of the study. Tables  
502 prepared for reporting the results of BE studies could also include the mean ratios  
503 (test/reference) for C<sub>max</sub> and AUC and their 90% confidence interval, or the currently  
504 recommended metrics for BE assessments.

505 These tables are not intended to be templates, but only to illustrate the type of information that  
506 should be considered by an applicant in designing the tables for biopharmaceutical studies.  
507 Applicants should also decide whether information and results from these studies are best  
508 presented in tables, text or figures in order to aid clarity. If, for example, results are best  
509 presented in text and figures, tables might be used simply to list the studies.

510 **2.7.2 Summary of Clinical Pharmacology Studies**

511 **2.7.2.1 Background and Overview**

512 This section should provide the reviewer with an overall view of the clinical pharmacology  
513 studies. These studies include clinical studies performed to evaluate human pharmacokinetics  
514 (PK), and pharmacodynamics (PD), and *in vitro* studies performed with human cells, tissues,  
515 or related materials (hereinafter referred to as human biomaterials) that are pertinent to PK  
516 processes. For vaccine products, this section should provide the reviewer with immune  
517 response data that support the selection of dose, dosage schedule, and formulation of the final  
518 product. Where appropriate, relevant data that are summarised in sections 2.7.1, 2.7.3 and  
519 2.7.4 can also be referenced to provide a comprehensive view of the approach and rationale  
520 for the development of the pharmacokinetic, pharmacodynamic, PK/PD and human  
521 biomaterial database. This section should not include detailed information about individual  
522 studies.

523 This section should begin with a brief overview of the human biomaterial studies that were  
524 conducted and that were intended to help in the interpretation of PK or PD data. Studies of  
525 permeability (e.g., intestinal absorption, blood brain barrier passage), protein binding, hepatic  
526 metabolism, and metabolic-based drug-drug interactions are particularly relevant. This should  
527 be followed by a brief overview of the clinical studies that were carried out to characterise PK  
528 and PD of the medicinal product, including studies of PK/PD relationships in healthy subjects  
529 and patients, and relevant effects of intrinsic and extrinsic factors on PK and PK/PD  
530 relationships<sup>4</sup>. Critical aspects of study design and data analysis should be noted, e.g., the  
531 choice of the single or multiple doses used, the study population, choice of the intrinsic or  
532 extrinsic factors that were studied, the choice of PD endpoints, and whether a traditional  
533 approach or a population approach was used to collect and analyse data to assess PK or PD.

534

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<sup>4</sup> In the ICH E5 guideline on Ethnic Factors in the Acceptance of Foreign Data, factors that may result in different responses to a drug in different populations are categorized as intrinsic ethnic factors or extrinsic ethnic factors. In this document, these categories are referred to as intrinsic factors and extrinsic factors, respectively.

535 **2.7.2.2 Summary of Results of Individual Studies**

536 A tabular listing of all clinical pharmacology studies should generally be provided (see 2.7.2.5  
537 Appendix), together with a narrative description of the relevant features and outcomes of each  
538 of the critical individual studies that provided *in vitro* or *in vivo* data and information relevant  
539 to PK, PD and PK/PD relationships. The narrative descriptions should be brief, e.g., similar to  
540 an abstract for a journal article, and should describe critical design features and critical results.  
541 Similar studies may be described together, noting the individual study results and any  
542 important differences among the studies. References or electronic links to the full report of  
543 each study should be included in the narratives.

544 Summaries of dose-response or concentration response (PK/PD) studies with  
545 pharmacodynamic endpoints should generally be included in this section. In some cases,  
546 however, when well-controlled dose-response PD or PK/PD studies provide important  
547 evidence of efficacy or safety, they should be placed in 2.7.3 or 2.7.4 as appropriate and  
548 referenced, but not summarised, here.

549 **2.7.2.3 Comparison and Analyses of Results Across Studies**

550 This section should use the results of all *in vitro* human biomaterial studies and PK, PD and  
551 PK/PD studies to characterise the PK, PD and PK/PD relationships of the drug. Results  
552 related to the inter- and intra-individual variability in these data and the intrinsic and extrinsic  
553 factors affecting these pharmacokinetic relationships should be discussed.

554 This section (typically with the use of text and tables) should provide a factual presentation of  
555 all data across studies pertinent to the following:

- 556 • *in vitro* drug metabolism and *in vitro* drug-drug interaction studies and their clinical  
557 implications.
- 558 • human PK studies, including the best estimates of standard parameters and sources of  
559 variability. The focus should be on evidence supporting dose and dose individualisation in  
560 the target patient population and in special populations, e.g., paediatric or geriatric  
561 patients, or patients with renal or hepatic impairment.
- 562 • comparison between single and repeated-dose PK
- 563 • population PK analyses, such as results based on sparse sampling across studies that  
564 address inter-individual variations in the PK or PD of the active drug substances that may  
565 be due to extrinsic or intrinsic factors.
- 566 • dose-response or concentration-response relationships. This discussion should highlight  
567 evidence to support the selection of dosages and dose intervals studied in the important  
568 clinical trials. In addition, information that supports the dosage instructions in the  
569 proposed labelling should be discussed in Section 2.7.3.4.
- 570 • major inconsistencies in the human biomaterial, PK, or PD database.
- 571 • PK studies that were performed to determine whether foreign clinical data could be  
572 extrapolated to the new region (see ICH E5). The result of the studies and analysis of the  
573 similarity of the PK data between regions or races should be summarised in this section.  
574 Such studies that use PD biomarkers (but do not evaluate clinical efficacy) may similarly  
575 be summarised here. An independent subsection can be created to summarise these kinds  
576 of data.

577

#### 578 2.7.2.4 *Special Studies*

579 This section should include studies that provide special types of data relevant to specific types  
580 of medicinal products. For immunogenicity studies and other studies in which data may  
581 correlate with PK, PD, safety, and/or efficacy data, explanations of such correlations should  
582 be summarised here. Any observed or potential effects on PK, PD, safety and/or efficacy  
583 should be considered in other appropriate sections of the Clinical Summary as well, with  
584 cross-referencing to this section. Human studies that address a specific safety issue should not  
585 be reported here, but instead should be reported in the Summary of Clinical Safety (section  
586 2.7.4).

#### 587 **Example 1: Immunogenicity**

588 For protein products and other products to which specific immunological reactions have been  
589 measured, data regarding immunogenicity should be summarised in this section. For vaccines  
590 or other products intended to induce specific immune reactions, immunogenicity data should  
591 be described in the efficacy section 2.7.3. Assays used should be briefly described and  
592 information about their performance (e.g., sensitivity, specificity, reliability, validity) should  
593 be summarised; the location in the application of detailed information should be cross-  
594 referenced.

595 Data regarding the incidence, titre, timing of onset and duration of antibody responses should  
596 be summarised for each type of antibody assay used (e.g., IgG by ELISA, neutralisation).  
597 Relationships of antibody formation to underlying disease, concomitant medication, dose,  
598 duration, regimen, and formulation should be explored and summarised. For drugs intended  
599 to be given as chronic, continuous therapy, any data on the impact of interruptions of therapy  
600 on antigenicity should be analysed and summarised.

601 It is particularly important to summarise analyses of potential clinically relevant correlates of  
602 immunogenicity, e.g., to determine the extent to which the presence of antibodies of a  
603 particular type or titer appears to correlate with alterations of PK, changes in PD, loss of  
604 efficacy, loss of adverse event profile, or development of adverse events. Particular attention  
605 should be paid to events that might be immunologically mediated (e.g., serum sickness) and  
606 events that might result from binding of cross-reactive endogenous substances by antibodies  
607 to the administered drug.

#### 608 **Example 2: Clinical microbiology**

609 For antimicrobial or antiviral medicinal products, *in vitro* studies to characterise the spectrum  
610 of activity are an important part of the programme of studies relevant to clinical efficacy.  
611 Clinical efficacy studies that include characterisation of the susceptibility of the clinical  
612 isolates as a part of the efficacy determination should be included in Section 2.7.3, Summary  
613 of Clinical Efficacy. However, studies that evaluate such findings as the pattern of *in vitro*  
614 susceptibility of strains of bacteria from different parts of the world (not in the context of  
615 clinical efficacy study) would be included here.

#### 616 2.7.2.5 *Appendix*

617 Tables and figures should be embedded in the text of the appropriate sections when that  
618 enhances the readability of the document. Lengthy tables can be provided in the appendix at  
619 the end of the Section.

620 Table 2.7.2.1 is provided as an example of a tabular format for reporting information and  
621 results related to pharmacokinetic drug-drug interaction studies. Similar tables could be  
622 prepared for PK/PD studies, dose-response studies, studies of effects on human biomaterials,

623 and population PK studies. This table is not intended to be a template, but only to illustrate  
624 the type of information that should be considered by sponsors in designing their own tables.  
625 Applicants should also decide whether information and results from clinical pharmacology  
626 studies are best presented in tables, text or figures in order to aid clarity. If, for example,  
627 results are best presented in text and figures, the tables might simply list the studies.

628 In designing tables, if any, for various types of other clinical pharmacology studies such as  
629 those listed below, applicants should consider including the following types of information.  
630 These examples are for illustrative purposes only and the sponsor should decide which  
631 information needs to be presented.

- 632 • metabolism studies using human biomaterials: biomaterials used (e.g., microsomes,  
633 hepatocytes), probe drugs, enzymatic pathways and % contribution and relevant kinetic  
634 parameters (e.g.,  $V_{max}$ ,  $K_m$ ).
- 635 • *in vitro* studies of drug-drug interactions using human biomaterials: for studies of other  
636 drugs inhibiting the new drug, the metabolite(s) inhibited, enzymatic pathways affected,  
637 range of inhibitor concentrations used,  $IC_{50}$  and  $K_i$  values and proposed mechanism of  
638 inhibition should be included. For studies of the new drug inhibiting other drugs, the  
639 drugs and metabolites inhibited should be included, along with the information mentioned  
640 above.
- 641 • population PK studies: co-variates studied, number and type of subjects or patients  
642 studied, summary statistical parameters and final estimates of mean ( $\pm$  standard deviation)  
643 PK parameters.

### 644 **2.7.3 Summary of Clinical Efficacy**

645 A separate Section 2.7.3 should be provided for each indication, although closely related  
646 indications can be considered together. When more than one Section 2.7.3 is submitted, the  
647 sections should be labelled 2.7.3 pneumonia, 2.7.3 URI, etc.

#### 648 **2.7.3.1 Background and Overview of Clinical Efficacy**

649 This section should describe the program of controlled studies and other pertinent studies in  
650 the application that evaluated efficacy specific to the indication(s) sought. Any results of these  
651 studies that are pertinent to evaluation of safety should be discussed in Section 2.7.4,  
652 Summary of Clinical Safety.

