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REQUIREMENTS FOR PHARMACEUTICALS FOR HUMAN USE

ICH HARMONISED GUIDELINE

**BIOEQUIVALENCE FOR IMMEDIATE-
RELEASE SOLID ORAL DOSAGE FORMS
M13A**

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M13A

ICH Consensus Guideline

TABLE OF CONTENTS

1	INTRODUCTION	1
1.1	Objective.....	1
1.2	Background.....	1
	1.2.1 <i>Bioequivalence</i>	1
	1.2.2 <i>Data Integrity</i>	2
1.3	Scope	2
2	GENERAL PRINCIPLES IN ESTABLISHING BIOEQUIVALENCE	3
2.1	Study Design for Pharmacokinetic Endpoint Bioequivalence Studies.....	3
	2.1.1 <i>Study Population</i>	3
	2.1.2 <i>Study Design</i>	4
	2.1.3 <i>Sample Size for Bioequivalence Studies</i>	4
	2.1.4 <i>Comparator and Test Products</i>	5
	2.1.5 <i>Fasting and Fed Study Conditions</i>	5
	2.1.6 <i>Dose or Strength to be Studied</i>	8
	2.1.7 <i>Moieties to be Measured</i>	9
	2.1.7.1 <i>Parent versus Metabolite</i>	9
	2.1.7.2 <i>Enantiomers versus Racemates</i>	10
	2.1.8 <i>Sampling</i>	10
	2.1.8.1 <i>First Point C_{max}</i>	11
	2.1.8.2 <i>Long Half-life Drugs and Truncated AUC Considerations</i>	11
	2.1.8.3 <i>Early Exposure</i>	11
2.2	Data Analysis for Non-Replicate Study Design	12
	2.2.1 <i>Considerations for the Bioequivalence Analysis Population</i>	12
	2.2.1.1 <i>Removal of Data Due to Low Exposure</i>	12
	2.2.2 <i>Presentation of Data</i>	13

2.2.2.1	<i>Concentration Time Data</i>	13
2.2.2.2	<i>Pharmacokinetic Analysis</i>	13
2.2.2.3	<i>Potency Differences in Lots</i>	14
2.2.3	<i>Statistical Analysis</i>	14
2.2.3.1	<i>General Considerations</i>	14
2.2.3.2	<i>Crossover Design Studies</i>	15
2.2.3.3	<i>Carry-over</i>	15
2.2.3.4	<i>Parallel Design Studies</i>	16
2.2.3.5	<i>Multi-Group Design Studies</i>	16
2.2.4	<i>Bioequivalence Criteria</i>	17
2.2.5	<i>Multiple Comparator and Multiple Test Product Studies</i>	17
2.2.5.1	<i>Multiple Comparator Products</i>	17
2.2.5.2	<i>Multiple Test Products</i>	17
3	SPECIFIC TOPICS	18
3.1	Endogenous Compounds	18
3.2	Other Immediate-Release Dosage Forms	19
3.2.1	<i>Orally Disintegrating Tablets</i>	19
3.2.2	<i>Chewable Tablets</i>	20
3.2.3	<i>Oral Suspensions</i>	20
3.3	Fixed Dose Combination.....	20
3.4	pH-Dependency	21
4	DOCUMENTATION	22
5	GLOSSARY	23

1 **1 INTRODUCTION**

2 **1.1 Objective**

3 This guideline is intended to provide recommendations on conducting bioequivalence (BE) studies
4 during both development and post approval phases for orally administered immediate-release (IR)
5 solid oral dosage forms designed to deliver drugs to the systemic circulation, such as tablets,
6 capsules, and granules/powders for oral suspension.

7 Deviations from the recommendations in this guideline may be acceptable if appropriate scientific
8 justification is provided. Applicants are encouraged to consult the regulatory authority(ies) when
9 an alternate approach is proposed or taken.

10 **1.2 Background**

11 **1.2.1 Bioequivalence**

12 BE for IR solid oral dosage forms with systemic action is largely established via clinical
13 pharmacokinetic (PK) BE studies or comparative *in vitro* dissolution studies. In addition to the
14 oral dosage forms stated above, the PK principles of this guideline are generally applicable to non-
15 orally administered drug products with immediate action in which reliance on systemic exposure
16 measures is suitable for establishing BE, e.g., certain rectal, inhalation, and nasal drug products.

17 BE assessment for these oral dosage forms is important for establishing therapeutic equivalence
18 for generic drug products to their respective comparator products. In addition, there may be
19 situations in new (innovator) drug development when demonstration of BE may be critical for
20 approval decisions. Furthermore, BE studies are used by innovator and generic product developers
21 for supporting post-approval formulation and/or manufacturing process changes.

22 Two drug products containing the same drug substance(s) are considered bioequivalent if their
23 relative bioavailability (BA) (rate and extent of drug absorption) after administration in the same
24 molar dose lies within acceptable predefined limits. These limits are set to ensure comparable *in*
25 *vivo* performance, i.e., similarity in terms of safety and efficacy.

26 The Biopharmaceutics Classification System (BCS)-based biowaiver may be used to waive *in vivo*
27 BE studies for certain orally administered IR solid oral dosage forms as delineated in ICH M9,

28 *Biopharmaceutics Classification System-Based Biowaivers.*

29 **1.2.2 Data Integrity**

30 BE studies should be conducted according to the principles and recommendations in ICH E6, *Good*
31 *Clinical Practice*. In conducting BE studies, sponsors, study investigators, and service providers,
32 e.g., contract research organisations or laboratories, should ensure that the data generated are
33 attributable, legible, contemporaneously documented, original (or a certified copy),
34 accurate, complete, and traceable. The ultimate responsibility for the quality and integrity of the
35 study data submitted to a regulatory authority lies with the applicant.

36 **1.3 Scope**

37 M13A is the first guideline in the series to describe the scientific and technical aspects of study
38 design and data analysis to support BE assessment for orally administered IR solid oral dosage
39 forms. How regulatory decisions may be made based on BE assessment is out of the scope of this
40 guideline.

41 Acceptance of comparator products across regulatory jurisdictions could reduce the burden of
42 multiple clinical trials demonstrating BE against local comparator products. However, in many
43 regions this is governed by local laws rather than scientific guidelines. Therefore, the acceptance
44 of comparator products across regions is not in the scope of M13A. However, study designs
45 containing multiple comparator products or test products are included in M13A to take some initial
46 steps to reduce the associated burden without prejudice to regional legal requirements.

