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3 COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE (CHMP)

4 **Guideline on the pharmacokinetic and clinical evaluation**  
5 **of modified release dosage forms**  
6 **(EMA/CPMP/EWP/280/96 Corr1)**  
7 **Draft XXIII**

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9 This guideline replaces Guideline on Modified Release Oral and Transdermal Dosage Forms Section II  
10 (Pharmacokinetic and Clinical Evaluation (EMA/CPMP/EWP/280/96 Corr\*))  
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Comments should be provided using this [template](#). The completed comments form should be sent to [PKWPsecretariat@ema.europa.eu](mailto:PKWPsecretariat@ema.europa.eu).

<b>Keywords</b>	<b><i>Modified release, prolonged release, delayed release, transdermal drug delivery systems (TDDS), bioequivalence, pharmacokinetics, biowaiver, in vitro dissolution, generics</i></b>
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14 Guideline on the pharmacokinetic and clinical evaluation  
15 of modified release dosage forms  
16 (EMA/CPMP/EWP/280/96 Corr1)

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## 69 Executive summary

70 The primary purpose of this guideline is to define the studies necessary to investigate the efficacy,  
71 safety, biopharmaceutic and pharmacokinetic properties of modified release and transdermal dosage  
72 forms in man and to set out general principles for designing, conducting and evaluating such studies.  
73 The revision of the Note for Guidance on the Investigation of Bioavailability and Bioequivalence  
74 (EWP/QWP/1401/98) generated the necessity of consequential adjustments. Furthermore the guideline  
75 provides updated requirements for transdermal drug delivery systems (TDDS) and addresses  
76 recommendations for specific modified release formulations, e.g. for intramuscular/subcutaneous depot  
77 formulations.

## 78 1. Introduction (background)

### 79 1.1. Types of Modified release and dosage forms

80 Modified release dosage forms are formulations where the rate and/or site of release of the active  
81 ingredient(s) is different from that of the immediate release dosage form administered by the same  
82 route. This deliberate modification is achieved by special formulation design and/or manufacturing  
83 methods. Modified release dosage forms covered by this guideline include orally, intramuscularly,  
84 subcutaneously administered modified release and transdermal dosage forms.

- 85 • **Prolonged release dosage forms:** Prolonged release dosage forms are modified release  
86 dosage forms showing a slower release than that of an immediate release dosage form  
87 administered by the same route.
- 88 • **Delayed release dosage form:** The release of the active substance from such modified  
89 release dosage forms is delayed for a certain period after administration or application of the  
90 dosage. The subsequent release is similar to that of an immediate release dosage form.
- 91 • **Multiphasic release dosage forms:**
  - 92 ○ **Biphasic Release:** The first phase of drug release is determined by the immediate  
93 release dose fraction providing a therapeutic drug level shortly after administration.  
94 The second extended release phase provides the dose fraction required to maintain an  
95 effective therapeutic level for a prolonged period.
  - 96 ○ **Pulsatile Release:** Pulsatile drug release is intended to deliver a burst of drug release  
97 at specific time intervals.
- 98 • **Multiple-unit:** A multiple unit dosage form contains a plurality of units e.g. pellets or beads  
99 each containing release controlling excipients, e.g. in a gelatine capsule or compressed in a  
100 tablet
- 101 • **Single-unit:** The single-unit dosage forms consist of only one unit, e.g. osmotic tablet.
- 102 • **Intramuscular/subcutaneous Depot formulations:** A depot injection is usually a  
103 subcutaneous or intramuscular product which releases its active compound continuously over a  
104 certain period of time. Subcutaneous depot formulations include implants.
- 105 • **Transdermal drug delivery systems (TDDS):** A TDDS or transdermal patch is a flexible  
106 pharmaceutical preparation of varying size containing one or more active substance(s) to be  
107 applied on the intact skin for systemic availability.

108 There are two main types of transdermal patch systems depending on how the drug substance  
109 is dispersed in other patch components: matrix and reservoir systems. Drug release from  
110 matrix systems is based on the diffusion of soluted drug substance from the patch. Reservoir  
111 systems contain a specific liquid drug compartment and release is controlled by a membrane.

## 112 **1.2. Rationale for Development**

113 The development of a modified release formulation has to be based on a well-defined clinical need and  
114 on an integration of physiological, pharmacodynamic and pharmacokinetic considerations.

115 The dossier submitted in support of an application for a marketing authorisation must provide a  
116 complete justification of:

- 117 ➤ The physical form of the modified release device and the mechanism of the release form;
- 118 ➤ The choice of the dosage form, defining the in vitro and in vivo performance of the product;
- 119 ➤ The choice of active substance contents per unit of the dosage form;
- 120 ➤ The clinical rationale for the new dosage form, particularly in relation to the proposed  
121 indications and posology.

### 122 **1.2.1. The clinical rationale**

123 A *prolonged release dosage form* may be acceptable if the active substance can produce the desirable  
124 clinical effect with a different PK profile than that resulting from an immediate-release form. A  
125 prolonged release formulation may offer the following advantages over an immediate-release form:

- 126 • reduced fluctuations in drug plasma concentrations, which may result in more continuous  
127 effects and/or reduced incidence and/or intensity of adverse drug reactions,
- 128 • lower frequency of administration and thereby potentially improvement of patient compliance.
- 129 • non-oral route of administration (IM/SC and TDDS)

130 A *biphasic modified release form* may be considered if a rapid onset of action is required in addition to  
131 subsequent prolonged release characteristics.

132 Development of a *delayed release dosage form* may be considered to protect the active substance from  
133 the acid environment of the stomach, to protect the stomach from the active substance, or when the  
134 active substance is intended to be released in a defined segment of the intestine. Delayed release  
135 forms are generally not adequate for conditions requiring a rapid onset of action.

136 Development of a *pulsatile release dosage form* may be considered when treatment needs to be  
137 adjusted to a circadian rhythm of the underlying condition or when lower frequency of dosing is  
138 desirable, but the fluctuating plasma concentration profile of the immediate-release formulation is  
139 necessary for efficacy.

### 140 **1.2.2. Considerations for use and posology**

141 The conditions of administration of the modified release formulation and, where appropriate, its use in  
142 conjunction with an immediate release formulation should be clearly outlined in the following  
143 situations:

- 144 ➤ At the initiation of treatment;

- 145       ➤ When titration is required;
- 146       ➤ For maintenance of therapeutic effect;
- 147       ➤ In the management of acute conditions;
- 148       ➤ In special populations such as the elderly, children, and patients with renal or hepatic  
149       insufficiency. Lack of dose strengths of the modified-release form to cover all required dose  
150       levels, e.g. a lower dose for special populations, should be justified.
- 151       When appropriate, recommendations should be given for switching between immediate release and  
152       modified release formulations. If applicable, specific recommendations should be provided to ensure  
153       optimum conditions of use (e.g. instructions not to chew or crush tablets etc.).

## 154       **2. Scope**

155       This guideline is to define the studies necessary to investigate modified release drug delivery systems  
156       in man and to set out general principles for designing, conducting and evaluating respective studies.  
157       However, the precise types and number of tests to be performed have to be defined on a case-by-case  
158       basis taking into consideration the intrinsic properties of the active substance, the route of  
159       administration, the type of the delivery system and the intended therapeutic indication(s). The  
160       guideline deals with oral formulations, intramuscular depot formulations, subcutaneous implants, and  
161       transdermal dosage forms containing chemically defined drug substances.