653 The section should begin with a brief overview of the design of the controlled studies that  
654 were conducted to evaluate efficacy. These studies include dose-response, comparative  
655 efficacy, long-term efficacy, and efficacy studies in population subsets. Critical features of  
656 study design should be discussed, e.g., randomisation, blinding, choices of control treatment,  
657 choice of patient population, unusual design features such as crossover or randomised  
658 withdrawal designs, use of run-in periods, other methods of “enrichment”, study endpoints,  
659 study duration, and prespecified plans for analysis of the study results. Although this section is  
660 intended to focus on clinical investigations, nonclinical data and clinical pharmacology data  
661 may also be referenced as appropriate to provide a comprehensive summary of human  
662 experience related to efficacy. This section should not include detailed information about  
663 individual studies.

#### 664 **2.7.3.2 Summary of Results of Individual Studies**

665 A tabular listing of all studies that provided (or were designed to provide) information  
666 relevant to product efficacy should generally be provided (see the section 2.7.3.6 Appendix),

667 together with narrative descriptions for important studies. The narrative descriptions should be  
668 brief, e.g., similar to an abstract for a journal article, and should describe critical design  
669 features and critical results. Similar studies may be described together, noting the individual  
670 study results and any important differences among the studies. For studies that also  
671 contributed significantly to the safety analysis, study narratives should include information  
672 about the extent of exposure of study subjects to the test drug or control agent, and how safety  
673 data were collected. These narratives can be abstracted from the synopses of the clinical  
674 study reports (ICH E3). References or electronic links to the full report of each study should  
675 be included in the narratives.

676 Narratives of any bridging studies using clinical endpoints, i.e., certain studies intended to  
677 evaluate the ability to extrapolate certain types of foreign clinical data to the new region (see  
678 ICH E5), should be included in this section. An analysis of the results of such studies, together  
679 with other information (e.g., PK and PD data) that addresses the ability to extrapolate the  
680 efficacy and safety results of foreign studies, should be performed if necessary. The  
681 conclusions of such an analysis should be noted at the start of Section 2.7.3.3.2, Comparison  
682 of Efficacy Results of All Studies, and the full report of the analysis should be provided in  
683 Module 5.

### 684 **2.7.3.3 Comparison and Analyses of Results Across Studies**

685 Using text, figures, and tables as appropriate (see the section 2.7.3.6 Appendix), the  
686 subsections of 2.7.3.3 should summarise all available data that characterise the efficacy of the  
687 drug. This summary should include analyses of all data, irrespective of their support for the  
688 overall conclusion and should, therefore, discuss the extent to which the results of the relevant  
689 studies do or do not reinforce each other. Any major inconsistencies in the data regarding  
690 efficacy should be addressed and any areas needing further exploration should be identified.

691 The section will generally utilise two kinds of analyses: comparison of results of individual  
692 studies, and analysis of data combined from various studies. Details of analyses that are too  
693 extensive to be reported in a summary document should be presented in a separate report, to  
694 be placed in Module 5, Section 5.3.5.3.

695 This section should also cross-reference important evidence from section 2.7.2, such as data  
696 that support the dosage and administration section of the labelling. These data include dosage  
697 and dose interval recommended, evidence pertinent to individualisation of dosage and need  
698 for modifications of dosage for specific subgroups (e.g., paediatric or geriatric subjects, or  
699 subjects with hepatic or renal impairment), and data relevant to dose-response or  
700 concentration response (PK/PD) relationships.

#### 701 **2.7.3.3.1 Study Populations**

702 The demographic and other baseline characteristics of patients across all efficacy studies  
703 should be described. The following should be included:

- 704 • the characteristics of the disease (e.g., severity, duration) and prior treatment in the study  
705 subjects, and study inclusion/exclusion criteria
- 706 • differences in baseline characteristics of the study populations in different studies or  
707 groups of studies.
- 708 • any differences between populations included in critical efficacy analyses and the overall  
709 patient population that would be expected to receive the drug when it is marketed should  
710 be noted.

- 711 • assessment of the number of patients who dropped out of the studies, time of withdrawal  
712 (a defined study day or visit during treatment or follow up period), and reasons for  
713 discontinuation.

714 Tabular presentations that combine and compare study populations across studies may be  
715 useful.

#### 716 *2.7.3.3.2 Comparison of Efficacy Results of all Studies*

717 The results of any bridging studies using clinical endpoints, i.e., certain studies used to  
718 evaluate the ability to extrapolate certain types of foreign clinical data to the new region (see  
719 ICH E5), should be summarised in this section. An analysis of the similarity of efficacy in  
720 subjects between regions, as well as any other information that may support extrapolation of  
721 the efficacy data to the new region, should be summarised here. An independent subsection  
722 can be created to summarize these kinds of data.

723 The results from all studies designed to evaluate the drug’s efficacy should be summarised  
724 and compared, including studies with inconclusive or negative results. Important differences  
725 in study design such as endpoints, control group, study duration, statistical methods, patient  
726 population, and dose should be identified.

727 Comparisons of results across studies should focus on pre-specified primary endpoints.  
728 However, when the primary endpoints involved different variables or time points in different  
729 efficacy studies, it may be useful to provide cross-study comparisons of important data  
730 elements that were obtained in all studies. If results over time are important, results of studies  
731 may be displayed in a figure that illustrates the change over time in each study.

732 Confidence intervals for treatment effects should be given to aid in the interpretation of point  
733 estimates. If differences are shown between placebo and test drugs in the change from  
734 baseline, the baseline values and the magnitude of effect in all treatment groups, including  
735 placebo and active controls (if used), should generally be presented in the table or in text  
736 accompanying a figure. If the objective of an active control trial was to show equivalence or  
737 non-inferiority, the difference or the ratio of outcomes between treatments should be given  
738 with the confidence interval. The results should be evaluated by using the predefined criteria  
739 for defining equivalence or non-inferiority and the rationale for the criteria and support for the  
740 determination that the study (studies) had assay sensitivity should be provided (see ICH E10).

741 Important differences in outcomes between studies with a similar design should be delineated  
742 and discussed. Cross-study comparisons of factors that may have contributed to differences in  
743 outcomes should be described.

744 If a meta-analysis of the clinical studies is performed, it should be clear whether this analysis  
745 is conducted according to a predefined protocol or is a post hoc exercise. Any differences in  
746 trial designs or populations, or in efficacy measurements between trials should be described to  
747 allow assessment of the relevance and validity of the results and conclusions (See ICH E9). A  
748 detailed description of the methodology and results of the meta-analysis should generally be  
749 submitted in a separate report (section 5.3.5.3 of Module 5).

#### 750 *2.7.3.3.3 Comparison of Results in Sub-populations*

751 The results of individual studies or overview analyses of efficacy in specific populations  
752 should be summarised in this section. The purpose of these comparisons should be to show  
753 whether the claimed treatment effects are observed consistently across all relevant sub-  
754 populations, especially those where there are special reasons for concern. The comparisons  
755 may highlight apparent variations in efficacy that require further investigation and discussion.

756 The limitations of such analyses, however, should be recognised (ICH E9), and it is important  
757 to note that their purpose is not to provide the basis for specific claims, nor to attempt to  
758 improve the evidence of efficacy in situations where the overall results are disappointing.

759 Given the limited sample sizes in individual studies, analyses across multiple studies should  
760 be performed to evaluate effects of major demographic factors (age, sex, and race) and of  
761 other predefined or relevant intrinsic and extrinsic factors (e.g., disease severity, prior  
762 treatment, concomitant illness, concomitant drugs, alcohol, tobacco, and body weight) on  
763 efficacy. Factors of special interest may arise from general concerns (e.g., the elderly) or from  
764 specific issues that are related to the pharmacology of the drug or that have arisen during  
765 earlier drug development. Efficacy in the paediatric population should be routinely analysed in  
766 applications for a proposed indication that occurs in children. Depending on the data set, if  
767 extensive, detailed efficacy analyses are performed, they can be placed in Module 5, with the  
768 results of those analyses reported here.

#### 769 **2.7.3.4 Analysis of Clinical Information Relevant to Dosing Recommendations**

770 This section should provide an integrated summary and analysis of all data that pertain to the  
771 dose-response or blood level-response relationships of effectiveness (including dose-blood  
772 level relationships), and thus have contributed to dose selection and choice of dose interval.  
773 Relevant data from nonclinical studies may be referenced, and relevant data from  
774 pharmacokinetic studies, other clinical pharmacology studies, and controlled and uncontrolled  
775 clinical studies should be summarised to illustrate these dose-response or blood level-response  
776 relationships. For pharmacokinetic and pharmacodynamic studies from which data have been  
777 summarised in Section 2.7.2.2, it may be appropriate to draw upon those data in this summary  
778 while cross-referencing the summaries in Section 2.7.2.2, without repeating those summaries.

779 While the interpretation of how these data support specific dosing recommendations should be  
780 supplied in the Clinical Overview document, the individual study results and any cross-study  
781 analyses that will be used to support the dosing recommendations (including the  
782 recommended starting and maximal doses, the method of dose titration, and any other  
783 instructions regarding individualisation of dosage) should be summarised here. Any identified  
784 deviations from relatively simple dose-response or blood-level response relationships due to  
785 non-linearity of pharmacokinetics, delayed effects, tolerance, enzyme induction, etc. should be  
786 described.

787 Any evidence of differences in dose-response relationships that result from a patient's age,  
788 sex, race, disease, or other factors should be described. Any evidence of different  
789 pharmacokinetic or pharmacodynamic responses should also be discussed, or discussions in  
790 Section 2.7.2 can be cross-referenced. The ways in which such differences were looked for,  
791 even if no differences were found, should be described (e.g., specific studies in  
792 subpopulations, analysis of efficacy results by subgroup, or blood level determinations of the  
793 test drug).

#### 794 **2.7.3.5 Persistence of Efficacy and/or Tolerance Effects**

795 Available information on persistence of efficacy over time should be summarised. The  
796 number of patients for whom long-term efficacy data are available, and the length of  
797 exposure, should be provided. Any evidence of tolerance (loss of therapeutic effects over  
798 time) should be noted. Examination of any apparent relationships between dose changes over  
799 time and long-term efficacy may be useful.

800 The primary focus should be on controlled studies specifically designed to collect long-term  
801 efficacy data, and such studies should be clearly differentiated from other, less rigorous,

802 studies such as open extension studies. This distinction also applies to specific studies  
803 designed for evaluation of tolerance and withdrawal effects. Data concerning withdrawal or  
804 rebound effects pertinent to product safety should be presented in the safety section (see  
805 section 2.7.4).