47 The second guideline in the series, M13B, will describe biowaiver considerations for additional
48 strengths not investigated in BE studies.

49 The third guideline in the series, M13C, will include data analysis and BE assessment for 1) highly
50 variable drugs, 2) drugs with narrow therapeutic index, and 3) complex BE study design and data
51 analysis considerations, e.g., adaptive BE study design.

52 These guidelines do not cover PK study design or data analysis to support BA assessment for new
53 drug development in support of intended use or dosing recommendations in drug labelling, e.g.,
54 relative BA assessment, food effect, drug-drug interactions, special population studies, bridging

55 formulations without the necessity to demonstrate BE, and studies to support changes in dosing
56 regimens or routes of administration. In such cases, study design and decision criteria may be
57 based on the objective of the study and availability of other information including exposure-
58 response and proposed labelling.

59 **2 GENERAL PRINCIPLES IN ESTABLISHING BIOEQUIVALENCE**

60 **2.1 Study Design for Pharmacokinetic Endpoint Bioequivalence Studies**

61 **2.1.1 Study Population**

62 The subject population for BE studies should be selected with the aim of permitting detection of
63 differences in the *in vivo* release characteristics between pharmaceutical products. In order to
64 reduce variability not related to differences between products, the studies should normally be
65 performed in healthy subjects unless the drug carries safety concerns that make this approach
66 unethical. Conducting BE studies in healthy subjects is regarded as adequate in most instances to
67 detect formulation differences and to allow extrapolation of the results to populations for which
68 the product is intended.

69 The subject inclusion and exclusion criteria should be clearly stated in the study protocol. Subjects
70 should be at least 18 years of age and preferably have a Body Mass Index between 18.5 and 30.0
71 kg/m². If a drug product is intended for use in both sexes, it is recommended the study include
72 male and female subjects.

73 Subjects should be screened for suitability by means of clinical laboratory tests, a medical history,
74 and a physical examination. Depending on the drug's therapeutic class and safety profile, special
75 medical investigations and precautions may have to be carried out before, during, and after the
76 completion of the BE study. The risk to women of childbearing potential should be considered,
77 and the investigators should ensure that female subjects are not pregnant or lactating during the
78 BE study and the follow-up. Subjects should preferably be non-nicotine users and without a history
79 of alcohol or drug abuse. Phenotyping and/or genotyping of subjects may be considered for safety
80 or PK reasons.

81 If the investigated active substance is known to have adverse effects and the pharmacological
82 effects or risks are considered unacceptable for healthy subjects, the study may instead be

83 conducted in a targeted patient population under suitable precautions and supervision.

84 **2.1.2 Study Design**

85 A randomised, single-dose, two-period, two-sequence crossover study design is recommended
86 when comparing two formulations, as single-dose studies provide the most sensitive conditions to
87 detect differences in the rate and extent of absorption. Treatment periods should be separated by a
88 sufficiently long washout period, e.g., at least 5 elimination half-lives. In general, the highest to-
89 be-marketed strength should be used in a BE study. If the highest strength of a product cannot be
90 administered to healthy subjects for safety and/or tolerability reasons, a single-dose study
91 conducted in healthy subjects using a lower strength may be possible (see Section 2.1.6) or
92 alternatively, if feasible given the drug product under investigation, a single-dose study conducted
93 in patients using the highest proposed strength could be considered.

94 A multiple-dose study may be conducted in patients if a single-dose study cannot be conducted in
95 either healthy subjects for safety and/or tolerability reasons or in patients for ethical reasons. For
96 a multiple-dose study, the study protocol should include an appropriate number of dosage
97 administrations to reach steady-state, which could be justified using an appropriate sampling
98 scheme, i.e., concentrations at the end of the dosing interval should be sampled sequentially until
99 C_{tau} is stable. The washout of the last dose of the first treatment period can overlap with the
100 accumulation of the second treatment. The accumulation period should be sufficiently long to
101 reach the new steady-state after switching and allow the elimination of the drug from the previous
102 treatment, e.g., at least 5 elimination half-lives.

103 For drugs with long elimination half-lives, a parallel design may be employed when a crossover
104 design is impractical due to the need for a prolonged washout period. In this situation, special care
105 should be taken to ensure similar subject demographics in each of the treatment groups.

106 Alternative study designs are acceptable, if scientifically justified.

107 **2.1.3 Sample Size for Bioequivalence Studies**

108 The number of subjects to be included in the BE study should be based on an appropriate sample
109 size calculation to achieve a pre-specified power and pre-specified type 1 error. A sufficient
110 number of subjects should be enrolled in the BE study to account for possible dropouts and/or

111 withdrawals. The use of “spare” subjects is not acceptable. Additional cohort(s) of subjects may
112 be added to the study, e.g., if the number of evaluable subjects falls below the calculated sample
113 size; however, this should be specified in the study protocol and done prior to any bioanalysis. The
114 number of evaluable subjects in a pivotal BE study should not be less than 12 for a crossover
115 design or 12 per treatment group for a parallel design.

116 **2.1.4 Comparator and Test Products**

117 A comparator product is the drug product accepted by regulatory agencies that an applicant can
118 use to compare against the test product in conducting a BE study.

119 The selection of the batch of the comparator product used in the BE study should be based on assay
120 content. It is advisable to investigate more than one batch of the comparator product when selecting
121 the batch of comparator product for use in the BE study.

122 The test product used in the BE study should be representative of the product to be marketed and
123 this should be discussed and justified by the applicant.

124 For pivotal BE studies, the test product used should meet the following criteria:

- 125 a) The production of batches used should provide a high level of assurance that the product
126 and process will be feasible on a commercial scale. The test product should usually
127 originate from a batch of at least 1/10 of production scale or 100,000 units, whichever is
128 greater, unless otherwise justified. In case of a production batch smaller than 100,000 units,
129 a full production batch is required.
- 130 b) Unless otherwise justified, the assayed content of the batch used as test product should not
131 differ by more than 5% from that of the batch used as comparator product, as determined
132 with the test procedure proposed for routine quality testing of the test product.

133 **2.1.5 Fasting and Fed Study Conditions**

134 BE studies should be conducted under standardised conditions that minimise variability to better
135 detect potential PK differences between drug products. For IR solid oral dosage forms, single-dose
136 BE studies conducted under fasting conditions typically provide greater discrimination between
137 the PK profiles of two products. Therefore, for the majority of these drug products, BE may be
138 demonstrated in a single study conducted under fasting conditions.