162       Separate guidance and standards are required for each of the circumstances in which an MR  
163       formulation might be developed. These circumstances fall into three groups:

- 164       ➤ Applications for modified release forms of new chemical entities (NCE)
- 165       ➤ Application for a modified release formulation of a drug that is authorised as an immediate  
166       release formulation
- 167       ➤ Abridged applications for modified release forms referring to a marketed modified release  
168       form, e.g. applications according to Article 10(1) or 10(3)

169       For generic prolonged release or delayed release products this guideline provides requirements on  
170       bioequivalence studies that are not covered by the current guideline on the investigation of  
171       bioequivalence (CPMP/EWP/QWP/1401/98).

## 172       **3. Legal basis and relevant guidelines**

173       This guideline should be read in conjunction with the Annex I of Directive 2001/83/EC as amended, as  
174       well as European and ICH guidelines for conducting clinical trials, including those on:

- 175       –       General considerations for clinical trials (ICH E8, CPMP/ICH/291/95)
- 176       –       Guideline for good clinical practice (ICH E6 (R1), CPMP/ICH/135/95)
- 177       –       Statistical principles for clinical trials (ICH E9, CPMP/ICH/363/96)
- 178       –       Structure and content of clinical study reports (ICH E3, CPMP/ICH/137/95)
- 179       –       CHMP guidance for users of the centralised procedure for generics/hybrid applications  
180       (EMA/CHMP/225411/2006)
- 181       –       Pharmacokinetic studies in man (Eudralex, Volume 3, 3CC3a)

- 182 – Quality of oral modified release products (EMA/ 492713/2012)
- 183 – Guideline on quality of transdermal patches (EMA/CHMP/QWP/911254/2011)
- 184 – Guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98)
- 185 – Fixed combination medicinal products (CPMP/EWP/240/95)
- 186 – Note for Guideline on the investigation of drug interactions (CPMP/EWP/560/95)
- 187 – Guideline on reporting the results of population pharmacokinetic analyses
- 188 (CHMP/EWP/185990/06)
- 189 – Clinical investigation of medicinal products in the paediatric population (ICH E11,
- 190 CPMP/ICH/2711/99)
- 191 – Studies in support of special populations: geriatrics (ICH E7, CPMP/ICH/379/95) and Questions
- 192 and Answers - EMA/CHMP/ICH/604661/2009

193 The guideline should also be read in conjunction with relevant guidelines on pharmaceutical quality.  
194 The test products used in the bioequivalence study must be prepared in accordance with GMP-  
195 regulations including Eudralex volume 4.

196 Clinical trials, including bioequivalence and pharmacokinetic studies, conducted in the EU/EEA have to  
197 be carried out in accordance with Directive 2001/20/EC. Trials conducted outside of the EU and  
198 intended for use in a Marketing Authorisation Application in the EU/EEA have to be conducted to the  
199 standards set out in Annex I of the community code, Directive 2001/83/EC as amended.

## 200 **4. Applications for modified release dosage forms of new** 201 **chemical entities**

202 If a new chemical entity is developed to be administered as a modified release dosage formulation, the  
203 submitted dossier should contain the appropriate pharmaceutical and chemical data, necessary  
204 preclinical studies and a complete clinical data package as for any full application.

### 205 ***4.1. Pharmacokinetic studies required for MR formulation of a new*** 206 ***chemical entity***

207 A complete pharmacokinetic data package is required for a new chemical entity developed as MR  
208 formulation. Additional documentation specific to the MR dosage form include studies evaluating  
209 factors affecting the biopharmaceutic performance of the modified release formulation (see section  
210 5.1.4 and 5.1.5).

211 In order to avoid a duplication of studies (e.g. time and dose dependency), it is advisable to conduct  
212 PK studies with the MR formulation as early as possible during clinical development. Initial phase I  
213 studies (e.g. first in man studies) are generally conducted with an oral solution or an immediate  
214 release formulation where basic pharmacokinetic characteristics of an active substance ( $T_{max}$ ,  $V_d$ ,  $Cl$ ,  
215 elimination half life, route(s) of excretion) are obtained. Interaction studies and studies in special  
216 populations should preferably be conducted with the modified release formulation. In addition to  
217 general pharmacokinetic investigations relevant to any new formulation (e.g. single and multiple dose  
218 PK parameters, food effect when relevant and dose proportionality), the mechanism for the control of  
219 drug release should be described. This is generally done through bioequivalence/relative bioavailability  
220 studies conducted using different formulations where, for instance, the amount of a release controlling

221 excipient varies if possible. The obtained pharmacokinetic profiles in vivo are recommended to be  
222 correlated with in vitro drug release profiles if possible (see Appendix II).

#### 223 **4.1.1. Food effect studies with oral modified release forms**

224 Food interactions may be related to the drug substance itself and/or the formulation, the latter being  
225 most important in the case of modified release (MR) products.

226 The optimal experimental conditions to produce a food effect include the ingestion of a predefined high  
227 fat meal immediately before dosing (see section 5.1.4.1).

228 Food effect studies for new MR formulations are recommended to be conducted early during drug  
229 development so that appropriate recommendations regarding intake in relation to food can be included  
230 in clinical efficacy and safety studies. This is also important from safety perspective as the risk for dose  
231 dumping should be evaluated before initiation of efficacy and safety studies.

232 To evaluate the influence of food on the absorption of the drug substance from the new formulation a  
233 2-way cross over study (MR formulation fasting and fed) may be sufficient. If there is a food effect on  
234 the MR formulation additional study(ies) with an oral solution can be considered, to evaluate if the food  
235 effect is related to the formulation or to the drug substance. In this situation, a single dose 4 way  
236 crossover study; MR fed and fasted + oral solution (or immediate release (IR) formulation if a solution  
237 is not feasible) fed and fasted can be conducted.

238 In case there is a marked food-effect, additional food-interaction studies might be needed to support  
239 dosing recommendations, i.e. studies of the effect of different kinds of food, studies investigating the  
240 effect of a meal taken at certain time period before and after the drug, etc. (see Note for Guidance on  
241 the investigation of drug interactions (CPMP/EWP/560/95)).

#### 242 **4.2. Pharmacokinetic Studies required for Transdermal Drug Delivery** 243 **Systems (TDDS) of a new chemical entity**

244 If a new chemical entity is developed to be administered as a TDDS formulation, the submitted dossier  
245 should contain the appropriate pharmaceutical and chemical data and a complete non-clinical and  
246 clinical data package as for any full application.

247 Generally, the kinetics of drug delivery from TDDS' is determined by the interplay between the active  
248 substance, the formulation and the skin. Studies should be conducted to evaluate drug transport  
249 characteristics and the rate limiting step that determines systemic availability i.e. drug release and/or  
250 skin reservoir and/or other formulation related particularities. Pharmacokinetic investigations should  
251 comprise single-dose and multiple-dose investigations considering particular aspects like e.g.  
252 application site-dependent absorption, fluctuation, lag-times and concentration time profile after patch  
253 removal. Aiming to establish an IVIVC is advisable. In case of several dose strengths, dose  
254 proportionality issues should be adequately addressed.