806 In long-term efficacy trials, the effect of premature discontinuation of therapy or switching to  
807 other therapies upon the assessment of the results should be considered. These issues might  
808 also be important for short term trials and should be addressed when discussing the results of  
809 these trials, if appropriate.

#### 810 **2.7.3.6 Appendix**

811 Tables and figures should be embedded in the text of the appropriate sections when that  
812 enhances the readability of the document. Lengthy tables can be provided in the appendix at  
813 the end of the Section.

814 Tables should identify all studies pertinent to the evaluation of efficacy (including studies that  
815 were terminated or are not yet completed, studies that failed to show effectiveness for any  
816 reason, studies available only as publications, studies reported in full technical reports (ICH  
817 E3), and studies described in abbreviated reports); and should provide the most important  
818 results of those studies. Note, however, that unplanned interim analyses on ongoing studies  
819 are generally not needed or encouraged. When more than one section 2.7.3 is provided for an  
820 application with more than one indication, usually each section should have its own appendix  
821 with tables.

822 Illustrative tables for an antihypertensive drug are provided, but these examples will not be  
823 relevant to every application. In general, applications will require tables and/or figures that  
824 are developed specifically for the particular drug class and the studies that were carried out.

825 Table 2.7.3.1 Description of Clinical Efficacy and Safety Studies

826 Table 2.7.3.2 Results of Efficacy Studies

#### 827 **2.7.4 Summary of Clinical Safety**

828 This section should be a summary of data relevant to safety in the intended patient population,  
829 integrating the results of individual clinical study reports as well as other relevant reports, e.g.,  
830 the integrated analyses of safety that are routinely submitted in some regions.

831 The display of safety-related data can be considered at three levels (ICH E3):

- 832 – The extent of exposure (dose, duration, number of patients, type of patients) should be  
833 examined to determine the degree to which safety can be assessed from the database.
- 834 – The more common adverse events and changes in laboratory tests should be identified and  
835 classified, and their occurrence should be summarised.
- 836 – Serious adverse events (defined in ICH E2A) and other significant adverse events (defined  
837 in ICH E3) should be identified and their occurrence should be summarised. These events  
838 should be examined for frequency over time, particularly for drugs that may be used  
839 chronically.

840 The safety profile of the drug, described on the basis of analysis of all clinical safety data,  
841 should be outlined in a detailed, clear, and objective manner, with use of tables and figures.

842

## 843 **2.7.4.1 Exposure to the Drug**

### 844 *2.7.4.1.1 Overall Safety Evaluation Plan and Narratives of Safety Studies*

845 The overall safety evaluation plan should be described briefly, including special  
846 considerations and observations concerning the nonclinical data, any relevant pharmacological  
847 class effects, and the sources of the safety data (controlled trials, open studies, etc). A tabular  
848 listing of all clinical studies that provided safety data, grouped appropriately, should generally  
849 be provided (see the section 2.7.4.7 Appendix). In addition to studies that evaluated efficacy  
850 and safety, and uncontrolled studies that generate safety information, this section includes  
851 studies that consider special safety issues. Examples would include studies to compare  
852 particular adverse event rates for two therapies, to assess safety in particular demographic  
853 subsets, to evaluate withdrawal or rebound phenomena, or to evaluate particular adverse  
854 events (e.g., sedation, sexual function, effects on driving, absence of a class adverse effect).  
855 Studies in indications for which approval is not being sought in the current application and  
856 ongoing studies would also be included here if they contribute to the safety analysis.

857 Narrative descriptions of these studies should be provided here, except that narrative  
858 descriptions for studies that contributed both efficacy and safety data should be included in  
859 Section 2.7.3.2 and cross-referenced here. The narratives should provide enough detail to  
860 allow the reviewer to understand the exposure of study subjects to the test drug or control  
861 agent, and how safety data were collected (including the methods used and the extent of safety  
862 monitoring of the subjects enrolled in the individual studies). If some studies are not analysed  
863 separately but are grouped for safety analysis, that should be noted, and a single narrative  
864 description can be provided.

### 865 *2.7.4.1.2 Overall Extent of Exposure*

866 A table (see example provided in the section 2.7.4.7 Appendix) and appropriate text should be  
867 generated to summarise the overall extent of drug exposure from all phases of the clinical  
868 study development programme. The table should indicate the numbers of subjects exposed in  
869 studies of different types and at various doses, routes, and durations. If a large number of  
870 different doses and/or durations of exposure were used, these can be grouped in a manner  
871 appropriate for the drug. Thus, for any dose or range of doses, duration of exposure can be  
872 summarised by the number of subjects exposed for specific periods of time, such as 1 day or  
873 less, 2 days to 1 week, 1 week to 1 month, 1 month to 6 months, 6 months to 1 year, more  
874 than 1 year (ICH E3). In some applications it may be important to identify diagnostic  
875 subgroups and/or groups receiving specific concomitant therapies deemed particularly  
876 relevant to safety assessment in the intended use.

877 The dose levels used for each subject in this presentation could be the maximum dose  
878 received by that subject, the dose with longest exposure, and/or the mean daily dose, as  
879 appropriate. In some cases, cumulative dose may be pertinent. Dosage may be given as the  
880 actual daily dose or on a mg/kg or mg/m<sup>2</sup> basis, as appropriate. If available, drug  
881 concentration data (e.g., concentration at the time of an adverse event, maximum plasma  
882 concentration, area under curve) may be helpful in individual subjects for correlation with  
883 adverse events or changes in laboratory variables.

884 It is assumed that all subjects who were enrolled and received at least one dose of the  
885 treatment are included in the safety analysis; if that is not so, an explanation should be  
886 provided.

887

888 **2.7.4.1.3 Demographic and Other Characteristics of Study Population**

889 A summary table should provide the reader with an overview of the demographic  
890 characteristics (Table 2.7.4.2) of the population that was exposed to the therapeutic agent  
891 during its development. Choice of age ranges used should take into account considerations  
892 discussed in ICH E7 [Studies in Support of Special Populations: Geriatrics] and ICH E11  
893 [Clinical Investigation of Medicinal Products in the Paediatric Population]. If the relative  
894 exposure of demographic groups in the controlled trials differed from overall exposure, it may  
895 be useful to provide separate tables.

896 In addition, one or more tables should show the relevant characteristics of the study  
897 population, and the numbers of subjects with special characteristics. Such characteristics  
898 could include:

- 899 – Severity of disease
- 900 – Hospitalisation
- 901 – Impaired renal function
- 902 – Concomitant illnesses
- 903 – Concomitant use of particular medications
- 904 – Geographical location

905 If these characteristics are distributed differently in controlled trials versus the overall  
906 database, it will generally be useful to present tables on both groupings.

907 The text accompanying the table(s) should mention any imbalance(s) between the drug and  
908 placebo and/or comparator regarding any of the above demographic characteristics,  
909 particularly if they could lead to differences in safety outcomes.

910 If certain subjects were excluded from studies (concomitant illness, severity of illness,  
911 concomitant medications), this fact should be noted.

912 Separate demographic tables should be provided for every indication, although closely related  
913 indications can be considered together, if study subject characteristics are such that risks are  
914 believed to be the same.

915 **2.7.4.2 Adverse Events**

916 **2.7.4.2.1 Analysis of Adverse Events**

917 Data on the frequency of adverse events should be described in text and tables. Text should  
918 appear in the appropriate subsections of Section 2.7.4.2.1 and the tables that are not embedded  
919 in the text should be placed in the section 2.7.4.7 Appendix.

920 All adverse events occurring or worsening after treatment has begun ("treatment emergent  
921 signs and symptoms," those adverse events not seen at baseline and those that worsened even  
922 if present at baseline) should be summarised in tables listing each event, the number of  
923 subjects in whom the event occurred and the frequency of occurrence in subjects treated with  
924 the drug under investigation, with comparator drugs, and with placebo. Such tables could also  
925 present results for each dose and could be modified to show, e.g., adverse event rates by  
926 severity, by time from onset of therapy, or by assessment of causality.

927 When most of the relevant safety data are derived from a small number of studies (e.g., one or  
928 two studies), or when very different study subject populations were enrolled in the studies that  
929 were performed, presentation of data by study will often be appropriate. When the relevant

930 exposure data is not concentrated in a small number of studies, however, grouping the studies  
931 and pooling the results to improve precision of estimates and sensitivity to differences should  
932 generally be considered.

933 While often useful, pooling of safety data across studies should be approached with caution  
934 because in some cases interpretation can be difficult, and it can obscure real differences. In  
935 cases where differences are apparent, it is more appropriate to present the data by study. The  
936 following issues should be considered:

- 937 • it is most appropriate to combine data from studies that are of similar design, e.g.,  
938 similar in dose, duration, methods of determining adverse events, and population.
- 939 • if the incidence for a particular adverse event differs substantially across the  
940 individual studies in a pool, the pooled estimate is less informative.
- 941 • any study with an unusual adverse event pattern should be presented separately.
- 942 • the appropriate extent of analysis depends on the seriousness of the adverse event  
943 and the strength of evidence of drug causation. Differences in rates of drug-  
944 related, serious events or events leading to discontinuation or dosage change  
945 deserve more investigation, whereas rates of other adverse events do not merit  
946 elaborate analysis.
- 947 • examination of which subjects experience extreme laboratory value abnormalities  
948 ("outliers") may be useful in identifying subgroups of individuals who are at  
949 particular risk for certain adverse events.

950 Groups of studies that could be used in pooled safety analyses include:

- 951 • all controlled studies or subsets of controlled studies, such as all placebo-  
952 controlled studies, studies with any positive control, studies with a particular  
953 positive control, or studies of particular indications (and thus carried out in  
954 different populations). These groupings are considered the best source of  
955 information about the more common adverse events and can distinguish drug-  
956 related events from spontaneous events. Rates in control and treatment groups  
957 should be compared.
- 958 • all studies, excluding short-term studies in healthy subjects.  
959 This grouping is most useful for evaluating rarer events.
- 960 • all studies using a particular dose route or regimen, or a particular concomitant  
961 therapy.
- 962 • studies in which adverse event reports are elicited by checklist or direct  
963 questioning, or studies in which events are volunteered.
- 964 • pools of studies by region.

965 It is almost always useful to carry out the first two groupings; the others chosen would vary  
966 from drug to drug and should be influenced by inspection of individual study results.  
967 Whatever methods are used, it should be recognised that, as for results of single studies, any  
968 numerical rate is often only a rough approximation of reality.