139 However, food can have a differential, formulation-dependent impact on the absorption of drug
140 substances from drug products that are of high risk (see “High-risk products” section below),
141 which would preclude the extrapolation of BE under fasting conditions to fed conditions. In such
142 cases, BE under fed conditions also needs to be demonstrated.

143 The design of a BE study with regard to the use of fasting and/or fed conditions depends on the
144 dosing instructions of the comparator product as well as the properties of the drug substance and
145 product formulation. A rationale should be provided for the selection of the type of BE study(ies)
146 (fasting or fed or both) and meal type, e.g., fat and calorie content, based on the understanding of
147 the comparator product and the test product (high or non-high risk) as described below. The
148 rationale can be supported by modelling, e.g., appropriately validated/qualified physiologically-
149 based pharmacokinetic (PBPK) modelling or semi-mechanistic absorption models.

150 In addition, safety-related aspects need to be considered when selecting the appropriate condition
151 for a BE study regarding food intake. If safety concerns make it unethical to administer a single
152 dose of the drug product under either fed or fasted conditions, the BE study should be conducted
153 under the condition with less safety concerns.

154 For non-high-risk products, the following is recommended:

- 155 • For a product that is labelled to be taken only under fasting conditions or can be taken
156 under fasting or fed conditions i.e., without regard to food, a single BE study conducted
157 under fasting conditions is recommended to demonstrate bioequivalence.
- 158 • For a product that is labelled to be taken only with food due to PK reasons, e.g.,
159 enhancing absorption or reducing variability, a single BE study conducted under fed
160 conditions is recommended to demonstrate bioequivalence.
- 161 • For a product that is labelled to be taken only with food due to tolerability reasons, e.g.,
162 stomach irritation, a single BE study conducted under either fasting or fed conditions is
163 acceptable.

164 High-risk products:

165 High-risk products are those where the complexity of the formulation design or manufacturing
166 process leads to an increased likelihood that *in vivo* performance will be impacted differently by

167 varying gastrointestinal (GI) conditions between the fasted and fed states. For these products,
168 performance differences related to differences in formulation and/or manufacturing process may
169 not be detected with a single BE study, i.e., results from a fasting BE study may not be extrapolated
170 to predict fed BE study outcome or vice versa, thus both fasting and fed BE studies should be
171 conducted. For example, some drug products containing low solubility drug substances (as defined
172 by the BCS low solubility criterion described in ICH M9) have complex formulation and/or
173 manufacturing methods (such as solid dispersions, microemulsions, lipid-based formulations,
174 nanotechnologies, or other specialised technologies) to ensure sufficient solubility of the drug
175 substance and dissolution of the drug products or to manage the impact of food. For these high-
176 risk products, BE studies should be conducted under both fasting and fed conditions, irrespective
177 of the product labelling with regard to food intake, except when safety concerns make it unethical
178 to administer a single dose of the drug product under either fed or fasted conditions. Then the BE
179 study should be conducted under the condition with less safety concerns.

180 Especially for low solubility drug substances, the comparator product may be the result of an
181 extensive formulation and/or manufacturing process development program, obtaining for instance
182 a specific formulation without a food effect. If the test product uses a substantially different
183 manufacturing technology or particle size control method from the comparator, or if substantially
184 different excipients are used in the test and comparator that are likely to impact dissolution,
185 solubility, or permeability, this may warrant the need for BE studies under fasting and fed
186 conditions.

187 The above principles with regard to fasting and fed study conditions also apply when BE studies
188 are deemed necessary to bridge formulation and/or manufacturing process changes during pre- or
189 post-marketing phases.

190 Standardisation with regard to meals and water:

191 For studies conducted under fasting conditions, subjects should be fasted for at least 10 hours
192 before drug administration. Subjects should be allowed water as desired, except for 1 hour before
193 and 1 hour after drug administration. The dose should be administered with a standardised volume
194 of water, in the range of 150 to 250 millilitres (ml). No food should be allowed for at least 4 hours
195 post-dose on each day of drug administration and meals taken should be standardised with respect

196 to composition and timing.

197 In the case of studies conducted under fed conditions, the same controls should be employed with
198 the exception that a pre-dose meal should be provided. For a fed BE study, it is recommended that
199 subjects start the meal 30 minutes before administration of the drug product and consume the meal
200 within 30 minutes.

201 If BE studies are conducted under both fasting and fed conditions, i.e., for high-risk products, the
202 BE study conducted under fed conditions should be conducted using a meal that has the potential
203 to cause the greatest effect on GI physiology. The meal should be a high-fat (approximately 50%
204 of total caloric content of the meal) and high-calorie (approximately 800 to 1000 kcal) meal, which
205 should derive approximately 150, 250, and 500-600 kcal from protein, carbohydrate, and fat,
206 respectively. It is recognised that there may be situations where it is appropriate to administer a
207 pre-dose meal with a different caloric/fat content from these recommendations, e.g., for studies
208 performed in patient populations who cannot tolerate the recommended meal composition.

209 If, however, only one BE study conducted under fed conditions is needed for a non-high-risk
210 product, either a high-fat, high-calorie meal or a low-fat, low-calorie meal, e.g., a meal of
211 approximately 500 kcal with approximately 25% of calories from fat, may be administered. If the
212 type of meal to be consumed at the time of drug product administration is clearly specified in the
213 comparator product labelling, then this meal should be employed in the BE study.

214 The composition of the meal to be administered should be described with regard to protein,
215 carbohydrate, and fat content (specified in grams, kcal, and relative caloric content (%)) in the
216 study protocol.

217 In all situations, subjects should abstain from foods and drinks that may interact with circulatory,
218 GI transporter, GI enzymatic, hepatic, or renal function, e.g., alcoholic or caffeinated drinks, or
219 certain fruit juices such as grapefruit juice, during a suitable period before and during the study.

220 **2.1.6 Dose or Strength to be Studied**

221 In case of an application with multiple strengths, the strength to be used in the BE study depends
222 on the dose proportionality in PK and solubility of the analyte. Generally, the highest to-be-
223 marketed strength can be administered as a single unit. Selection of a lower strength may also be

224 accepted if the highest strength cannot be administered to healthy subjects for safety and/or
225 tolerability reasons and dose proportional PK, i.e., area under the concentration vs time curve
226 (AUC) and C_{\max} , has been documented over the range of strengths. If warranted to achieve
227 sufficient bioanalytical sensitivity, multiple units of the highest strength can be administered,
228 provided the total single-dose remains within the labelled dose range and the total dose is safe for
229 administration to the study subjects.