255 In addition to conventional phase I studies skin irritation, sensitisation (see also appendix 1),  
256 phototoxicity, patch adhesion and, in general, the effect of sauna and sun cream on the patch adhesion  
257 (see also Guideline on quality of transdermal patches EMA/CHMP/QWP/911254/2011) should be  
258 investigated.

259 **4.3. Pharmacokinetic Studies required for intramuscular/subcutaneous**  
260 **Depot formulations of a new chemical entity**

261 Studies should be conducted to evaluate drug transport characteristics and the rate limiting step that  
262 determines systemic availability i.e. drug release and/or other formulation related particularities.  
263 Pharmacokinetic investigations should comprise single-dose and multiple-dose investigations  
264 considering particular aspects like e.g. application site-dependent absorption, fluctuation and lag-  
265 times. Aiming to establish an IVIVC is advisable. In case of several dose strengths, dose  
266 proportionality issues should be adequately addressed.

267 **5. Application for a modified release formulation of a**  
268 **substance that is authorised as an immediate release**  
269 **formulation**

270 Modified release forms are developed based on the rationale that there is a relationship between the  
271 pharmacological/toxicological response and the characteristics of systemic exposure to the active  
272 substance/metabolite(s). The aim of the modified release formulation is therefore, in most cases, to  
273 reach a similar total exposure (AUC) to active substance as for the immediate release formulation. This  
274 does not necessitate that the same nominal doses are given (the modified release formulation may  
275 have a different extent of absorption).

276 In general modified-release formulations are not bioequivalent to their immediate release form.  
277 Consequently PK data alone may not be sufficient for evaluating whether the benefit/risk ratio of the  
278 modified release formulation is comparable to the corresponding doses of the immediate release form.  
279 Therefore additional clinical data will generally be required.

280 Whenever the strength of the new modified release formulation differs from those approved for the  
281 immediate release product this difference and the possible resulting different dosage regime has to be  
282 highlighted very clearly in SmPC, PL and labelling as most important routine risk minimisation  
283 measures to avoid medication errors. The applicant has to prove that the benefits of the new  
284 formulation outweigh the potential risks linked with this product.

285 The new formulation should be characterised in appropriate pharmacokinetic, pharmacodynamic and  
286 clinical efficacy/safety studies. Recommendations regarding pharmacokinetic studies to characterise  
287 the formulation is given in section 5.1 and the need for therapeutic studies in section 5.2. Additional  
288 studies may in certain cases be needed, e.g. pharmacokinetic studies to characterise the metabolic  
289 profile may be required in case the modified release product is administered by a new route of  
290 administration.

291 Toxicological, pharmacological or clinical tests to define the intrinsic properties of the active substance  
292 are not required assuming a similar total systemic exposure of active substance/metabolites for the  
293 modified and immediate release formulations.

294 The marketed immediate release product of the same active substance should serve as the reference  
295 product. The final market formulation should in general be used in the pharmacokinetic and  
296 therapeutic studies, unless it can be justified that differences between the study formulation and final  
297 market formulation do not affect release characteristics and bioavailability.

298 **5.1. Pharmacokinetic studies**

299 The purpose of these studies is to characterise the modified release formulation in vivo by investigating

- 300 • the rate and extent of absorption
- 301 • fluctuations in drug concentrations at steady state
- 302 • inter-subject variability in pharmacokinetics arising from the drug formulation
- 303 • dose proportionality
- 304 • factors affecting the performance of the modified release formulation
- 305 • the risk of unexpected release characteristics (e.g. dose dumping)

306 The studies are based on concentration measurements of the active substance and/or metabolite(s) or,  
307 occasionally, in conjunction with determination of an acute pharmacodynamic effect.

308 The studies can be performed either in healthy volunteers or in patients.

309 Whenever multiple dose studies are performed it should be demonstrated that steady state has been  
310 reached. In case of no accumulation (i.e. insignificant levels at the end of the dosing interval) multiple  
311 dose studies are not required since steady state is achieved after a single dose.

### 312 **5.1.1. Rate and extent of absorption, fluctuation**

313 Rate and extent of absorption from a modified release formulation should be evaluated by comparison  
314 with an immediate release formulation following single dosing and generally also repeated dosing.

315 The pharmacokinetic parameters of interest may be for single dose studies  $AUC_{(0-t)}$ ,  $AUC_{(0-\infty)}$ , residual  
316 area,  $C_{max}$ ,  $t_{max}$  and  $t_{lag}$  and for multiple dose studies  $AUC_{(0-\tau)}$ ,  $t_{max,ss}$ ,  $C_{max,ss}$ ,  $C_{min,ss}$  and fluctuation.  
317 The pharmacokinetic parameter(s) chosen as primary for the comparison, i.e. the parameter(s)  
318 considered most likely to reflect efficacy and safety should be justified.

319 It should be demonstrated that the modified release formulation has the claimed release  
320 characteristics. This should ideally be demonstrated through deconvolution of the concentration-time  
321 data for the modified release formulation to an appropriate immediate release formulation (see  
322 Appendix II for more detail) to obtain the cumulative absorption (or in vivo release) versus time profile  
323 for the modified release formulation. Both the cumulative amount absorbed and rate of absorption  
324 versus time should be used to support the claimed release characteristics.

325 Fluctuation in drug concentrations should be studied following repeated dosing. Unless otherwise  
326 justified, the modified release product should produce similar or less fluctuations as the immediate  
327 release product.

328 In those cases where the modified release formulation is to be administered to patients already treated  
329 with an immediate release dosage form (switching), the time to achieve steady state concentration  
330 after switching should be addressed to define appropriate dosing instructions.

### 331 **Dose levels and strengths to be evaluated**

332 If the active substance and the MR formulation (see section 5.1.3) exhibit linear pharmacokinetic  
333 properties it may be sufficient to compare the modified release formulation and the immediate release  
334 formulation after single and multiple dose administration at one dose level.

335 If the active substance or the MR formulation (see section 5.1.3) exhibit non-linear pharmacokinetics  
336 (in the therapeutic plasma-concentration range) it is necessary to compare the modified release  
337 formulation and the immediate release formulation at least at the highest and the lowest dose level. If  
338 the IR and MR formulation display different extent of non-linearity additional strengths may need to be  
339 compared. This also applies if the composition of the strengths is not quantitatively proportional.

## 340 **5.1.2. Variability**

341 The inter-individual variability of the pharmacokinetic parameters of interest should be determined in  
342 the single dose or multiple dose studies described in section 5.1.1 and should be compared between  
343 the modified and immediate release formulation. The variability of the modified release formulation  
344 should preferably not exceed that of the immediate release formulation.

## 345 **5.1.3. Dose proportionality**

346 Whenever there are several strengths or when several single units can be taken simultaneously to  
347 achieve the desired dose, dose proportionality for different strengths / doses of the modified release  
348 formulations should be adequately addressed. Dose proportionality should be evaluated by means of a  
349 single dose and multiple dose study where the PK parameters of interest of all the strengths/doses are  
350 compared after dose adjustment.

## 351 **5.1.4. Factors affecting the performance of a modified drug formulation**

### 352 **5.1.4.1. Food**

353 The influence of food on the bioavailability of oral modified release formulations must be investigated.

354 The optimal experimental conditions to produce a food effect include the ingestion of a predefined  
355 high-fat high-calorie meal immediately before dosing. It is recommended that subjects should start the  
356 meal 30 minutes prior to administration of the drug product and finish this meal within 30 minutes.