969 When a decision is made to pool data from several studies, the rationale for selecting the  
970 method used for pooling should be described. It is common to combine the numerator events  
971 and the denominators for the selected studies. Other methods for pooling results across studies

972 are available, e.g., weighting data from studies on the basis of study size or inversely to their  
973 variance.

974 If substantial differences are seen between clinical trials in the rates of adverse events, these  
975 differences should be noted and possible reasons should be discussed (e.g., relevant  
976 differences in study populations, in dose administration, or in methods of collecting adverse  
977 event data).

978 Adverse events should be described as shown in the individual study report (ICH E3). In  
979 combining data from many studies, it is important to use standardised terms to describe events  
980 and collect synonymous terms under a single preferred term. This can be done with a standard  
981 dictionary, and the MedDRA terminology (ICH M1 guideline) should be used. Until  
982 MedDRA can be fully implemented, other dictionaries can be used, but should be specified.  
983 Frequencies should be presented for preferred terms and for appropriately defined groupings.  
984 Examination of which adverse events led to change in therapy (discontinuation of drug use,  
985 change in dose, need for added therapy) can help in assessing the clinical importance of  
986 adverse events. These rates can be added to the adverse event rate tables, or can be presented  
987 in separate tables. Overall discontinuation rates by study may be useful but it is also important  
988 to specify the particular adverse events leading to discontinuation in a separate table. The  
989 preferred terms should be grouped by body system and arranged by decreasing frequency.

#### 990 *2.7.4.2.1.1 Common Adverse Events*

991 Tabular displays of adverse event rates (see the section 2.7.4.7 Appendix) should be  
992 used to compare rates in treatment and control groups. For this analysis it may be  
993 helpful to combine the event severity categories and the causality categories, if they  
994 are used, leading to a simpler side-by-side comparison of treatment groups. It should  
995 be noted that while causality categories may be reported, if used, the presentation of  
996 the data should include total adverse events (whether deemed related or unrelated to  
997 treatment); evaluations of causality are inherently subjective and may exclude  
998 unexpected adverse events that are in fact treatment related. Additionally,  
999 comparisons of rates of adverse events between treatment and control groups in  
1000 individual trials should be summarised here. It is often useful to tabulate rates in  
1001 selected trials (see example table 2.7.4.4, in the Section 2.7.4.7 Appendix).

1002 It is usually useful to examine more closely the more common adverse events that  
1003 seem to be drug related (e.g., those that show that a dose response and/or a clear  
1004 difference between drug and placebo rates) for relationship to relevant factors,  
1005 including:

- 1006 - dosage;
- 1007 - mg/kg or mg/m<sup>2</sup> dose;
- 1008 - dose regimen;
- 1009 - duration of treatment;
- 1010 - total dose;
- 1011 - demographic characteristics such as age, sex, race;
- 1012 - concomitant medication use;
- 1013 - other baseline features such as renal status;
- 1014 - efficacy outcomes;

1015 - drug concentration, where available.

1016 It may also be useful to summarise the results of examination of time of onset and  
1017 duration for these drug-related events.

1018 Rigorous statistical evaluations of the possible relationship of specific adverse events  
1019 to each of the above factors are often unnecessary. It may be apparent from initial  
1020 display and inspection of the data that there is no evidence of a significant relationship  
1021 to demographic or other baseline features. In that case, no further analysis of these  
1022 particular factors is needed. Further, it is not necessary that all such analyses be  
1023 presented in this report. When the safety analyses are too extensive to be presented in  
1024 detail in this report, they may be presented in a separate report in Module 5, section  
1025 5.3.5.3, and summarised here.

1026 Under certain circumstances, life table or similar analyses may be more informative  
1027 than reporting of crude adverse event rates.

#### 1028 2.7.4.2.1.2 *Deaths*

1029 A table in the Section 2.7.4.7 Appendix should list all deaths occurring while on study  
1030 (including deaths that occurred shortly following treatment termination, e.g., within 30  
1031 days or as specified in the study protocol, as well as all other deaths that occurred later  
1032 but may have resulted from a process that began during studies). Only deaths that are  
1033 clearly disease-related per protocol definitions and not related to the investigational  
1034 product, either in studies of conditions with high mortality such as advanced cancer or  
1035 in studies where mortality from disease is a primary study endpoint, should be  
1036 excepted from this listing (it is assumed, however, that these deaths would still be  
1037 reported in the individual ICH E3 study reports). Even these deaths should be  
1038 examined for any unexpected patterns between study arms, and further analysed if  
1039 unexplained differences are observed. Deaths should be examined individually and  
1040 analysed on the basis of rates in individual trials and appropriate pools of trials,  
1041 considering both total mortality and cause-specific deaths. Potential relationships to  
1042 the factors listed in Section 2.7.4.2.1.1 should also be considered. Although cause-  
1043 specific mortality can be difficult to determine, some deaths are relatively easy to  
1044 interpret. Thus deaths due to causes expected in the patient population (heart attacks  
1045 and sudden death in an angina population) are individually not considered to be  
1046 informative, but even one death due to a QT interval prolongation-associated  
1047 arrhythmia, aplastic anaemia, or liver injury may be informative. Special caution is  
1048 appropriate before an unusual death is attributed to concomitant illness.

#### 1049 2.7.4.2.1.3 *Other Serious Adverse Events*

1050 Summaries of all serious adverse events (other than death but including the serious  
1051 adverse events temporally associated with or preceding the deaths) should be  
1052 displayed. Serious adverse events that occurred after the drug use was discontinued  
1053 should be included in this section. The display should include major laboratory  
1054 abnormalities, abnormal vital signs, and abnormal physical observations that are  
1055 considered serious adverse events using the ICH E2A definitions. Results of analyses  
1056 or assessments of serious adverse events across studies should be presented. Serious  
1057 events should be examined for frequency over time, particularly for drugs that may be  
1058 used chronically. Potential relationships to the factors listed in Section 2.7.4.2.1.1  
1059 should also be considered.

#### 1060 2.7.4.2.1.4 *Other Significant Adverse Events*

1061 Marked haematologic and other laboratory abnormalities (other than those meeting the  
1062 definition of serious) and any events that led to a substantial intervention (premature  
1063 discontinuation of study drug, dose reduction, or substantial additional concomitant  
1064 therapy), other than those reported as serious adverse events, should be displayed.

1065 Events that led to premature discontinuation of study drug represent an important  
1066 safety concern and deserve particular attention in the analysis of drug safety for two  
1067 reasons. First, even for expected events (based on pharmacologic activity), the need to  
1068 discontinue (or otherwise alter) treatment reflects the severity and perceived  
1069 importance of the event to patient and physician. Second, discontinuation may  
1070 represent a drug-related event not yet recognised as drug related. Adverse events  
1071 leading to treatment discontinuation should be considered possibly drug-related even if  
1072 this was not recognised initially and even if the event was thought to represent  
1073 intercurrent illness. Reasons for premature treatment discontinuations should be  
1074 discussed and rates of discontinuations should be compared across studies and  
1075 compared with those for placebo and/or active control treatment. In addition, the study  
1076 data should be examined for any potential relationships to the factors listed in Section  
1077 2.7.4.2.1.1.

#### 1078 *2.7.4.2.1.5 Analysis of Adverse Events by Organ System or Syndrome*

1079 Assessment of the causality of, and risk factors for, deaths, other serious events, and  
1080 other significant events is often complicated by the fact that they are uncommon. As a  
1081 result, consideration of related events as a group, including less important events of  
1082 potentially related pathophysiology, may be of critical value in understanding the  
1083 safety profile. For example, the relationship to treatment of an isolated sudden death  
1084 may become much clearer when considered in the context of cases of syncope,  
1085 palpitations, and asymptomatic arrhythmias.

1086 It is thus generally useful to summarise adverse events by organ system so that they  
1087 may be considered in the context of potentially related events including laboratory  
1088 abnormalities. Such presentations of adverse events by organ system should be placed  
1089 in subsections of section 2.7.4.2.1.5, labelled as 2.7.4.2.1.5.1, 2.7.4.2.1.5.2, etc., and  
1090 titled by the organ system under consideration. The list of organ systems to be  
1091 addressed and the approach to grouping certain events should be selected as  
1092 appropriate to best present the adverse event data for the medicinal product. If some  
1093 adverse events tend to occur in syndromes (e.g., influenza-like syndrome, cytokine  
1094 release syndrome), the sponsor may choose to create some subsections of 2.7.4.2.1.5  
1095 for syndromes rather than organ systems.

1096 The same data and summarisations should generally not be repeated in more than one  
1097 subsection of Section 2.7.4.2.1. Instead, a summary presentation may be placed in one  
1098 subsection and cross-referenced as needed in the other.

#### 1099 *2.7.4.2.2 Narratives*

1100 The locations in the application of individual narratives of patient deaths, other serious  
1101 adverse events, and other significant adverse events deemed to be of special interest because  
1102 of clinical importance (as described in ICH E3 individual study reports) should be referenced  
1103 here for the convenience of the reviewer. The narratives themselves should be a part of the  
1104 individual study reports, if there is such a report. In cases where there is no individual study  
1105 report (e.g., if many open studies are pooled as part of a safety analysis and are not  
1106 individually described), narratives can be placed in Module 5, Section 5.3.5.3. Narratives

1107 should not be included here, unless an abbreviated narrative of particular events is considered  
1108 critical to the summary assessment of the drug.

### 1109 **2.7.4.3 Clinical Laboratory Evaluations**

1110 This section should describe changes in patterns of laboratory tests with drug use. Marked  
1111 laboratory abnormalities and those that led to a substantial intervention should be reported in  
1112 section 2.7.4.2.1.3 or 2.7.4.2.1.4. If these data are also presented in this section, this duplicate  
1113 reporting should be made clear for the reviewer. The appropriate evaluations of laboratory  
1114 values will in part be determined by the results seen, but, in general, the analyses described  
1115 below should be provided. For each analysis, comparison of the treatment and control groups  
1116 should be carried out, as appropriate and as compatible with study sizes. In addition, normal  
1117 laboratory ranges should be given for each analysis (ICH E3). Where possible, laboratory  
1118 values should be provided in standard international units.