230 For non-proportional increases in AUC and/or C_{\max} with increased dose there may be a difference
231 between different strengths in the sensitivity to detect potential differences between formulations.
232 To assess dose proportionality, the applicant should consider all available data regarding dose
233 proportionality. Assessment of dose proportionality should consider single-dose studies only.

234 For drugs with a more than proportional increase in AUC and/or C_{\max} with increasing dose over
235 the therapeutic dose range, the BE study should in general be conducted at the highest strength.

236 For drugs with a less than proportional increase in AUC and/or C_{\max} with increasing dose over the
237 therapeutic dose range, BE should be established at the lowest strength if this situation is due to
238 saturation of absorption. If the less than proportional increase in AUC and/or C_{\max} with increasing
239 dose is due to limited drug solubility, BE studies should be conducted at both the lowest and highest
240 strengths. If the reason for non-dose proportionality is unknown, BE studies should generally be
241 conducted at both the lowest and highest strengths.

242 **2.1.7 Moieties to be Measured**

243 **2.1.7.1 Parent versus Metabolite**

244 Demonstration of BE should be based on the analysis of the parent drug because the concentration-
245 time profile of the parent drug is usually considered more sensitive to detect a difference between
246 formulations than metabolite data. This also applies to prodrugs. However, some prodrugs are
247 rapidly eliminated resulting in difficulties in demonstrating BE based on parent drug data, because
248 the parent drug levels are too low to allow reliable bioanalytical measurement. In this situation, it
249 is acceptable to demonstrate BE based on a primary metabolite, i.e., a first-step metabolite of the
250 parent drug, without measurement of the parent compound.

251 In rare cases, demonstration of BE based on the parent drug alone may not be sufficient and the

252 primary active metabolite should also be considered, e.g., drugs that have metabolites formed
253 through gut wall or gut lumen metabolism that contribute to efficacy or safety. This is intended to
254 address situations in which the formation of the metabolite could be influenced by formulation
255 differences, which may not be detectable when measuring systemic levels of the parent drug.

256 **2.1.7.2 Enantiomers versus Racemates**

257 The use of an achiral bioanalytical assay to measure the racemate is generally acceptable.
258 However, a stereoselective assay measuring individual enantiomers in BE studies should be
259 employed when it is known that all of the following conditions have been met:

- 260 a) the enantiomers exhibit different pharmacodynamic properties,
- 261 b) the enantiomers exhibit different PK properties, and
- 262 c) the exposure (AUC) ratio of enantiomers is modified by a difference in the rate of
263 absorption.

264 It is sufficient to demonstrate BE for only the active enantiomer in cases where one enantiomer is
265 inactive (or makes a low contribution) with respect to both safety and efficacy.

266 **2.1.8 Sampling**

267 The sampling schedule in a BE study should cover the concentration-time curve, including a pre-
268 dose sample, samples in the absorption phase, frequent samples around the expected T_{max} , and
269 sufficient samples after T_{max} to ensure a reliable estimate of the extent of exposure, which is
270 achieved when $AUC_{(0-t)}$ covers at least 80% of $AUC_{(0-inf)}$. This period is usually at least three times
271 the terminal half-life of the drug, unless a suitable truncated AUC, e.g., $AUC_{(0-72h)}$, is used. To
272 permit calculation of the relevant PK parameters, a sufficient number of samples should be
273 collected per subject per period, distributed across all phases of disposition.

274 The exact times at which the samples are taken should be recorded to obtain the elapsed time
275 relative to drug administration and sampling should be spaced such that C_{max} , $AUC_{(0-t)}$, and k_{el} can
276 be estimated accurately.

277 There may be considerable inaccuracies in the estimates of k_{el} if the constant is estimated from
278 linear regression based on a small number of data points. To reduce these inaccuracies, it is
279 recommended that three or more data points in the terminal log-linear phase of the concentration-

280 time curve be used to estimate k_{el} .

281 In multiple-dose studies, the pre-dose sample should be taken immediately before dosing, i.e.,
282 within 5 minutes of dosing, and the last sample is recommended to be taken within 10 minutes of
283 the nominal time for the dosage interval to ensure an accurate determination of $AUC_{(0-\tau_{SS})}$.

284 **2.1.8.1 First Point C_{max}**

285 The sampling schedule should include frequent sampling around the anticipated T_{max} to provide a
286 reliable estimate of C_{max} . In particular, the occurrence of C_{max} at the first post-dose sampling time
287 point should be avoided by careful consideration of the known pharmacokinetic properties of the
288 drug and selection of a suitable early sampling schedule. Datasets where C_{max} occurs at the first
289 post-dose sampling time may result in exclusion of the data from affected subjects from the
290 analysis.

291 **2.1.8.2 Long Half-life Drugs and Truncated AUC Considerations**

292 Truncating AUC for orally administered IR drug products known to exhibit longer elimination
293 half-lives, i.e., 24 hours or longer, mitigates the clinical challenge of prolonged sampling and
294 follow-up. For such products, $AUC_{(0-72h)}$ may be used in place of $AUC_{(0-t)}$ for comparison of the
295 extent of absorption. Seventy-two hours is considered to be adequate to ensure completion of GI
296 transit of the drug product and absorption of the drug substance.

297 **2.1.8.3 Early Exposure**

298 For orally administered IR drug products, BE can generally be demonstrated by measurement of
299 rate and extent of absorption, i.e., C_{max} and $AUC_{(0-t)}$. However, in some situations, C_{max} and
300 $AUC_{(0-t)}$ may be insufficient to adequately assess the BE between two products, e.g., when the
301 early onset of action is clinically relevant. In these cases, an additional PK parameter, such as area
302 under the concentration vs. time curve between two specific time points (pAUC), may be applied.
303 This pAUC is typically evaluated from the time of drug administration until a predetermined time-
304 point that is related to a clinically relevant pharmacodynamic measure. Samples should be spaced
305 such that the pAUC can be estimated accurately.

306 **2.2 Data Analysis for Non-Replicate Study Design**

307 **2.2.1 Considerations for the Bioequivalence Analysis Population**

308 It is imperative that all criteria for study subject inclusion into the BE analysis population be clearly
309 defined in the study protocol. Any exclusions from the BE analysis population should be
310 documented prior to bioanalytical analysis, e.g., subjects that are withdrawn from the study, have
311 protocol violations, or experience GI disturbances potentially affecting absorption.