357 The meal should be a high-fat (approximately 50 percent of total caloric content of the meal) and high-  
358 calorie (approximately 800 to 1000 kcal) meal. This test meal should derive approximately 150, 250,  
359 and 500-600 kcal from protein, carbohydrate, and fat, respectively. The composition of the meal  
360 should be described with regard to protein, carbohydrate and fat content (specified in grams, calories  
361 and relative caloric content (%)).

362 The design of the food effect study depends on which other studies that are conducted comparing the  
363 new oral modified release formulation with the approved immediate release formulation and if there is  
364 a clinically significant food effect on the immediate release formulation.

365 If there is no food effect on the immediate-release formulation, a 2-way cross-over study comparing  
366 the modified release formulation in fasted and fed states could be sufficient (given that other studies  
367 compare the modified release and the immediate release formulations under fasting conditions).

368 In case of a clinically significant food effect for the immediate release formulation, a 4-way cross-over  
369 study comparing the modified release formulation in fasted and fed states and the immediate release  
370 formulation in fasted and fed states could be useful to quantify the food effect on each formulation.

371 Whenever there are several strengths, the food effect can be investigated for one of the strengths only  
372 if the products are proportional in composition (e.g. multi-particulate dosage forms or proportional  
373 tablets), having the same manufacturing process, exhibit linear pharmacokinetics and their dissolution  
374 profiles are similar in a range of dissolution media. Generally, the highest strength should be tested,  
375 unless otherwise justified. In case the above conditions are not fulfilled, it is necessary to investigate  
376 the food effect at the highest and the lowest strengths or the extreme cases based on a bracketing  
377 approach.

378 For the assessment of food effect besides AUC and  $C_{max}$ , it may also be valuable to compare the  
379 modified release characteristics by verifying that the shape of the concentration – time profiles are not  
380 significantly altered.

381 The clinical relevance of the effect of food should be discussed both from an efficacy and a safety  
382 perspective. When needed, dose recommendations with respect to intake of the product in relation to  
383 meals should be given. Additional studies with other types of food or with intake of the product at  
384 certain time intervals before and after a meal may be needed to support the proposed dose  
385 recommendations (see also CPMP/EWP/560/95 Guideline on the investigation of drug interactions)

386 If the formulation or the manufacturing process is changed during drug development a new evaluation  
387 of the food effect for the final formulation may be needed.

388 Different type of administration: The labelling of certain multiple unit formulations can recommend that  
389 the product can be opened and the pellets/beads can e.g. be sprinkled on soft foods, dispersed in a  
390 glass of non-carbonated water and swallowed without chewing or administered through a gastric tube.  
391 For the labelling to indicate this additional type of administration, additional *in vitro* dissolution testing  
392 showing equivalence between the closed and the opened formulation is necessary. The absence of BE  
393 studies imitating the additional options of administration should be justified.

#### 394 **5.1.4.2. Gastro-intestinal function**

395 If an oral modified release formulation is often be co-administered with active substances affecting  
396 gastrointestinal physiology (e.g. opioids) it is necessary to investigate the performance of the oral  
397 modified release formulation during these conditions.

398 If the oral modified release formulation is intended for patients with markedly altered gastrointestinal  
399 function the modified release formulation may need to be studied also in those patients.

#### 400 **5.1.4.3. Unexpected release characteristics (e.g. dose dumping)**

401 Unintended, rapid drug release of the entire amount or a significant fraction of the active substance  
402 contained in a modified release dosage form is often referred to as "dose dumping". Depending on the  
403 therapeutic indication and the therapeutic index of an active substance, dose-dumping can pose a  
404 significant risk to patients, either due to safety issues or diminished efficacy or both.

405 For modified release formulations the risk for unexpected release resulting in unforeseen exposure  
406 should be excluded. If dose dumping is observed (e.g. much higher peak exposure with an inadequate  
407 modified release profile) or suspected (e.g. absence of levels of a labile active substance in gastro-  
408 resistant formulation for some subjects) the product should be reformulated to avoid this deficiency of  
409 the biopharmaceutical quality.

410 Much higher peak exposure might also be observed in prolonged release products due to active  
411 substance release in the stomach for an extended period of time with a subsequent absorption of the  
412 released dose once the gastric content is emptied. As this unintended increased exposure is not related  
413 to product failure, dosing recommendations should be implemented to avoid a prolonged residence in  
414 the stomach.

#### 415 **Effects of alcohol**

416 Some modified-release oral dosage forms contain active substances and/or excipients that exhibit  
417 higher solubility in ethanolic solutions compared to water. Concomitant consumption of alcoholic  
418 beverages with such products may possibly induce dose dumping.

419 For such formulations, *in vitro* studies of the release in alcohol solutions should be performed. Where  
420 accelerated active substance release is seen *in vitro* either at high or low alcohol concentrations over a  
421 short period of time or at lower alcohol concentrations over a longer period of time, the product should  
422 be reformulated. Only in those cases where it can be justified that an *in vitro* alcohol interaction cannot

423 be avoided by reformulation, could an in vivo study be accepted, in order to substantiate that such an  
424 interaction is unlikely to occur in vivo.

425 The in vivo investigation of alcohol-induced dose-dumping should compare the systemic exposure  
426 when the modified release product is ingested with a reasonable amount of alcohol on an empty  
427 stomach. The results of the study should be assessed not only with respect to the clinical relevance of  
428 the group mean change but also to the clinical consequences of the observed individual ratios.

429 If a significant dose-dumping effect is likely in vivo and cannot be avoided by reformulation, the  
430 benefit/risk of the product needs to be carefully considered. Contraindicating alcohol as only measure  
431 is generally not considered an appropriate means to address a formulation interaction with alcohol.  
432 Information on relevant interactions with alcohol, in case of possible clinically relevant potentiation or a  
433 harmful additive effect should be given in the product information.

434 In addition other label warnings and risk management strategies need to be discussed.

### 435 **5.1.5. Other points to consider**

#### 436 **5.1.5.1. Special populations**

437 Different physiological conditions (e.g. transit times, pH, food intake) in vegetarian, paediatric and  
438 elderly patients should be taken into consideration especially when designing oral once daily MR  
439 formulations.

#### 440 **5.1.5.2. Influence of site of application on plasma levels (SC/IM depot formulations, TDDS)**

441 The effect of different sites of application of SC/IM depot formulations or TDDS on the absorption of  
442 the active substance should be investigated if the application site is not limited to one body area.

443 Safety and tolerability at the site of application should be assessed.

444 In case of SC/IM depot formulations or TDDS it should be investigated that not only the plasma levels  
445 are within the therapeutic concentrations at the end of the dosing interval but also how the plasma  
446 levels decrease after removal of the depot formulation or TDDS.

#### 447 **5.1.5.3. Multiphasic modified release products**

448 Rarely a modified release preparation has been developed solely in order to mimic a TID or QID dosage  
449 schedule. In these cases the modified release preparation should be equivalent with the immediate  
450 release formulation given in the dose schedule that is imitated.

#### 451 **5.1.5.4. Prolonged residence time in the stomach**

452 Gastric emptying of single unit dosage forms that do not disintegrate in the stomach may be prolonged  
453 and highly erratic. The consequences of this effect on the enteric coating of delayed release  
454 formulations are largely unpredictable. If for an acid labile active substance release occurs prior to  
455 stomach emptying degradation of the active substance can result and non-existing concentration  
456 profiles can be obtained.