1119 A brief overview of the major changes in laboratory values across the clinical studies should  
1120 be provided. Laboratory data should include haematology, clinical chemistry, urinalysis and  
1121 other data as appropriate. Each parameter at each time over the course of the study (e.g., at  
1122 each visit) should be described at the following three levels:

- 1123 • the central tendency, i.e., the group mean and median values,
- 1124 • the range of values, and the number of subjects with abnormal values or with abnormal  
1125 values of a certain size (e.g. twice the upper limit of normal, 5 times the upper limit;  
1126 choices should be explained). When data are pooled from centres with differences in  
1127 normal laboratory ranges, the methodology used in pooling should be described. The  
1128 analysis of individual subject changes by treatment group can be shown with a variety of  
1129 approaches (e.g., shift tables, see ICH E3 for examples).
- 1130 • individual clinically important abnormalities, including those leading to discontinuations.  
1131 The significance of the laboratory changes and the likely relation to the treatment should  
1132 be assessed (e.g., by analysis of such features as relationship to dose, relation to drug  
1133 concentration, disappearance on continued therapy, positive dechallenge, positive  
1134 rechallenge, and the nature of concomitant therapy). Potential relationships to other factors  
1135 listed in Section 2.7.4.2.1.1 should also be considered.

### 1136 **2.7.4.4 Vital Signs, Physical Findings, and Other Observations Related to Safety**

1137 The manner of presenting cross-study observations and comparisons of vital signs (e.g., heart  
1138 rate, blood pressure, temperature, respiratory rate), weight and other data (e.g.,  
1139 electrocardiograms, X-rays) related to safety should be similar to that for laboratory variables.  
1140 If there is evidence of a drug effect, any dose-response or drug concentration-response  
1141 relationship or relationship to individual variables (e.g., disease, demographics, concomitant  
1142 therapy) should be identified and the clinical relevance of the observation described.  
1143 Particular attention should be given to changes not evaluated as efficacy variables and to those  
1144 considered to be adverse events. Particular attention should be given to studies that were  
1145 designed to evaluate specific safety issues, e.g., studies of QT interval prolongation.

### 1146 **2.7.4.5 Safety in Special Groups and Situations**

#### 1147 **2.7.4.5.1 Intrinsic Factors**

1148 This section should summarise safety data pertinent to individualising therapy or patient  
1149 management on the basis of demographic and other factors defined as "intrinsic ethnic  
1150 factors" in ICH E5. These factors include age, sex, height, weight, lean body mass, genetic

1151 polymorphism, body composition, other illness and organ dysfunction. Safety in the paediatric  
1152 population should be routinely analysed in applications for a proposed indication that occurs  
1153 in children. Analysis of the impact of such factors on safety outcomes should have been  
1154 presented in other sections but should be summarised here, together with pertinent PK or other  
1155 information, e.g., in patients with renal or hepatic disease. If a sufficiently large number of  
1156 subjects with a given co-morbid condition such as hypertension, heart disease, or diabetes,  
1157 was enrolled, analyses should be carried out to assess whether the co-morbid condition  
1158 affected the safety of the drug under study. Cross reference should be made to the tables or  
1159 description of adverse events when analyses of such sub-groups has been carried out.

#### 1160 *2.7.4.5.2 Extrinsic Factors*

1161 This section should summarise safety data pertinent to individualising therapy or patient  
1162 management on the basis of factors defined as "extrinsic ethnic factors" in ICH E5. These are  
1163 factors associated with the patient environment. Examples are the medical environment, use  
1164 of other drugs (see 2.7.4.5.3, Drug Interactions), use of tobacco, use of alcohol, and food  
1165 habits.

1166 For example, if a potential interaction with alcohol is suggested by the metabolic profile, by  
1167 the results of studies, by post-marketing experience, or by information on similar drugs,  
1168 information should be provided here.

#### 1169 *2.7.4.5.3 Drug Interactions*

1170 Studies on potential drug-drug or drug-food interactions should be summarised in the  
1171 Summary of Clinical Pharmacology Studies section of the CTD (Section 2.7.2). The potential  
1172 impact on safety of such interactions should be summarised here, based on PK, PD, or clinical  
1173 observations. Any observed changes in the adverse event profile, changes in blood levels  
1174 thought to be associated with risk, or changes in drug effects associated with other therapy  
1175 should be presented here.

#### 1176 *2.7.4.5.4 Use in Pregnancy and Lactation*

1177 Any information on safety of use during pregnancy or breast-feeding that becomes available  
1178 during clinical development or from other sources should be summarised here.

#### 1179 *2.7.4.5.5 Overdose*

1180 All available clinical information relevant to overdose, including signs/symptoms, laboratory  
1181 findings, and therapeutic measures/treatments and antidotes (if available) should be  
1182 summarised and discussed. Information on the efficacy of specific antidotes and dialysis  
1183 should be provided if available.

#### 1184 *2.7.4.5.6 Drug Abuse*

1185 Any relevant studies/information regarding the investigation of the dependence potential of a  
1186 new therapeutic agent in animals and in humans should be summarised and cross-referenced  
1187 to the nonclinical summary. Particularly susceptible patient populations should be identified.

#### 1188 *2.7.4.5.7 Withdrawal and Rebound*

1189 Any information or study results pertinent to rebound effects should be summarised. Events  
1190 that occur, or increase in severity, after discontinuation of double-blind or active study  
1191 medication should be examined to see if they are the result of withdrawal of the study  
1192 medication. Particular emphasis should be given to studies designed to evaluate withdrawal  
1193 and/or rebound.

1194 Data concerning tolerance should be summarised under section 2.7.3.5 in the Summary of  
1195 Clinical Efficacy.

1196 **2.7.4.5.8 Effects on Ability to Drive or Operate Machinery or Impairment of Mental Ability**

1197 Safety data related to any impairment in the senses, co-ordination, or other factor that would  
1198 result in diminished ability to drive a vehicle or operate machinery or that would impair  
1199 mental ability should be summarised. This includes relevant adverse effects reported in safety  
1200 monitoring (e.g., drowsiness) and specific studies concerning effects on ability to drive or  
1201 operate machinery or impairment of mental ability.

1202 **2.7.4.6 Post-marketing Data**

1203 If the drug has already been marketed, all relevant post-marketing data available to the  
1204 applicant (published and unpublished, including periodic safety update reports if available)  
1205 should be summarised. The periodic safety update reports can be included in Module 5.  
1206 Details of the number of subjects estimated to have been exposed should be provided and  
1207 categorised, as appropriate, by indication, dosage, route, treatment duration, and geographic  
1208 location. The methodology used to estimate the number of subjects exposed should be  
1209 described. If estimates of the demographic details are available from any source, these should  
1210 be provided.

1211 A tabulation of serious events reported after the drug is marketed should be provided,  
1212 including any potentially serious drug interactions.

1213 Any post-marketing findings in subgroups should be described.

1214 **2.7.4.7 Appendix**

1215 Tabular presentations should be provided that summarise the important results from all studies  
1216 pertinent to the evaluation of safety and particularly to support product labelling.

1217 Tables and figures should be embedded in the text of the appropriate sections when that  
1218 enhances the readability of the document. Lengthy tables can be provided in the appendix at  
1219 the end of the Section.

1220 A few illustrative tables are provided, but a clinical summary will routinely need tables and  
1221 figures that have been developed for the particular drug, drug class, and clinical indication(s).

1222 See sections 2.7.4.2.1, 2.7.4.2.2.3, and 2.7.4.3 of this guidance for additional discussion  
1223 regarding the content of section 2.7.4 tables.

1224 Table 2.7.4.1 Study Subject Drug Exposure by Mean Daily Dose and Duration of Exposure

1225 Table 2.7.4.2 Demographic Profile of Patients in Controlled Trials

1226 Table 2.7.4.3 Incidence of Adverse Events in Pooled Placebo and Active Controlled  
1227 Trials

1228 Table 2.7.4.4 Incidence of Adverse Events in the Largest Trials

1229 Table 2.7.4.5 Patient Withdrawals by Study: Controlled Trials

1230 Table 2.7.4.6 Listing of Deaths

1231 **2.7.5 Literature References**

1232 A list of references cited in the Clinical Summary should be provided. Copies of all important  
1233 references should be provided in Module 5, Section 5.4. The reference list should indicate

1234 which references are available in Module 5, Section 5.4. All references that have not been  
1235 provided should be available upon request.

1236 **2.7.6 Synopses of Individual Studies**

1237 The ICH E3 guideline (Structure and Content of Clinical Study Reports) suggests inclusion of  
1238 a study synopsis with each clinical study report, and provides one example of a format for  
1239 such synopses.

1240 This section should include the table entitled Listing of Clinical Studies, described in  
1241 guidance for Module 5, followed by all individual study synopses organised in the same  
1242 sequence as the study reports in Module 5.

1243 It is expected that one synopsis will be prepared per study for use in all regions, and that the  
1244 same synopsis will be included in this section and as part of the clinical study report in  
1245 Module 5. The length of a synopsis will usually be up to 3 pages, but a synopsis for a more  
1246 complex and important study may be longer, e.g. 10 pages. Within the individual synopsis,  
1247 tables and figures should be used as appropriate to aid clarity.

1248 **Table 2.7.1.1**

1249

**Summary of Bioavailability Studies**

Study Ref. No.	Study Objective	Study Design	Treatments (Dose, Dosage Form, Route) [Product ID]	Subjects (No.(M/F) type Age: mean (range))	Mean Parameters (+/- SD)						Study Report Location
					Cmax (mg/L)	Tmax (hr)	AUC* (mg/L x hr)	Cmin** (mg/L)	T1/2 (hr)	Other	
192 (Japan)	Pilot relative BA study comparing the absorption from a 200mg tablet batch to a 200mg reference batch.	Open, randomized, cross-over, single 200 mg dose	200mg Tab., p.o. [17762]	20 (10/10) Healthy volunteer 27 y (20-35)	83 ± 21	1	217 ± 20		3.1		
			200mg Tab., p.o. [19426]		80 ± 32	0.5	223 ± 19	2.9			
195 (Japan)	Comparative BA study of xx under fasted and fed conditions	Open, randomized, cross-over, single dose	200mg Tab, p.o. [19426]	30 (15/15) Healthy volunteer 32 y (26-50)	83 ± 21	1	217 ± 20				
					120 ± 30	2	350 ± 40				

1250 AUC\* : AUC<sub>TAU</sub> or AUC<sub>inf</sub>

1251 Cmin\*\* : For multiple dose studies

1252 **Table 2.7.1.2**

1253

**Summary of *In vitro* Dissolution Studies**

Study Ref. No.	Product ID/Batch No.	Dosage Form	Conditions	No. of Dosage Units	Collection times			Study Report Location
					Mean % Dissolved (range)			
1821	979-03	25mg Cap.	Dissolution: Apparatus 2 (USP) Speed of Rotation: 50 rpm Medium/Temperature: Water 37°	12	10 42 (32-49) (%)	20 71 (58-85)	30 (min) 99 (96-100)	