312 **2.2.1.1 Removal of Data Due to Low Exposure**

313 BE studies are studies with a smaller number of subjects compared to other clinical trials. An
314 extreme value in the dataset can have a large impact on the outcome of the BE study. Although
315 statistical tests may identify extreme values in the PK variables, such data should not be removed
316 from the statistical analysis of BE studies solely on this basis. Data should only be removed from
317 the statistical analysis based on protocol violations which are contemporaneously documented. A
318 prospective plan should be included in the study protocol for removing data from the BE statistical
319 analysis.

320 An exception to the above can be made for a subject without measurable concentrations or only
321 very low concentrations following either comparator or test product administration. A subject is
322 considered to have very low concentrations if the AUC for that period is less than 5% of the
323 geometric mean AUC of the product in question, which should be calculated without inclusion of
324 data from the subject. These very low concentrations are considered the result of subject non-
325 compliance and should, as far as possible, be avoided by documenting mouth check of subjects
326 after administration of study medication to ensure the subjects have swallowed the drug product.
327 The exclusion of data for this reason will only be accepted in exceptional cases (in general with
328 no more than 1 subject in each study) and may bring the reliability of dose administration into
329 question.

330 Data from redosing studies are not considered evidence to support removal of extreme values from
331 the statistical analysis.

332 Note that all subject data should be submitted and potential extreme values flagged with
333 appropriate documentation as part of the application.

334 **2.2.2 Presentation of Data**335 **2.2.2.1 Concentration Time Data**

336 For both the test and comparator products, the drug concentration in a suitable biological fluid,
337 e.g., plasma, serum or blood, determined at each sampling time point should be tabulated for each
338 subject participating in the study, along with descriptive statistics. These data should be presented
339 on the original scale, i.e., as unadjusted, measured drug concentrations. Deviations from the
340 protocol, e.g., missed samples or samples with significant time deviation, should be clearly
341 identified. Drug concentrations in study samples should be measured in accordance with ICH M10,
342 *Bioanalytical Method Validation and Study Sample Analysis*.

343 Two concentration-time graphs (linear and log-linear) should be provided for both the test and
344 comparator products for each individual subject. In addition, two concentration-time graphs (linear
345 and log-linear) should be provided for both the test and comparator products for the mean drug
346 concentrations of all subjects. For the individual subject concentration-time graphs, the drug
347 concentrations should be plotted against time using the actual sampling times. For the mean
348 concentration-time graphs the drug concentrations should be plotted using the nominal sampling
349 times.

350 **2.2.2.2 Pharmacokinetic Analysis**

351 For single-dose studies, the following PK parameters should be tabulated for each subject-
352 formulation combination: 1) primary parameters for analysis: $AUC_{(0-t)}$, C_{max} , and, where
353 applicable, pAUC, and 2) additional parameters for analysis to assess the acceptability of the
354 bioequivalence study: $AUC_{(0-inf)}$, $AUC_{(0-t)}/AUC_{(0-inf)}$, T_{max} , k_{el} , and $t_{1/2}$. For single-dose studies,
355 $AUC_{(0-t)}$ should cover at least 80% of $AUC_{(0-inf)}$. If the $AUC_{(0-t)}/AUC_{(0-inf)}$ percentage is less than
356 80% in more than 20% of the observations, then the validity of the study may need to be discussed
357 in the submission. If the AUC is truncated at 72 hours for long half-life drugs, the primary AUC
358 parameter for analysis is $AUC_{(0-72h)}$ and the following additional parameters are not required:
359 $AUC_{(0-inf)}$, $AUC_{(0-t)}/AUC_{(0-inf)}$, k_{el} , and $t_{1/2}$.

360 Summary statistics to be reported include geometric mean, median, arithmetic mean, standard
361 deviation, coefficient of variation, number of observations, minimum, and maximum. Each

362 variable should be computed using the actual time of sampling for each concentration data point.
363 The non-compartmental methods used to derive the PK parameters from the raw data should be
364 reported, e.g., linear trapezoidal method for AUC and the number of data points of the terminal
365 log-linear phase used to estimate the terminal elimination rate constant (k_{el}).

366 For multiple-dose studies, applicants should document appropriate dosage administration and
367 sampling to demonstrate the attainment of steady-state. For steady-state studies, the following PK
368 parameters should be tabulated: 1) primary parameters for analysis: C_{maxSS} and $AUC_{(0-tauSS)}$, and 2)
369 additional parameters for analysis: C_{tauSS} , C_{minSS} , C_{avSS} , degree of fluctuation, swing, and T_{max} .

370 Any concentration reported as below the lower limit of quantification (LLOQ) should be treated
371 as zero in PK parameter calculations. Values below the LLOQ are to be omitted from the
372 calculation of K_{el} and $t_{1/2}$.

373 **2.2.2.3 Potency Differences in Lots**

374 The results from the potency assay of the test and comparator products should be submitted and
375 the test product batch should be within 5% of the comparator product batch. In exceptional cases
376 where a comparator product batch with a measured drug content within 5% of a test product batch
377 cannot be obtained, a potency correction may be accepted with supporting justification, e.g.,
378 potency data from multiple lots of comparator product, pending market availability, and
379 considering the totality of evidence. If potency correction is to be used, this intention should be
380 pre-specified in the study protocol. Analysis should be provided for both uncorrected data and for
381 potency-corrected data. If the potency correction is justifiable, the applicable BE standards should
382 be met on potency-corrected data.

383 **2.2.3 Statistical Analysis**

384 **2.2.3.1 General Considerations**

385 The statistical analyses should include all data for all subjects who provide evaluable data for the
386 products being compared. Decisions made to exclude subjects from the BE analysis population,
387 e.g., due to incomplete sampling or protocol violation, should be documented at the end of the
388 clinical blood sampling portion of the study and prior to subject sample analysis. A study will not
389 be considered acceptable if there are fewer than 12 evaluable subjects for a crossover analysis or

390 for each treatment arm for a parallel analysis.

391 The assessment of BE is based on 90% confidence intervals for the geometric mean ratios
392 (test/comparator) for the primary PK parameters under consideration. This method is equivalent
393 to two one-sided t-tests with the null hypotheses of bioinequivalence at the 5% significance level.
394 The data should be transformed prior to analysis using a logarithmic transformation.

395 The model to be used for the analysis should be pre-specified in the study protocol. The statistical
396 analysis should take into account sources of variation that can be reasonably assumed to have an
397 effect on the response variable.