457 Furthermore the release of the active substance may be considerably delayed due to a prolonged  
458 residence in the stomach. Therefore the sampling period should be designed such that measurable  
459 concentrations are obtained, taking into consideration not only the half-life of the active substance but  
460 also the possible occurrence of this effect to make sure that influence of delayed gastric emptying is  
461 adequately characterised.

## 462 **5.2. Therapeutic studies**

463 As a principle, comparative clinical efficacy and safety data are needed in addition to PK data for  
464 modified release products developed after the immediate release formulation, unless adequately  
465 justified. As the efficacy and safety of the immediate release product is known, the major issue would  
466 be to demonstrate that the new modified release formulation is as safe and effective as the existing  
467 formulation. Additional benefits of the new formulation should be shown or justified, if claimed.

468 However, in exceptional cases, if the assessment of concentration-effect relationship indicates that  
469 there is a well-defined relationship between plasma concentration(s) of the active substance /active  
470 metabolite(s) and clinical response, clinical trials may be considered unnecessary. In this case the  
471 same or a better level of efficacy and safety has to be concluded from PK/PD studies.

472 When assessing PK/PD relationships for modified-release products, the differential effects on efficacy  
473 and safety due to differences in rate of absorption and fluctuation should be determined since it is  
474 important not only to establish concentration - effect relationships, but also to determine the  
475 significance of differences in the shape of the steady state concentrations versus time profile for a  
476 modified release product regimen as compared to the approved immediate release product regimen.  
477 Tolerance to therapeutic effects and toxic effects related to drug exposure, concentration, absorption  
478 rate and fluctuation should also be examined as part of the PK/PD assessment. Therefore, it is  
479 essential to investigate the profile shape versus PD relationships.

### 480 **5.2.1. Waiving of therapeutic studies**

481 In principle therapeutic studies are necessary.

482 However, therapeutic studies might be waived when:

- 483 • bioequivalence between the immediate release and the modified release product is shown in  
484 terms of  $C_{max}$ ,  $C_{min}$  and AUC at steady state because the modified product is developed to  
485 actually mimic the performance of an immediate release product and its dosage regimen e.g. a  
486 pulsatile multiphasic release dosage form containing pellets with different lag time.
- 487 • bioequivalence between the immediate release and the modified release product is shown in  
488 terms of  $C_{max}$ ,  $C_{min}$  and AUC at steady state despite differences in the shape of the plasma  
489 concentration-time profile if it is possible to justify that the difference in shape has no  
490 relevance for efficacy and safety based on the exposure – response and profile shape -  
491 response relationships.
- 492 • there is a well-defined therapeutic window in terms of safety and efficacy, the rate of input is  
493 known not to influence the safety and efficacy profile or the risk for tolerance development and  
494 strict bioequivalence between the immediate release and the modified release product is shown  
495 in terms of AUC at steady state and  $C_{max,ss}$  for the MR formulation is below the  $C_{max,ss}$  for the  
496 IR formulation and  $C_{min,ss}$  for the MR formulation is above the  $C_{min,ss}$  for the IR formulation.

### 497 **5.2.2. How to design clinical studies**

498 Comparative studies should be adequately designed and conducted to assess the intensity and  
499 duration of the therapeutic effect and undesirable effects of the modified release formulation in  
500 comparison with the authorised immediate release formulation. Studies should establish the clinical  
501 benefit of the new formulation relative to the authorised immediate release formulation. In addition to  
502 specific guidelines the following considerations should be taken into account:

503 In the assessment of the efficacy and safety of certain therapeutic classes it is necessary to measure  
504 the effects of the formulation throughout a 24-hour period and particularly at the end of dosage  
505 interval (e.g. assessment of breakthrough pain).

506 The different effects of medicinal products having different dose thresholds:

- 507 • Therapeutic activity is quantified with reference to the pharmacodynamic or clinical effects  
508 normally adopted as criteria for the assessment of efficacy in the concerned therapeutic class.
- 509 • In general an extrapolation cannot be made to indications other than those investigated in the  
510 trial. However, this may be possible if it is appropriately justified by the applicant.
- 511 • In cases when the prolonged therapeutic activity may alter the safety profile of drug during  
512 chronic dosing, safety studies may be required.

513 Clinical trials which compare the modified release form and the immediate release formulation on the  
514 basis of equal exposure may be planned to demonstrate non-inferiority of therapeutic efficacy or  
515 equivalence. In either situation, the design and analysis of the trials should consider the  
516 recommendations of ICH E9.

517 Whether these pharmacodynamic/clinical studies should show equivalence or non- inferiority as  
518 compared to the standard formulation depends on the direction of the effect or safety issue at stake.  
519 In case efficacy and safety are closely related equivalence studies are needed for showing that the  
520 effect studied remains within the equivalence margins. If it is acceptable to investigate only efficacy  
521 and it is not expected that formulations have different safety, a demonstration of non-inferiority might  
522 be sufficient.

523 The type of studies that are required depends on whether appropriate, pharmacodynamic endpoints  
524 can be defined, whether the relationship between the pharmacodynamic markers and clinical efficacy is  
525 known, whether assay sensitivity is guaranteed and whether a non-inferiority margin or equivalence  
526 margin can be defined.

527 Such equivalence and non-inferiority studies may include a placebo arm beside the immediate and  
528 modified release preparation. A placebo arm or an additional active arm with a lower dose is  
529 mandatory if assay sensitivity of the trial cannot be guaranteed (see ICH E10).

530 In addition, equivalence margins or non-inferiority margins have to be defined and justified  
531 irrespective whether the endpoint is based on pharmacodynamic measurement or clinical variable.

532 If for a modified release product an indication is claimed that is different from that of the immediate  
533 release formulation a clinical development plan in accordance with existing guidelines or the state of  
534 the art is required.

535 When superiority is claimed it has to be proven with clinical trials.

536 If a claim is made for fewer systemic adverse reactions for the modified release form, this has to be  
537 substantiated.

## 538 **6. Abridged application for modified release forms referring** 539 **to a marketed modified release form**

540 For orally administered products, bioequivalence studies of modified release formulations are  
541 recommended to be conducted by comparing two formulations (test versus reference) of the same  
542 pharmaceutical form. A generic MR formulation should be compared with the MR formulation that is  
543 either the originator or the line extension of an IR originator formulation, with which bioequivalence is

544 claimed. The general recommendations regarding study design, conduct, evaluation and reporting of  
545 bioequivalence studies detailed in the Guideline on Bioequivalence (CPMP/EWP/QWP1401/98) are  
546 applicable also for bioequivalence studies for modified release products. Aspects specific to MR  
547 formulations are detailed in this section.

548 If two products with the same dosage form differ in their release controlling excipients or mechanism  
549 they can be considered generics if they are bioequivalent in vivo after single dose in the fasted and fed  
550 state (see section 6.1) as well as under multiple dose conditions, if needed.

551 Studies are in general recommended to be conducted in healthy volunteers. However, if it is not  
552 possible to conduct studies in healthy volunteers for safety reasons, studies can be conducted in  
553 patients, preferably after both single and multiple dose administration in line with recommendations  
554 below. If it is not feasible to conduct single dose studies in patients, these can be replaced by multiple  
555 dose studies.