1254

1255 **Table 2.7.2.1**

1256

**Summary of Drug-Drug Interaction PK Studies**

Study/ Protocol # (Country)	Product ID/Batch # (NME)	Study Objective	Study Design	# Subjects Entered/ Completed (M/F)	HV/P <sup>1</sup> (Age: Mean, range)	Treatments		Mean Pharmacokinetic Parameters (%CV) Substrate Drug					Mean ratio <sup>2</sup> Confidence interval		Location
						Substrate	Interacting Drug	Cmax	Tmax	AUC	T1/2	CL/kg	Cmax	AUC	
001 (USA)	19B Batch 0034	Effect of warfarin on Drug X	Randomized, Cross over	(8M/4F )/ (7M/4F )	HV (34, 20- 41)	Drug X 100 mg bid x 7d	Placebo	45 (18) Φg/mL	2.0 (30) hr	456 (24) Φg*hr/ mL	4.25 (30) hr	0.05 (20) mL/min/kg	1.16 1.01- 1.30	1.16 1.03- 1.34	
						Drug X 100 mg bid x 7d	Warfarin 10 mg qd x 7d	52 (20) Φg/mL	2.1 (35) hr	530 (27) Φg*hr/ mL	4.75 (35) hr	0.04 (22) mL/min/kg			
001 (USA)	19B Batch 0034	Effect of drug X on warfarin	Randomized, Cross over	(8M/4F )/ (7M/4F )	HV (34, 20- 41)	Warfarin 10 mg qd x 7d	Placebo	12 (25) Φg/mL	1.5 (30) hr	60 (37) Φg*hr/ mL	40 (35) hr	0.04 (30) mL/min/kg	1.08 0.92- 1.24	1.07 0.92- 1.18	
						Warfarin 10 mg qd x 7d	drug X 100 mg bid x 7d	13 (20) Φg/mL	1.45 (27) hr	64 (39) Φg*hr/ mL	42 (37) hr	0.39 (34) mL/min/kg			

002 (UK)	19B2 Batch 0035	Effect of Cimetidine on Drug X	Cross over, Single sequence	(4M/8F ) (4M/8F )	HV (30, 19- 45)	Drug X 50 mg bid x 5d	Placebo	49 (18) Φ/mL	2.1 (30) hr	470 (24) Φg*hr/ mL	4.4 (30) hr	0.05 (20) mL/min/kg	1.22 1.03- 1.40	1.36 1.11- 1.53	
						Drug X 50 mg bid x 5d	Cimetidine 200 mg bid x 5d	60 (10) Φg/mL	2.2 (30) hr	640 (24) Φg*hr/ mL	5.2 (30) hr	0.03 (20) mL/min/kg			

1257 <sup>1</sup>HV=Healthy Volunteers, P=Patients

1258 <sup>2</sup>Value for substrate with interacting drug / value with placebo

1259

1260

Table 2.7.3.1

## Description of Clinical Efficacy and Safety Studies

Study ID	Number of Study Centers Location(s)	Study start Enrollment status, date  Total enrollment / Enrollment goal	Design Control type	Study & Ctrl Drugs Dose, Route  & Regimen	Study Objective	# subs by arm entered/compl.	Duration	Gender M/F  Median Age (Range)	Diagnosis  Inclusion Criteria	Primary Endpoint(s)
PG-2476	1  U. Antarctica	Aug-94  Completed Apr 98  50 / 50	Randomised, double blind, parallel Placebo	TP: 30 mg po bid  Pbo	Efficacy and Safety	27/24  23/21	4 weeks	27/23  38 (20-64)	Mild hypertension  Diastolic 90-100  Systolic 150-170	Change from baseline systolic and diastolic pressure at 4 weeks.
PG-2666	4	May-98	Randomised, open label, parallel	TP: 100 mg po bid	Efficacy and Safety,	34/30	4 weeks, followed by 12 weeks open-label	66/60	Mild hypertension  Systolic 150-170	Change from baseline systolic and diastolic pressure at 4 weeks and at 12 weeks.

Affiliated Physicians of Florida,	Ongoing as of May 2001	Placebo and Dose-response	TP: 50 mg po bid	Long-term efficacy and safety	30/28		55 (24-68)	Diastolic 90-100	
Smith & Jones CRO	126/400		TP: 25 mg po bid		34/32				
			Placebo		28/26				

1261

1262

**Table 2.7.3.2****Results of Efficacy Studies**

Study	Treatment Arm	# Enrolled/Completed	Mean systolic and diastolic BP			Primary Endpoint  Placebo- subtracted change in DBP at 40 weeks	Statistical test / P value	Secondary Endpoints  % normalised* *  (ITT analysis)	Other Comments
			Baseline	20 wks	40 wks				
PG-  2678	TP: 100 mg po bid	34/30	162/96	140/85	138/84	6	88		
	TP: 50 mg po bid	30/28	165/97	146/87	146/87	4	78		
	TP: 25 mg po bid	34/32	167/96	148/88	148/88	2	50		
	TP: 10 mg po bid	26/20	162/95	153/93	153/93	-4	20		
	Placebo	28/26	166/97	160/92	159/91		30		

1263

\*\*Provide definition

1264

1265

<b>Table 2.7.4.1</b> <b>Study Subject Drug Exposure by Mean Daily Dose and Duration of Exposure</b> <b>Intravenous formulation      N=      Cutoff Date:</b>								
<b>Duration (Weeks)</b>	<b>Mean Daily Dose (mg)</b>						<b>Total (Any Dose)</b>	<b>Percent</b>
	<b>0 &lt; Dose ≤ 5mg</b>	<b>5 &lt; Dose ≤ 10mg</b>	<b>10 &lt; Dose ≤ 20mg</b>	<b>20 &lt; Dose ≤ 30mg</b>	<b>30 &lt; Dose ≤ 50mg</b>	<b>50mg &lt; Dose</b>		
0 < Dur ≤ 1								
1 < Dur ≤ 2								
2 < Dur ≤ 4								
4 < Dur ≤ 12								
12 < Dur ≤ 24								
24 < Dur ≤ 48								
48 < Dur ≤ 96								
Dur >96								
Total (Any Duration)								
Percent								

1266 Similar tables can be generated for median, for modal, and for maximum dose, or for dose of longest exposure. The same table can be generated  
 1267 for any pool of studies and any subgroup of interest, e.g., on the basis of age groupings, sex, ethnic factors, comorbid conditions, concomitant  
 1268 medications, or any combination of these factors.

1269 Dose can also be expressed as mg/kg, mg/m<sup>2</sup>, or in terms of plasma concentration if such data are available.

1270

<b>Table 2.7.4.2</b>			
<b>Demographic Profile of Patients in Controlled Trials Cutoff Date:</b>			
	<b>Treatment Groups</b>		
	<b>Test Product N =</b>	<b>Placebo N =</b>	<b>Active Control N =</b>
<b>Age (years)</b> Mean $\pm$ SD Range	50 $\pm$ 15 20-85		
<b>Groups</b> <18 18 - 40 40 - 64 65 - 75 >75	N (%) N (%) N (%) N (%) N (%)	N (%) N (%) N (%) N (%) N (%)	N (%) N (%) N (%) N (%) N (%)
<b>Sex</b> Female Male	N (%) N (%)	N (%) N (%)	N (%) N (%)
<b>Race</b> Asian Black Caucasian Other	N (%) N (%) N (%) N (%)	N (%) N (%) N (%) N (%)	N (%) N (%) N (%) N (%)
<b>Other Factors</b>			

**Table 2.7.4.3**

**Incidence of Adverse Events in Pooled Placebo and Active Controlled Trial Database**

Body System / Adverse Event	Test Drug			Placebo n = 425	Active Control 1 20 mg n = 653	Active Control 2	
	All doses n = 1685	10 mg n = 968	20 mg n = 717			50 mg n = 334	100 mg n = 546
Body as a whole							
Dizziness	19 (1%)	7 (1%)	12 (2%)	6 (1%)	23 (4%)	1 (<1%)	3 (1%)
Etc.							
Cardiovascular							
Postural Hypotension	15 (1%)	10 (1%)	5 (1%)	2 (<1%)	7 (1%)	6 (2%)	12 (2%)
Etc.							
Gastrointestinal							
Constipation							

1271

1272

Table 2.7.4.4

## Incidence of Adverse Events in Individual Studies

## Reported incidence by Treatment Groups

Body System / Adverse Event	Study 95-0403			Study 96-0011		Study 97-0007		Study 98-0102s
	Drug x 60 mg bid N =104	Drug x 30 mg bid N =102	Placebo N = 100	Drug x 60 mg bid N = 500	Placebo N=495	Drug x 60 mg bid N=200	Drug y 100 mg qd N=200	Drug x 60 mg bid N=800
Body as a whole								
Dizziness	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
Etc.	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
Cardiovascular								
Postural Hypotension								
Etc.								
Gastrointestinal								
Constipation								

**Table 2.7.4.5  
Patient Withdrawals<sup>5</sup> by Study: Controlled Trials  
Cutoff Date:**

Studies		Total Withdrawal				Reason for Withdrawal			Number without post-withdrawal efficacy data	
		Total	Male/ Female	Age > 65	Race (identify groupings) ///	Adverse Events N (%)	Lack of Efficacy N (%)	Other N (%)	N	(%)
Study XXX	Drug X Placebo	<i>N (%)</i>	<i>N (%) / N (%)</i>	<i>N (%)</i>	<i>N (%) / N (%) / N (%)</i>					
Study AAA	Drug X Comparator A									
Study BBB	Drug X Comparator B									
Study	Drug X									

<sup>5</sup> Withdrawals are all subjects who were enrolled but did not complete the planned course of treatment (includes subjects who discontinued treatment or changed to a different treatment prematurely and/or were lost to follow-up)

---

CCC	Comparator C								
<b>All Trials</b>									

1273 Note: withdrawal data can be subdivided by dose level, if that appears to be useful.

1274

1275

<b>Table 2.7.4.6</b> <b>Listing of Deaths</b> <b>Treatment: Test Product</b> <b>Cutoff Date:</b>											
<b>Trial / Source<sup>1</sup></b>	<b>Center</b>	<b>Patient ID</b>	<b>Age (yrs)</b>	<b>Sex</b>	<b>Dose (mg)</b>	<b>Duration of exposure (Days)</b>	<b>Diagnosis</b>	<b>Cause of Death</b>	<b>Other medications</b>	<b>Other medical conditions</b>	<b>Location of narrative description</b>

1276 <sup>1</sup>PM = deaths from postmarketing experience

1277 This listing should include all deaths meeting the inclusion rule, whether arising from a clinical trial or from any secondary source, e.g.,  
 1278 postmarketing experience. In electronic applications, a link to the narrative or other documentation regarding the event should be provided.