398 The report on the data analysis should be sufficiently detailed to enable the PK and the statistical
399 analyses to be repeated, e.g., data on actual time of blood sampling after dose, drug concentrations,
400 the values of the PK parameters for each subject in each period, and the randomisation scheme
401 should be provided.

402 *2.2.3.2 Crossover Design Studies*

403 Conventional two-treatment, two-period, two-sequence randomised crossover design studies
404 should be analysed using an appropriate parametric method, e.g., ANOVA. The tables resulting
405 from such analyses including the appropriate statistical tests of all effects in the model should be
406 submitted, e.g., a summary of the testing of Sequence, Subject within Sequence, Period, and
407 Formulation effects should be presented. In general, the primary analyses should include all data
408 for all subjects who provide evaluable data for both the test and comparator products.

409 *2.2.3.3 Carry-over*

410 A test for carry-over is not considered relevant and no decisions regarding the analysis, e.g.,
411 analysis of the first period only, should be made on the basis of such a test. In crossover studies,
412 the potential for carry-over can be directly addressed by examination of the pre-treatment plasma
413 concentrations in period 2 and beyond if applicable, e.g., period 3 in a 3-period study.

414 If there are subjects for whom the pre-dose concentration is greater than 5% of the C_{\max} value for
415 the subject in that period, then the pivotal statistical analysis should be performed excluding the
416 data from that subject.

417 **2.2.3.4 Parallel Design Studies**

418 The statistical analysis for parallel design studies should reflect independent samples.
419 Demographic characteristics or other relevant covariates known to affect the PK should be
420 balanced across groups, to the extent possible. The use of stratification in the randomisation
421 procedure based on a limited number of known relevant factors is therefore recommended. Those
422 factors are also recommended to be accounted for in the pre-defined primary statistical analysis.
423 Post hoc and data-driven adjustments are not acceptable for the primary statistical analysis.

424 **2.2.3.5 Multi-Group Design Studies**

425 Sample size requirements and/or study logistics may necessitate studies to be conducted with
426 groups of subjects. The BE study should be designed to minimise the group effect in the study.
427 The combination of multiple factors may complicate the designation of group.

428 BE should be determined based on the overall treatment effect in the whole study population. In
429 general, the assessment of BE in the whole study population should be done without including the
430 Group by Treatment interaction term in the model, but applicants may also use other pre-specified
431 models, as appropriate. However, the appropriateness of the statistical model should be evaluated
432 to account for the multi-group nature of the BE study. Applicants should evaluate potential for
433 heterogeneity of treatment effect across groups, i.e., Group by Treatment interaction. If the Group
434 by Treatment interaction is significant, this should be reported and the root cause of the Group by
435 Treatment interaction should be investigated to the extent possible. Substantial differences in the
436 treatment effect for PK parameters across groups should be evaluated. Further analysis and
437 interpretation may be warranted in case heterogeneity across groups is observed.

438 In multicentre BE studies, when there are very few subjects in some sites, these subjects may be
439 pooled into one group for consideration in the statistical analysis. Rules for pooling subjects into
440 one group should be pre-specified and a sensitivity analysis is recommended.

441 Statistical methods and models should be fully pre-specified. Data-driven post hoc analysis is
442 highly discouraged but could be considered only in very rare cases where a very robust scientific
443 justification is provided.

444 2.2.4 Bioequivalence Criteria

445 For the majority of drug products, the PK parameters to demonstrate BE include C_{\max} and $AUC_{(0-t)}$.

446 For drugs with a long elimination half-life, $AUC_{(0-72h)}$ may be used in place of $AUC_{(0-t)}$ (see Section
447 2.1.8.2). For drugs where it is clinically relevant to assess the early exposure or early onset of
448 action, an additional PK parameter, pAUC, may be used to establish BE (see Section 2.1.8.3).

449 The 90% confidence interval for the geometric mean ratio of these PK parameters used to establish
450 BE should lie within a range of 80.00 - 125.00%.

451 2.2.5 Multiple Comparator and Multiple Test Product Studies**452 2.2.5.1 Multiple Comparator Products**

453 It may be necessary to demonstrate BE between a test product and multiple comparator products
454 to meet requirements from multiple jurisdictions. In such case, including comparator products
455 from different regions in one trial is acceptable to streamline the BE demonstration by conducting
456 one single higher-order crossover BE study with multiple comparator products.

457 Although there are multiple comparator products tested, multiplicity correction, i.e., alpha
458 adjustment, is not needed because comparator products are considered independent and region-
459 specific. Decisions will be made independently about a test product relative to a single comparator
460 product within a single jurisdiction. It is preferred for the statistical analysis to only test two at a
461 time and not all at once, making pairwise comparison within the analysis.

462 It is possible that the results meet the BE acceptance criteria with one region-specific comparator
463 product but not meet BE acceptance criteria with the other region-specific comparator product. In
464 such case, BE is demonstrated with one comparator product and not demonstrated with the other
465 comparator product. The protocol should specify the main objectives of the study and which
466 comparisons are to be performed.

467 Complete study results from all comparisons performed should be included in the clinical study
468 report.

469 2.2.5.2 Multiple Test Products

470 It may be necessary to demonstrate BE between multiple test products and the comparator product,

471 e.g., in order to include different test formulations that may be required due to drug development
472 needs. To streamline the demonstration of BE, it is permitted to conduct one single crossover BE
473 study with multiple test products.

474 The need to apply multiplicity correction in pivotal trials depends on the underlying objectives of
475 the trial:

476 a) If the objective is to achieve BE for all test formulations versus the comparator product,
477 then no alpha adjustment is needed.

478 b) If the objective is to show BE for any of the test formulations, then multiplicity
479 adjustment may be needed.

480 The objective of the trial and method for multiplicity correction should be pre-specified in the
481 study protocol.

482 **3 SPECIFIC TOPICS**

483 **3.1 Endogenous Compounds**

484 As endogenous compounds are identical to the drug that is being administered it can be challenging
485 to determine the amount of drug released from the dosage form and absorbed for BE assessment.
486 Therefore, in most cases, it is important to measure the baseline endogenous concentrations in
487 biological matrices, e.g., blood, plasma, or urine, and subtract these concentrations from the total
488 concentrations measured from each subject after the drug product is administered.

489 When the endogenous concentrations are influenced by diet, restricting or standardising the dietary
490 intake of the substance before and during the study should be considered.