556 In general a generic is meant to be bioequivalent with the innovator under fasted and fed conditions. A  
557 difference regarding formulation related food interactions indicates product differences thus  
558 contradicting the generic by definition. Accordingly, for products where bioequivalence can be shown in  
559 the SPC recommended condition but not in the non-recommended state due to less food effect, the  
560 product does not fulfil the requirements of a generic product, but could be eligible for an Article 10(3)  
561 application.

## 562 **6.1. Prolonged release formulations for oral administration**

563 Bioequivalence between two prolonged release formulations should be evaluated on the basis of  
564 studies designed to demonstrate that:

- 565 • the test formulation exhibits the claimed prolonged release characteristics of the reference;
- 566 • the active substance is not released unexpectedly from the test formulation (no dose  
567 dumping);
- 568 • performance of the test and the reference formulation is equivalent after single dose and at  
569 steady state;
- 570 • the effect of food on the in vivo performance is comparable for both formulations when a single  
571 dose study is conducted.

572 The following studies are generally required to demonstrate bioequivalence:

- 573 ➤ a single-dose fasting study comparing test and reference drug product
- 574 ➤ a single-dose fed study using a high-fat meal (see 5.1.4.1) comparing test and reference drug  
575 product
- 576 ➤ a multiple-dose study comparing test and reference drug product.

### 577 **Single dose studies**

578 One of the following schemes is recommended for single dose evaluation in fasting and fed state:

- 579 ➤ A four-period cross-over trial with four complementary sequences of four treatment conditions.  
580 Both the test and reference products should be assessed in the fasting state as well as after  
581 the administration of a high fat meal at a specified time before taking the drug.
- 582 ➤ Two cross-over trials. The first trial should compare the test and reference products under  
583 fasting conditions. The study treatments should be administered during two periods and with  
584 two sequences of treatment conditions. The second trial should compare the test and reference

585 formulations following the administration of a high-fat meal at a specified time before taking  
586 the study treatment, as well as the test formulation under fasting conditions. The trial should  
587 be conducted with three periods and three complementary sequences of drug administrations.

588 ➤ Two cross-over trials, both with two periods and two sequences of test and reference product  
589 administration. One trial should be conducted in the fasting state. The other trial should be  
590 conducted after the administration of a high fat meal at a specified time before taking the  
591 study treatment.

## 592 **Multiple dose studies**

593 A multiple dose study is needed unless a single dose study has been performed with the highest  
594 strength which has demonstrated that the mean  $AUC_{(0-\tau)}$  after the first dose covers more than 90% of  
595 mean  $AUC_{(0-\infty)}$  for both test and reference, and consequently a low extent of accumulation is expected.  
596 In this case bioequivalence needs to be demonstrated for additional parameters representing the shape  
597 of the plasma concentration versus time curve in the single dose study (see also section 6.8.2). An  
598 early  $AUC_{(0-\tau)}$  and a terminal  $AUC_{(0-\infty)}$  separated by a predefined time point, which is usually the half  
599 of the dosage interval are recommended, unless otherwise scientifically justified.

600 In all other cases, where accumulation is likely ( $AUC_{(0-\tau)}$  after the first dose covers less than 90% of  
601 mean  $AUC_{(0-\infty)}$ ) a multiple dose study is required. Generally, steady-state studies should be performed  
602 under the conditions concerning concomitant food intake recommended in the SmPC for the originator  
603 product. If the SmPC states that the product has to be taken in fed condition only the study should be  
604 performed in fed conditions, although it only needs to be high fat high calorie content on the day of  
605 profiling. If the SmPC states that the product should be taken in fasted state or irrespective of food  
606 intake the studies should be performed in fasted conditions.

607 In steady-state studies, the washout period of the previous treatment can overlap with the build-up of  
608 the second treatment (direct switching), provided the build-up period is sufficiently long (at least 5  
609 times the terminal half-life).

610 Whether the steady-state has been achieved is assessed by comparing at least three pre-dose  
611 concentrations for each formulation. The apparent half-life should also be taken into account.

612 Note:

613 The discussion of the opportunity of using equivalence in  $C_{\tau}$  in single dose studies as basis for waiving  
614 the multiple dose study has been recognized. However, there is not considered to be sufficient  
615 scientific evidence at the moment to encourage this approach.

### 616 **6.1.1. Strength(s) to be evaluated**

#### 617 **Single unit formulations**

618 For single unit formulations with multiple strengths the following considerations apply:

##### 619 A. Single dose studies

- 620 • If the reference SmPC recommends intake in the fasting state or irrespective of food intake,
  - 621 ○ Fasting state: a single dose study under fasting conditions is required for each
  - 622 strength. However a bracketing approach (see section 6.6) is also possible if justified.
  - 623 ○ Fed state: One single dose bioequivalence study at the highest strength conducted in
  - 624 fed state may be sufficient. The other strength(s) can be waived if the criteria
  - 625 described for waiver of strength described in section 4.1.6 of the Guideline on the
  - 626 investigation of bioequivalence (CPMP/EWP/QWP/1401/98) are fulfilled. However, if

627 the strengths of the test product do not fulfil these criteria or if proportional strengths  
628 have different size/shape two strengths representing the most extreme difference  
629 should be tested in fed state.

- 630 • If the reference SmPC recommends intake under fed conditions,
  - 631 ○ Fed state: a single dose study under fed conditions is required for each strength.
  - 632 However, a bracketing approach (see section 6.6) is also possible if justified.
  - 633 ○ Fasting state: One single dose bioequivalence study at the highest strength conducted
  - 634 in fasting state may be sufficient. The other strength(s) can be waived if the criteria
  - 635 described for waiver of strength described in section 4.1.6 of the Guideline on the
  - 636 investigation of bioequivalence (CPMP/EWP/QWP/1401/98) are fulfilled. However, if
  - 637 the strengths of the test product do not fulfil these criteria or if proportional strengths
  - 638 have different size/shape two strengths representing the most extreme difference
  - 639 should be tested in fasting state.

#### 640 B. Multiple dose studies

- 641 • A multiple dose study should be performed with the highest strength (unless it is shown that
- 642 there is no accumulation as detailed in section 6.1). The other strength(s) can be waived if the
- 643 criteria for waiver of strength described in section 4.1.6 of the Guideline on the investigation
- 644 of bioequivalence (CPMP/EWP/QWP/1401/98) are fulfilled.

#### 645 **Multiple unit formulations**

646 For multiple unit formulations of a medicinal product with several strengths, it is sufficient to conduct  
647 the studies listed in section 6.1 only at one strength if the compositions of the strengths are  
648 proportional, the formulations contain identical beads or pellets (and these are produced by the same  
649 manufacturer) and the dissolution profiles are similar fulfilling the criteria of the Guideline on the  
650 investigation of bioequivalence (CPMP/EWP/QWP/1401/98). If the pharmacokinetic of the originator  
651 modified release product are linear the studies can be conducted at any strength. If the  
652 pharmacokinetic of the originator modified release product are non-linear the studies must be  
653 conducted with the most sensitive strength as described in the Guideline on the investigation of  
654 bioequivalence (CPMP/EWP/QWP/1401/98).