1279 A footnote should describe the rule for including deaths in the table, e.g., all deaths that occurred during a period of drug exposure or within a  
 1280 period of up to 30 days following discontinuation from drug and also those occurring later but resulting from adverse events that had an onset  
 1281 during exposure or during the 30 day follow up period. Other rules may be equally appropriate.

1282 Similar lists should be provided for patients exposed to placebo and active control drugs.

1283

**MODULE 5 : CLINICAL STUDY REPORTS****1284 Preamble**

1285 Through the ICH process, a guideline has been published on the structure and content of  
 1286 clinical study reports (E3). This document provides guidance on the organisation of these  
 1287 study reports, other clinical data, and references within a Common Technical Document  
 1288 (CTD) for registration of a pharmaceutical product for human use. These elements should  
 1289 facilitate the preparation and review of a marketing application.

1290 This guideline is not intended to indicate what studies are required for successful registration.  
 1291 It indicates an appropriate organization for the clinical study reports that are in the  
 1292 application.

**1293 Detailed Organisation of Clinical Study Reports and Related Information in Module 5.**

1294 This guideline recommends a specific organization for the placement of clinical study reports  
 1295 and related information to simplify preparation and review of dossiers and to ensure  
 1296 completeness. The placement of a report should be determined by the primary objective of the  
 1297 study. Each study report should appear in only one section. Where there are multiple  
 1298 objectives, the study should be cross-referenced in the various sections. An explanation such  
 1299 as “not applicable” or “no study conducted” should be provided when no report or  
 1300 information is available for a section or subsection.

**1301 5.1 Table of Contents of Module 5**

1302 A Table of Contents for study reports should be provided.

**1303 5.1 Table of Contents of Module 5****1304 5.2 Tabular Listing of All Clinical Studies****1305 5.3 Clinical Study Reports****1306 5.3.1 Reports of Biopharmaceutic Studies**

1307 5.3.1.1 Bioavailability (BA) Study Reports

1308 5.3.1.2 Comparative BA and Bioequivalence (BE) Study Reports

1309 5.3.1.3 *In vitro-In vivo* Correlation Study Reports

1310 5.3.1.4 Reports of Bioanalytical and Analytical Methods for Human  
 1311 Studies

**1312 5.3.2 Reports of Studies Pertinent to Pharmacokinetics using  
 1313 Human Biomaterials**

1314 5.3.2.1 Plasma Protein Binding Study Reports

1315 5.3.2.2 Reports of Hepatic Metabolism and Drug Interaction Studies

1316 5.3.2.3 Reports of Studies Using Other Human Biomaterials

**1317 5.3.3 Reports of Human Pharmacokinetic (PK) Studies**

1318 5.3.3.1 Healthy Subject PK and Initial Tolerability Study Reports

1319 5.3.3.2 Patient PK and Initial Tolerability Study Reports

1320 5.3.3.3 Intrinsic Factor PK Study Reports

1321 5.3.3.4 Extrinsic Factor PK Study Reports

1322	5.3.3.5	Population PK Study Reports
1323	<b>5.3.4</b>	<b>Reports of Human Pharmacodynamic (PD) Studies</b>
1324	5.3.4.1	Healthy Subject PD and PK/PD Study Reports
1325	5.3.4.2	Patient PD and PK/PD Study Reports
1326	<b>5.3.5</b>	<b>Reports of Efficacy and Safety Studies</b>
1327	5.3.5.1	Study Reports of Controlled Clinical Studies Pertinent to the
1328		Claimed Indication
1329	5.3.5.2	Study Reports of Uncontrolled Clinical Studies
1330	5.3.5.3	Reports of Analyses of Data from More Than One Study
1331	5.3.5.4	Other Clinical Study Reports
1332	<b>5.3.6</b>	<b>Reports of Post-Marketing Experience</b>
1333	<b>5.3.7</b>	<b>Case Report Forms and Individual Patient Listings</b>
1334	<b>5.4</b>	<b>Literature References</b>

1335 **5.2 Tabular Listing of All Clinical Studies**

1336 A tabular listing of all clinical studies and related information should be provided. For each  
1337 study, this tabular listing should generally include the type of information identified in Table  
1338 5.1 of this guideline. Other information can be included in this table if the applicant  
1339 considers it useful. The sequence in which the studies are listed should follow the sequence  
1340 described in Section 5.3 below. Use of a different sequence should be noted and explained in  
1341 an introduction to the tabular listing

1342 **5.3 Clinical Study Reports**

1343 **5.3.1 Reports of Biopharmaceutic Studies**

1344 BA studies evaluate the rate and extent of release of the active substance from the medicinal  
1345 product. Comparative BA or BE studies may use PK, PD, clinical, or *in vitro* dissolution  
1346 endpoints, and may be either single dose or multiple dose. When the primary purpose of a  
1347 study is to assess the PK of a drug, but also includes BA information, the study report should  
1348 be submitted in Section 5.3.1, and referenced in Sections 5.3.1.1 and/or 5.3.1.2.

1349 **5.3.1.1 Bioavailability (BA) Study Reports**

1350 BA studies in this section should include

- 1351 • studies comparing the release and systemic availability of a drug substance from a solid  
1352 oral dosage form to the systemic availability of the drug substance given intravenously or  
1353 as an oral liquid dosage form
- 1354 • dosage form proportionality studies, and
- 1355 • food-effect studies.

1356 **5.3.1.2 Comparative BA and Bioequivalence (BE) Study Reports**

1357 Studies in this section compare the rate and extent of release of the drug substance from  
1358 similar drug products (e.g., tablet to tablet, tablet to capsule). Comparative BA or BE studies  
1359 may include comparisons between

- 1360 • the drug product used in clinical studies supporting effectiveness and the to-be-marketed  
1361 drug product,
- 1362 • the drug product used in clinical studies supporting effectiveness and the drug product  
1363 used in stability batches, and
- 1364 • similar drug products from different manufacturers.

### 1365 **5.3.1.3 In Vitro – In Vivo Correlation Study Reports**

1366 *In vitro* dissolution studies that provide BA information, including studies used in seeking to  
1367 correlate *in vitro* data with *in vivo* correlations, should be placed in Section 5.3.1.3. Reports  
1368 of *in vitro* dissolution tests used for batch quality control and/or batch release should be  
1369 placed in the Quality section of the CTD.

### 1370 **5.3.1.4 Reports of Bioanalytical and Analytical Methods for Human Studies**

1371 Bioanalytical and/or analytical methods for biopharmaceutical studies or *in vitro* dissolution  
1372 studies should ordinarily be provided in individual study reports. Where a method is used in  
1373 multiple studies, the method and its validation should be included once in Section 5.3.1.4 and  
1374 referenced in the appropriate individual study reports.

### 1375 **5.3.2 Reports of Studies Pertinent to Pharmacokinetics Using Human Biomaterials**

1376 Human biomaterials is a term used to refer to proteins, cells, tissues and related materials  
1377 derived from human sources that are used *in vitro* or ex vivo to assess PK properties of drug  
1378 substances. Examples include cultured human colonic cells that are used to assess  
1379 permeability through biological membranes and transport processes, and human albumin that  
1380 is used to assess plasma protein binding. Of particular importance is the use of human  
1381 biomaterials such as hepatocytes and/or hepatic microsomes to study metabolic pathways and  
1382 to assess drug-drug interactions with these pathways. Studies using biomaterials to address  
1383 other properties (e.g., sterility or pharmacodynamics) should not be placed in the Clinical  
1384 Study Reports Section, but in the Nonclinical Study Section (Module 4).

#### 1385 **5.3.2.1 Plasma Protein Binding Study Reports**

1386 Ex vivo protein binding study reports should be provided here. Protein binding data from PK  
1387 blood and/or plasma studies should be provided in Section 5.3.3.

#### 1388 **5.3.2.2 Reports of Hepatic Metabolism and Drug Interaction Studies**

1389 Reports of hepatic metabolism and metabolic drug interaction studies with hepatic tissue  
1390 should be placed here.

#### 1391 **5.3.2.3 Reports of Studies Using Other Human Biomaterials**

1392 Reports of studies with other biomaterials should be placed in this section.

### 1393 **5.3.3 Reports of Human Pharmacokinetic (PK) Studies**

1394 Assessment of the PK of a drug in healthy subjects and/or patients is considered critical to  
1395 designing dosing strategies and titration steps, to anticipating the effects of concomitant drug  
1396 use, and to interpreting observed pharmacodynamic differences. These assessments should  
1397 provide a description of the body's handling of a drug over time, focusing on maximum  
1398 plasma concentrations (peak exposure), area-under-curve (total exposure), clearance, and  
1399 accumulation of the parent drug and its metabolite(s), in particular those that have  
1400 pharmacological activity.

1401 The PK studies whose reports should be included in Sections 5.3.3.1 and 5.3.3.2 are generally  
1402 designed to (1) measure plasma drug and metabolite concentrations over time, (2) measure  
1403 drug and metabolite concentrations in urine or faeces when useful or necessary, and/or (3)  
1404 measure drug and metabolite binding to protein or red blood cells.

1405 On occasion, PK studies may include measurement of drug distribution into other body  
1406 tissues, body organs, or fluids (e.g., synovial fluid or cerebrospinal fluid), and the results of  
1407 these tissue distribution studies should be included in Section 5.3.3.1 to 5.3.3.2, as  
1408 appropriate. These studies should characterise the drug's PK and provide information about  
1409 the absorption, distribution, metabolism, and excretion of a drug and any active metabolites in  
1410 healthy subjects and/or patients. Studies of mass balance and changes in PK related to dose  
1411 (e.g., determination of dose proportionality) or time (e.g., due to enzyme induction or  
1412 formation of antibodies) are of particular interest and should be included in Sections 5.3.3.1  
1413 and/or 5.3.3.2. Apart from describing mean PK in normal and patient volunteers, PK studies  
1414 should also describe the range of individual variability. In the ICH E5 guideline on Ethnic  
1415 Factors in the Acceptance of Foreign Data, factors that may result in different responses to a  
1416 drug in different populations are categorised as intrinsic ethnic factors or extrinsic ethnic  
1417 factors. In this document, these categories are referred to as intrinsic factors and extrinsic  
1418 factors, respectively. Additional studies can also assess differences in systemic exposure as a  
1419 result of changes in PK due to intrinsic (e.g., age, gender, racial, weight, height, disease,  
1420 genetic polymorphism, and organ dysfunction) and extrinsic (e.g., drug-drug interactions,  
1421 diet, smoking, and alcohol use) factors. Reports of PK studies examining the influence of  
1422 intrinsic and extrinsic factors on exposure should be organised in Sections 5.3.3.3 and 5.3.3.4,  
1423 respectively.