491 The exact method for baseline correction should be pre-specified and justified in the study
492 protocol. Multiple baseline endogenous concentrations should be measured from each subject in
493 the time period before administration of the study drug. The time-averaged baseline or time-
494 matched baseline concentrations are subtracted from post-dose concentrations for those subjects
495 in an appropriate manner consistent with the PK properties of the drug. For the time-averaged
496 method, either the mean or median value may be used.

497 Baseline concentrations should be determined for each period and baseline correction should be
498 period specific. It should be ensured that the washout period is of an adequate duration because
499 carry-over effects cannot be readily detected. If a baseline correction results in a negative
500 concentration value, the value should be set equal to zero.

501 PK and statistical analyses should be performed on both baseline uncorrected and baseline
502 corrected data. In general, determination of BE should be based on the baseline corrected data.

503 Alternatively, the need for baseline correction may be avoided by enrolling study subjects with
504 low or no production of the endogenous compounds.

505 **3.2 Other Immediate-Release Dosage Forms**

506 **3.2.1 Orally Disintegrating Tablets**

507 Orally Disintegrating Tablets (ODTs) should be administered in BE studies according to the
508 comparator product labelling with regard to intake of water.

509 If the comparator product labelling states that the ODT can be taken with or without water, the test
510 and comparator products should be administered in the BE study without water, as this is
511 considered to be the more discriminating scenario. BE of the test and comparator ODT products
512 taken with water can then be inferred.

513 For new intended label use/instructions, e.g., ODT as an extension to another orally administered
514 IR drug product, BE studies may be conducted to determine whether the ODT is BE to the
515 comparator product. In this scenario, the ODT product should be administered according to its
516 intended labelling and compared with the comparator product administered as per its labelling.

517 If the new intended label use/instructions states that the ODT can be taken with or without water,
518 a 3-arm BE study is recommended to determine BE of the ODT administered with and without
519 water compared to the comparator product administered as per its labelling.

520 In studies evaluating ODTs without water, it is recommended to wet the mouth by swallowing a
521 small amount of water, e.g., 20 ml, directly before applying the ODT on the tongue. It is
522 recommended not to allow fluid intake earlier than 1 hour after administration.

523 Other oral formulations such as orodispersible films, buccal tablets or films, and sublingual tablets
524 may be handled in a similar way to that described above for ODTs.

525 **3.2.2 Chewable Tablets**

526 Chewable tablets should be administered in BE studies according to the comparator product
527 labelling with regard to intake of water.

528 If the comparator product labelling states that the chewable tablets can be taken with or without
529 water, the test and comparator products should be administered in the BE study without water, as
530 this is considered to be the more discriminating scenario. BE of the test and comparator chewable
531 tablet products taken with water can then be inferred.

532 For new intended label use/instructions, e.g., chewable tablets as an extension to another orally
533 administered IR drug product, BE studies may be conducted to determine whether the chewable
534 tablet is BE to the comparator product. In this scenario, the chewable tablet product should be
535 administered according to its intended labelling and compared with the comparator product
536 administered as per its labelling.

537 If the new intended label use/instructions state that the chewable tablets can be taken with or
538 without water, a 3-arm BE study is recommended to determine BE of the chewable tablets
539 administered with and without water compared to the comparator product administered as per its
540 labelling.

541 **3.2.3 Oral Suspensions**

542 For tablets, granules, and powders labelled as being only intended to be dispersed in a liquid before
543 administration as an oral suspension, BE studies should be conducted according to the comparator
544 product labelling.

545 For new intended label use/instructions (not included in the comparator product labelling), the test
546 product should be administered according to its intended labelling and compared with the
547 comparator product administered as per its labelling.

548 **3.3 Fixed Dose Combination**

549 The BE study design for fixed-dose combination products should follow the principles described

550 in this guideline. BE should be determined using a PK sampling scheme suitable for the
551 determination of the PK parameters of the individual components (drugs) and employing
552 bioanalytical methods validated for the determination of the individual drugs in the presence of
553 the other component(s) in the combination product. PK parameters to be assessed and reported are
554 those that would normally be required for each drug if it were in the formulation as a single entity.
555 BE should be demonstrated for all components (drugs) in the fixed-dose combination product
556 according to the principles described in this guideline. Failure to demonstrate BE for one
557 component of the fixed-dose combination results in failure to demonstrate BE for the proposed
558 fixed-dose combination product as a whole.

559 **3.4 pH-Dependency**

560 The absorption of drug substances with pH-dependent solubility may be influenced by the gastric
561 pH. This impact on drug absorption can be altered due to the use of, for instance, pH stabilising
562 excipients or a specific salt-form in the formulation. Moreover, the formulation of the final
563 marketed comparator product may be the result of an extensive formulation development program,
564 obtaining for instance a specific formulation without an effect on drug absorption due to gastric
565 pH differences. This is especially relevant in cases where it is foreseen that the product will be
566 taken with acid reducing drug products, e.g., proton pump inhibitors, or is going to be used in
567 certain populations, e.g., patients with achlorhydria. Therefore when, relative to the comparator
568 product, there are qualitative or quantitative differences in the pH stabilising excipient(s),
569 significant differences in manufacturing process, or differences in salt form that possess a different
570 pH dependent solubility, BE under normal fasting conditions between the two products may not
571 ensure BE of the two products in a gastric pH-altered situation, e.g., in the presence of a pH-
572 modifying drug product. In such a situation, an additional BE study with concomitant treatment of
573 a pH-modifying drug product would generally be necessary to demonstrate BE.

574 Applicants may provide a scientific justification to demonstrate that a BE study in a gastric pH-
575 altered situation may not be needed. Such a justification should be based on the totality of evidence
576 referring to the pH-solubility profile of the drug substance, impact of excipients, formulation and
577 manufacturing design, e.g., formulation designed to overcome pH effects, extent of the differences
578 between the test and comparator products, and comparative dissolution testing at multiple pHs.
579 Modelling, e.g., appropriately validated/qualified PBPK modelling or semi-mechanistic

580 absorption models, and virtual BE simulation may be used to further assess the risk of
581 bioequivalence.

582 **4 DOCUMENTATION**

583 The report of the BE study should include the complete documentation of its protocol, conduct,
584 and evaluation. It should be written in accordance with ICH E3, *Structure and Content of Clinical*
585 *Study Reports*.

586 Names and affiliations of the responsible investigator(s), the site of the study, and the period of its
587 execution should be stated.