### 655 **6.2. Delayed release formulations**

656 The following studies are generally required to demonstrate bioequivalence:

- 657 ➤ a single-dose fasting study comparing test and reference product
- 658 ➤ a single-dose fed study using a high-fat meal (see 5.1.4.1) comparing test and reference
- 659 product

#### 660 **6.2.1. Strength(s) to be evaluated**

661 A similar approach as detailed for prolonged release forms regarding study design of single dose  
662 studies can be used (see 6.1).

#### 663 **Single unit formulations:**

- 664 • If the reference SmPC recommends intake under fasting state or irrespective of food intake,
  - 665 ○ Fasting state: a single dose study under fasting conditions is required for each
  - 666 strength. However a bracketing approach (see section 6.6) is also possible if justified.
  - 667 ○ Fed state: One single dose bioequivalence study at the highest strength conducted in
  - 668 fed state may be sufficient. The other strength(s) can be waived if the criteria
  - 669 described for waiver of strength described in section 4.1.6 of the Guideline on the

670 investigation of bioequivalence (CPMP/EWP/QWP/1401/98) are fulfilled. However, if  
671 the strengths of the test product do not fulfil these criteria or if proportional strengths  
672 have different size/shape two strengths representing the most extreme difference  
673 should be tested in fed state.

- 674 • If the reference SmPC recommends intake under fed conditions only,
  - 675 ○ Fed state: a single dose study under fed conditions is required for each strength.  
676 However a bracketing approach (see section 6.6) is also possible if justified
  - 677 ○ Fasting state: One single dose bioequivalence study at the highest strength conducted  
678 in fasting state may be sufficient. The other strength(s) can be waived if the criteria  
679 for waiver of strength described in section 4.1.6 of the Guideline on the investigation  
680 of bioequivalence (CPMP/EWP/QWP/1401/98) are fulfilled. However, if the strengths of  
681 the test product do not fulfil these criteria or if proportional strengths have different  
682 size/shape two strength representing the most extreme difference should be tested in  
683 fasting state.

684 When evaluating proportionality in composition, the proportionality of gastro-resistant coating with  
685 respect to the surface area (not to core weight) should be considered to have the same gastro-  
686 resistance (coating layer in mg/cm<sup>2</sup> surface).

#### 687 **Multiple unit formulations:**

688 For multiple unit formulations of a medicinal product with several strengths, it is sufficient to conduct  
689 the studies listed under 6.2 at one strength only, if the compositions of the strengths are proportional,  
690 the formulations contain identical beads or pellets (and these are produced by the same manufacturer)  
691 and the dissolution profiles are similar. If the pharmacokinetics of the originator delayed release  
692 product is linear the studies should be conducted at the highest strength unless otherwise justified. If  
693 the pharmacokinetic of the originator modified release product are non-linear the studies must be  
694 conducted with the most sensitive strength as described in the Guideline on the investigation of  
695 bioequivalence (CPMP/EWP/QWP/1401/98).

#### 696 **6.2.2. Prolonged residence time in the stomach**

697 Gastric emptying of single unit dosage forms that do not disintegrate in the stomach (e.g. enteric  
698 coated tablets) may be prolonged and highly erratic. The consequences of this effect on the enteric  
699 coating of delayed release formulations are largely unpredictable. If the active substance release  
700 occurs prior to stomach emptying degradation of the active substance can result and non-existing  
701 concentration profiles can be obtained. If the incidence of this outlier behaviour is observed with a  
702 comparable frequency in both, test and reference product, data of a period with non-existing profile  
703 can be excluded from statistical analysis provided that it has been pre-specified in the study protocol.  
704 In a 2-period trial this will result in the subject being removed from the analysis.

705 Furthermore the release of the active substance may be considerably delayed due to a prolonged  
706 residence in the stomach. Therefore the sampling period should be designed such that measurable  
707 concentrations are obtained, taking into consideration not only the half-life of the active substance but  
708 the possible occurrence of this effect as well.

### 709 **6.3. Multiphasic modified release products**

710 The regulatory criteria mentioned in this Guideline are also applicable in the assessment of  
711 bioequivalence for modified release products designed to achieve sequential release combining  
712 immediate and modified characteristics (e.g. biphasic-/ pulsatile-release).

713 If one of the release phases is prolonged, the type of studies required are those described in section  
714 6.1.

715 However additional pharmacokinetic parameters are needed to demonstrate bioequivalence for all  
716 phases (see section 6.8.1).

#### 717 **6.4. Intramuscular/Subcutaneous Depot Formulations**

718 The following studies are generally required:

- 719 ➤ a single-dose study comparing test and reference products
- 720 ➤ a multiple-dose study comparing test and reference products.

721 A multiple dose study is needed unless a single dose study has been performed with the highest  
722 strength which has demonstrated that:

- 723 • the mean  $AUC_{(0-t)}$  after the first dose covers more than 90% of mean  $AUC_{(0-\infty)}$  for both test and  
724 reference, and consequently a low extent of accumulation is expected

##### 725 **6.4.1. Strength to be evaluated**

726 Only one strength has to be investigated if the different strengths are proportional in composition and  
727 exhibit a similar in vitro dissolution profile. The strength should be selected based on the  
728 pharmacokinetic linearity and safety. If there are several non-proportional strengths a bracketing  
729 approach is possible.

730 If the originator product is marketed in only one concentration and the different doses are achieved by  
731 choosing the total volume to be injected any dose should be acceptable for a bioequivalence trial in  
732 case dose proportionality can be shown.

#### 733 **6.5. Transdermal Drug Delivery Systems (TDDS)**

734 A generic TDDS is defined by having the same amount of active substance released per unit time as  
735 compared to the reference TDDS. It is to note that this definition is different to the general definition of  
736 a generic since the overall amount of active substance could differ while the labelled amount of active  
737 substance released per unit time should be the same between a generic and the innovator TDDS.

738 Equivalence testing of TDDS should comprise both non-inferiority in terms of adhesion and  
739 bioequivalence. It is advisable to ensure adhesion equivalence prior to bioequivalence investigations in  
740 volunteers since inferior adhesion could invalidate the pharmacokinetic results and question the  
741 acceptability of the product. Bioequivalence of TDDS should generally be assessed after single dose as  
742 well as after multiple dose application. The study design including the site of application should be  
743 justified in terms of its sensitivity to detect formulation differences. The application site should be  
744 highly standardized and be the same for both test and reference.

745 Bioequivalence should be assessed using the same main characteristics and statistical procedures as  
746 for prolonged release formulations including fluctuation. In addition, evaluation of lag-times and profile  
747 shape is recommended.

##### 748 **6.5.1. Strength to be evaluated**

749 When the marketing authorisation of multiple strengths is required, bioequivalence study can be  
750 performed with the highest strength provided that:

- 751           ➤ the qualitative composition is the same for all strengths;
- 752           ➤ the strengths are proportional to the effective surface area of the patch and the lower  
753           dose strengths can be considered as "partial" areas of the highest dose strength;
- 754           ➤ there are similar dissolution/release profiles

755 In case of safety / tolerability limitations at the highest strength, the use of a lower strength is  
756 acceptable for size proportional formulations.

757 The test product should demonstrate a similar or less degree of local irritation, phototoxicity,  
758 sensitization, and similar or better adhesiveness to the skin as the reference product. In order to  
759 ensure equivalence in terms of safety, comparative state-of-the-art studies are required to investigate

- 760       • cutaneous tolerability, irritation and sensitisation (see appendix 1)
- 761       • the potential to produce phototoxic reactions
- 762       • adhesion characteristics

763 unless otherwise justified by e.g. very similar quantitative and qualitative composition.