1424 In addition to standard multiple-sample PK studies, population PK analyses based on sparse  
1425 sampling during clinical studies can also address questions about the contributions of intrinsic  
1426 and extrinsic factors to the variability in the dose-PK-response relationship. Because the  
1427 methods used in population PK studies are substantially different from those used in standard  
1428 PK studies, these studies should be placed in Section 5.3.3.5.

#### 1429 **5.3.3.1 Healthy Subject PK and Initial Tolerability Study Reports**

1430 Reports of PK and initial tolerability studies in healthy subjects should be placed in this  
1431 section.

#### 1432 **5.3.3.2 Patient PK and Initial Tolerability Study Reports**

1433 Reports of PK and initial tolerability studies in patients should be placed in this section.

#### 1434 **5.3.3.3 Intrinsic Factor PK Study Reports**

1435 Reports of PK studies to assess effects of intrinsic factors, should be placed in this section.

#### 1436 **5.3.3.4 Extrinsic Factor PK Study Reports**

1437 Reports of PK studies to assess effects of extrinsic factors, should be placed in this section.

#### 1438 **5.3.3.5 Population PK Study Reports**

1439 Reports of population PK studies based on sparse samples obtained in clinical trials including  
1440 efficacy and safety trials, should be placed in this section.

1441

1442 **5.3.4 Reports of Human Pharmacodynamic (PD) Studies**

1443 Reports of studies with a primary objective of determining the PD effects of a drug product in  
1444 humans should be placed in this section. Reports of studies whose primary objective is to  
1445 establish efficacy or to accumulate safety data, however, should be placed in Section 5.3.5.

1446 This section should include reports of 1) studies of pharmacologic properties known or  
1447 thought to be related to the desired clinical effects (biomarkers), 2) short-term studies of the  
1448 main clinical effect, and 3) PD studies of other properties not related to the desired clinical  
1449 effect. Because a quantitative relationship of these pharmacological effects to dose and/or  
1450 plasma drug and metabolite concentrations is usually of interest, PD information is frequently  
1451 collected in dose response studies or together with drug concentration information in PK  
1452 studies (concentration-response or PK/PD studies). Relationships between PK and PD effects  
1453 that are not obtained in well-controlled studies are often evaluated using an appropriate model  
1454 and used as a basis for designing further dose-response studies or, in some cases, for  
1455 interpreting effects of concentration differences in population subsets.

1456 Dose-finding, PD and/or PK-PD studies can be conducted in healthy subjects and/or patients,  
1457 and can also be incorporated into the studies that evaluate safety and efficacy in a clinical  
1458 indication. Reports of dose-finding, PD and/or PK/PD studies conducted in healthy subjects  
1459 should be placed in Section 5.3.4.1, and the reports for those studies conducted in patients  
1460 should be placed in Section 5.3.4.2.

1461 In some cases, the short-term PD, dose-finding, and/or PK-PD information found in  
1462 pharmacodynamic studies conducted in patients will provide data that contribute to  
1463 assessment of efficacy, either because they show an effect on an acceptable surrogate marker  
1464 (e.g., blood pressure) or on a clinical benefit endpoint (e.g., pain relief). Similarly, a PD  
1465 study may contain important clinical safety information. When these studies are part of the  
1466 efficacy or safety demonstration, they are considered clinical efficacy and safety studies that  
1467 should be included in Section 5.3.5, not in Section 5.3.4.

1468 **5.3.4.1 Healthy Subject PD and PK/PD Study Reports**

1469 PD and/or PK/PD studies having non-therapeutic objectives in healthy subjects should be  
1470 placed in this section

1471 **5.3.4.2 Patient PD and PK/PD Study Reports**

1472 PD and/or PK/PD studies in patients should be submitted in this section.

1473 **5.3.5 Reports of Efficacy and Safety Studies**

1474 This section should include reports of all clinical studies of efficacy and/or safety carried out  
1475 with the drug, conducted by the sponsor, or otherwise available, including all completed and  
1476 all ongoing studies of the drug in proposed and non-proposed indications. The study reports  
1477 should provide the level of detail appropriate to the study and its role in the application. ICH  
1478 E3 describes the contents of a full report for a study contributing evidence pertinent to both  
1479 safety and efficacy. Abbreviated reports can be provided for some studies (see ICH E3 and  
1480 individual guidance by region).

1481 Within Section 5.3.5, studies should be organised by design (controlled, uncontrolled) and,  
1482 within controlled studies, by type of control. Within each section, studies should be  
1483 categorized further, ordered by whether the study report is complete or abbreviated (ICH E3),  
1484 with completely reported studies presented first. Published reports with limited or no further  
1485 data available to the sponsor should be placed last in this section.

1486 In cases where the application includes multiple therapeutic indications, the reports should be  
1487 organized in a separate Section 5.3.5 for each indication. In such cases, if a clinical efficacy  
1488 study is relevant to only one of the indications included in the application, it should be  
1489 included in the appropriate Section 5.3.5; if a clinical efficacy study is relevant to multiple  
1490 indications, the study report should be included in the most appropriate Section 5.3.5 and  
1491 referenced as necessary in other Sections 5.3.5, e.g., Section 5.3.5A, Section 5.3.5B.

1492 **5.3.5.1 Study Reports of Controlled Clinical Studies Pertinent to the Claimed**  
1493 **Indication**

1494 The controlled clinical study reports should be sequenced by type of control:

- 1495 • Placebo control (could include other control groups, such as an active comparator or other  
1496 doses)
- 1497 • No-treatment control
- 1498 • Dose-response (without placebo)
- 1499 • Active control (without placebo)
- 1500 • External (Historical) control, regardless of the control treatment

1501 Within each control type, where relevant to assessment of drug effect, studies should be  
1502 organized by treatment duration. Studies of indications other than the one proposed in the  
1503 application, but that provide support for efficacy in the proposed use, should be included in  
1504 Section 5.3.5.1.

1505 Where a pharmacodynamic study contributes to evidence of efficacy, it should be included in  
1506 Section 5.3.5.1. The sequence in which studies were conducted is not considered pertinent to  
1507 their presentation. Thus, placebo-controlled trials, whether early or late, should be placed in  
1508 Section 5.3.5.1. Controlled safety studies, including studies in conditions that are not the  
1509 subject of the application, should also be reported in Section 5.3.5.1.

1510 **5.3.5.2 Study Reports of Uncontrolled Clinical Studies**

1511 Study reports of uncontrolled clinical studies (e.g., reports of open label safety studies) should  
1512 be included in Section 5.3.5.2. This includes studies in conditions that are not the subject of  
1513 the marketing application.

1514 **5.3.5.3 Reports of Analyses of Data from More than One Study**

1515 Many clinical issues in an application can be addressed by an analysis considering data from  
1516 more than one study. The results of such an analysis should generally be summarized in the  
1517 clinical summary documents, but a detailed description and presentation of the results of such  
1518 analyses are considered critical to their interpretation. Where the details of the analysis are  
1519 too extensive to be reported in a summary document, they should be presented in a separate  
1520 report. Such reports should be placed in Section 5.3.5.3. Examples of reports that would be  
1521 found in this section include: a report of a formal meta-analysis or extensive exploratory  
1522 analysis of efficacy to determine an overall estimate of effect size in all patients and/or in  
1523 specific subpopulations, and a report of an integrated analysis of safety that assesses such  
1524 factors as the adequacy of the safety database, estimates of event rates, and safety with respect  
1525 to variables such as dose, demographics, and concomitant medications. A report of a detailed  
1526 analysis of bridging, considering formal bridging studies, other relevant clinical studies, and  
1527 other appropriate information (e.g., PK and PD information), should be placed in this section  
1528 if the analysis is too lengthy for inclusion in the Clinical Summary.

1529 **5.3.5.4 Other Study Reports**

1530 This section can include:

- 1531 – Reports of interim analyses of studies pertinent to the claimed indications
- 1532 – Reports of controlled safety studies not reported elsewhere
- 1533 – Reports of controlled or uncontrolled studies not related to the claimed indication
- 1534 – Published reports of clinical experiences with the medicinal product that are not included  
1535 in Section 5.3.5.1. However, when literature is important to the demonstration or  
1536 substantiation of efficacy, it should be included in Section 5.3.5.1
- 1537 – Reports of ongoing studies

1538 **5.3.6 Reports of Post-Marketing Experience**

1539 For products that are currently marketed, reports that summarize marketing experience  
1540 (including all significant safety observations) should be included in Section 5.3.6.

1541 **5.3.7 Case Report Forms and Individual Patient Listings**

1542 Case report forms and individual patient data listings that are described as appendices 16.3  
1543 and 16.4 in the ICH clinical study report guideline, should be placed in this section when  
1544 submitted, in the same order as the clinical study reports and indexed by study.

1545 **5.4 Literature References**

1546 Copies of referenced documents, including important published articles, official meeting  
1547 minutes, or other regulatory guidance or advice should be provided here. This includes  
1548 copies of all references cited in the Clinical Overview, and copies of important references  
1549 cited in the Clinical Summary or in the individual technical reports that were provided in  
1550 Module 5, section 5.3. Only one copy of each reference should be provided. Copies of  
1551 references that are not included here should be immediately available on request.



Table 5.1 Listing of Clinical Studies

Type of Study	Study Identifier	Location of Study Report	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
BA	001	Vol 3, Sec. 1.1, p. 183	Absolute BA IV vs Tablet	Cross-over	Tablet, 50mg single dose, oral, 10 mg IV	20	Healthy Subjects	Single dose	Complete; Abbreviated
BE	002	Vol 4, Sec. 1.2, p. 254	Compare clinical study and to-be-marketed formulation	Cross-over	Two tablet formulations, 50 mg, oral	32	Healthy Subjects	Single dose	Complete; Abbreviated
PK	1010	Vol 6, Sec. 3.3, p. 29	Define PK	Cross-over	Tablet, 50mg single dose, oral	50	Renal Insufficiency	Single dose	Complete; Full
PD	020	Vol 6, Sec. 4.2, p. 147	Bridging study between regions	Randomised placebo-controlled	Tablet, 50mg, multiple dose, oral, every 8 hrs	24 (12 drug, 12 placebo)	Patients with primary hypertension	2 weeks	Ongoing; Interim

Efficacy	035	Vol 10, Sec. 5.1, p. 1286	Long term; Efficacy & Safety;  Population PK analysis	Randomised active- controlled	Tablet, 50mg, oral, every 8 hrs	300 (152 test drug, 148 active control)	Patients with primary hypertension	48 weeks	Complete; Full
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