588 Listing of inspection history for BE studies conducted at the relevant clinical and bioanalytical
589 site(s) for the 5 years preceding completion of the study should also be provided in the study report
590 (but may alternatively be provided elsewhere in the Common Technical Document (CTD)).

591 Comparator product name, strength, pharmaceutical form, batch number, manufacturer, expiration
592 date, and country of purchase should be stated.

593 Certificates of analysis, or equivalent documents, of comparator and test batches used in the study
594 should be included in an appendix to the study report.

595 The identity of the of the test product(s) used in the study should be provided, i.e., pharmaceutical
596 form, strength, batch number, and measured content (% of label claim). The batch size,
597 manufacturing date (and, if available, the expiry date) as well as the qualitative and quantitative
598 composition of the test product should also be indicated (but may alternatively be provided
599 elsewhere in the CTD).

600 Concentrations and PK data and statistical analyses should be presented in the level of detail
601 described in this guideline (see Section 2.2). The reporting format should include tabular and
602 graphical presentations showing individual and mean results and summary statistics.

603 Information on bioanalytical method validation and study sample analysis according to ICH M10
604 should be included in the appropriate section of Module 5 of the CTD.

605 The data generated should be properly documented and available for audit and inspection.
606 Essential documents should be archived in accordance with ICH E6 and applicable regulatory
607 requirements.

608 Data in a suitable electronic format should be submitted to enable the PK and the statistical
609 analyses to be repeated, e.g., data on actual times of blood sampling, drug concentrations, the
610 values of the PK parameters for each subject in each period, and the randomisation scheme.

611 Module 2.7.1 of the CTD should list all relevant BE studies conducted regardless of the study
612 outcome. Full study reports should be provided for the BE study(ies) upon which the applicant
613 relies for approval. For all other studies, synopses of the study reports (in accordance with ICH
614 E3) are sufficient. However, complete study reports for these studies should be available upon
615 request.

616 **5 GLOSSARY**

617 **Applicant:**

618 The entity submitting the application for marketing authorisation to the relevant regulatory
619 authority.

620 **AUC:**

621 Area under the concentration vs. time curve

622 **AUC_(0-inf):**

623 Area under the concentration vs. time curve extrapolated to infinity

624 **AUC_(0-t):**

625 Area under the concentration vs. time curve from time zero to the time of last quantifiable
626 concentration

627 **AUC_(0-tau_{SS}):**

628 Area under the concentration vs. time curve for one dosing interval at steady state

629 **AUC_(0-72h):**

630 Area under the concentration vs. time curve from time 0 to 72 hours

631 **Batch (or Lot):**

632 A specific quantity of material produced in a process or series of processes so that it is expected to
633 be homogeneous within specified limits. In the case of continuous production, a batch may
634 correspond to a defined fraction of the production. The batch size can be defined either by a fixed
635 quantity or by the amount produced in a fixed time interval.

636 **Batch Number (or Lot Number):**

637 A unique combination of numbers, letters, and/or symbols that identifies a batch (or lot) and from
638 which the production and distribution history can be determined.

639 **C_{avSS}:**

640 Average concentration observed during dosing interval at steady state ($AUC_{0-\tau}/\tau$)

641 **Chewable Tablets:**

642 An oral dosage form designed to facilitate chewing and swallowing by the patient rather than
643 swallowing a whole tablet. They must be chewed or crushed before swallowing.

644 **C_{max}:**

645 Maximum concentration after dosing

646 **C_{maxSS}:**

647 Maximum concentration observed during dosing interval at steady state

648 **C_{minSS}:**

649 Minimum concentration observed during dosing interval at steady state

650 **Comparator (Product):**

651 An investigational or marketed product, i.e., active control, or placebo, used as a reference in a
652 clinical trial. In the context of this guidance, a comparator product is the drug product accepted by
653 regulatory agencies that an applicant can use to compare against the test product in conducting a
654 BE study.

655 **C_{tau}:**

656 Concentration observed at end of dosing interval

657 **C_{tauSS}:**

658 Concentration observed at end of dosing interval at steady state

659 **Enantiomers:**

660 Compounds with the same molecular formula as the drug substance, which differ in the spatial
661 arrangement of atoms within the molecule and are nonsuperimposable mirror images.

662 **Endogenous Compounds:**

663 Compounds already present in the body either because the body produces them or because they
664 are present in a normal diet.

665 **Fluctuation:**

666 $[(C_{\max SS} - C_{\min SS}) / C_{avSS}]$

667 **Immediate-Release:**

668 Allows the drug to dissolve in the GI contents, with no intention of delaying or prolonging the
669 dissolution or absorption of the drug.

670 **kcal:**

671 A unit used to describe amount of energy in relation to food or energy burned with exercise. When
672 it comes to nutrition and exercise, kilocalories (kcal) and calories equal the same amount of energy.
673 One kcal (kilocalorie) equals 1 calorie in nutrition.

674 **k_{el} :**

675 The apparent terminal elimination rate constant of the drug.

676 **Orally Disintegrating Tablet:**

677 A solid dosage form which is designed to disintegrate and dissolve rapidly on contact with saliva
678 when placed on the tongue or in the oral cavity, thus eliminating the need to chew the tablet,
679 swallow an intact tablet, or take the tablet with water.

680 **pAUC:**

681 Area under the concentration vs. time curve between two specific time points

682 **Protocol:**

683 A document that describes the objective(s), design, methodology, statistical considerations, and
684 organisation of a trial. The protocol usually also gives the background and rationale for the trial,
685 but these could be provided in other protocol referenced documents. Throughout ICH E6, *Good*
686 *Clinical Practice*, the term protocol refers to protocol and protocol amendments.

687 **Racemate:**

688 A composite (solid, liquid, gaseous, or in solution) of equimolar quantities of two enantiomeric
689 species. It is devoid of optical activity.

690 **Spare Subject:**

691 A study subject that is included in the drug administration and sample collection regimens of a
692 study but, as per study protocol, whose data will only be included in the PK and statistical analysis
693 if the number of evaluable study subjects drops below a pre-specified number due to subject
694 dropouts and/or withdrawals (use of spare subjects is not acceptable).

695 **Sponsor:**

696 An individual, company, institution, or organisation which takes responsibility for the initiation,
697 management, and/or financing of a clinical trial.

698 **Swing:**

699 $[(C_{\max SS} - C_{\min SS}) / C_{\min SS}]$

700 **Tau:**

701 Dosing Interval

702 **T_{max}:**

703 Time to maximum observed concentration

704 **t_{1/2}:**

705 Half-life