764 For details regarding comparative adhesion tests reference is made to Guideline on quality of  
765 transdermal patches (EMA/CHMP/QWP/911254/2011).

## 766 **6.6. Bracketing approach**

767 Where bioequivalence assessment at more than two strengths is needed, e.g. because of deviation  
768 from proportional composition or for single unit formulations with proportional composition, a  
769 bracketing approach may be used in special cases, where the other waiver criteria (see Guideline on  
770 the investigation of bioequivalence CPMP/EWP/QWP/1401/98) are fulfilled. In this situation it can be  
771 acceptable to conduct two bioequivalence studies, if the strengths selected represent the extremes,  
772 e.g. the highest and the lowest strength or the two strengths differing most in composition or  
773 dissolution, so that any differences in composition or dissolution in the remaining strengths is covered  
774 by the two conducted studies.

775 However, for prolonged release formulations release-controlling excipients and mechanism should be  
776 the same for all strengths. The same is required for release controlling coatings for delayed release  
777 formulations.

## 778 **6.7. New strength for an already approved MR product**

779 Section 6 also applies to the development of a new strength within the existing dose range. For a new  
780 strength with proportional composition to approved strength(s) a bracketing approach may be  
781 applicable. For a new strength with non-proportional composition to approved strength(s), the new  
782 strength has to meet the requirements as described in relevant sections above (section 6.1-6.5).

783 A new strength outside the existing range requires a clinical development.

## 784 **6.8. Evaluation**

### 785 **6.8.1. Parameters to be analysed**

#### 786 **Single dose studies:**

787 In studies to determine bioequivalence after a single dose,  $AUC_{(0-t)}$ ,  $AUC_{(0-\infty)}$ , residual area,  $C_{max}$ ,  
788  $partialAUC$  and  $t_{max}$  should be determined. A truncated  $AUC_{(0-72h)}$  is not acceptable for MR products.

789 For multiphasic modified release products additional parameters to be determined include  $partialAUC$ ,  
790  $C_{max}$  and  $t_{max}$  in all phases. The time point for truncating the  $partialAUC$  should be based on the PK  
791 profile for the IR and the MR parts respectively and should be justified and pre-specified in the study  
792 protocol.

### 793 **Steady state studies:**

794 In studies to determine bioequivalence after a multiple dose administration  $AUC_{(0-\tau)}$ ,  $t_{max,ss}$ ,  $C_{max,ss}$ ,  
795  $C_{\tau,ss}$ , and fluctuation should be determined. In contrast to the need of characterisation of  $C_{min,ss}$  for new  
796 MR formulations, a comparison of  $C_{\tau,ss}$ , which is easier to determine, should be sufficient.

## 797 **6.8.2. Acceptance criteria**

798 Bioequivalence should be demonstrated by showing equivalence after statistical evaluation of the  
799 following parameters:

800 Single dose:  $AUC_{(0-t)}$ ,  $AUC_{(0-\infty)}$ ,  $C_{max}$ ,  $partialAUC$

801 Multiple dose:  $AUC_{(0-\tau)}$ ,  $C_{max,ss}$ ,  $C_{\tau,ss}$

802 For prolonged release products with no risk of accumulation (see section 6.1) a statistical evaluation of  
803 the following parameters has to show bioequivalence:

804 Single dose:  $AUC_{(0-t)}$ ,  $AUC_{(0-\infty)}$ ,  $C_{max}$  and a representative parameter of the shape of the curve  
805 (early and terminal  $partialAUCs$ )

806 The bioequivalence approach considering usual acceptance limits (80 – 125 %) is applicable for generic  
807 MR products (see CPMP/EWP/QWP/1401/98). Any widening of the acceptance criteria for  $C_{max}$  should  
808 follow the recommendations on highly variable drug products in the Guideline on the Investigation of  
809 Bioequivalence (CPMP/EWP/QWP/1401/98).

810 A similar approach can be used for widening the acceptance criteria for  $C_{max,ss}$ ,  $C_{\tau,ss}$ , and  $partialAUC$ .

811 For delayed and multiphasic release formulations differences in  $t_{max}$  is also recommended to be  
812 assessed, especially for products where a fast onset of action is important. A formal statistical  
813 evaluation of  $t_{max}$  is not required. However, there should be no apparent difference in median  $t_{max}$  and  
814 its range between test and reference product.

## 815 **6.9. Effects of alcohol**

816 For generic oral formulations, *in vitro* studies of the release in alcohol solutions should be performed.  
817 Where accelerated active substance release is seen *in vitro* either at high or low alcohol concentrations  
818 over a short period of time or at lower alcohol concentrations over a longer period of time, the product  
819 should be reformulated.

820 If the alcohol effect cannot be avoided and it is present also in the reference product, the applicant  
821 should justify / demonstrate that it lacks of clinical relevance.

## 822 **6.10. Further points to consider for bioequivalence studies**

823 The following issues should be handled in line with the recommendations for immediate release  
824 formulations stated in the Guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98)

- 825      ➤ Test and reference product
- 826      ➤ Subjects
- 827      ➤ Study conduct
- 828      ➤ Statistical evaluation of primary endpoints
- 829      ➤ Parent compound or metabolites
- 830      ➤ Enantiomers
- 831      ➤ Endogenous substances
- 832      ➤ Narrow therapeutic index drugs (in addition narrowing of the acceptance criteria of  $C_{\tau}$  might be
- 833      necessary)
- 834      ➤ Highly variable drugs or drug products
- 835      ➤ Linearity
- 836

## 837 Definitions

838	$AUC_{(0-t)}$ :	Area under the plasma concentration curve from administration to last
839		observed concentration at time t;
840	$AUC_{(0-\infty)}$ :	Area under the plasma concentration curve extrapolated to infinite time;
841	$AUC_{(0-72h)}$	Area under the plasma concentration curve from administration to 72h;
842	partial AUC:	partial AUC
843	$C_{max}$ :	Maximum plasma concentration;
844	residual area	Extrapolated area $(AUC_{(0-\infty)} - AUC_{(0-t)}) / AUC_{(0-\infty)}$ ;
845	$t_{max}$ :	Time until $C_{max}$ is reached;
846	$t_{1/2}$ :	Plasma concentration half-life;
847	$\lambda_z$ :	Terminal rate constant;
848	$AUC_{(0-\tau)}$ :	AUC during a dosage interval at steady state
849	$t_{max,ss}$ :	Time until $C_{max,ss}$ is reached
850	$C_{max,ss}$ :	Maximum plasma concentration at steady state
851	$C_{min,ss}$ :	Minimum plasma concentration at steady state
852	$C_{\tau}$ :	Concentration at the end of the dosing interval
853	$C_{\tau,ss}$ :	Concentration at the end of the dosing interval at steady state
854	$C_{av}$	average concentration during a dosing interval $(AUC_{(0-\tau)} / \tau)$
855	fluctuation	$[(C_{max} - C_{min}) / C_{av}]$
856	$t_{lag}$	lag time
857		

858 **Appendix I (sensitisation and irritation test for transdermal**  
859 **products)**

860 This appendix is intended to recommend study designs and scoring systems that can be used to test  
861 skin irritation and sensitization during development of transdermal products.

862 The condition of the skin may influence the absorption of an active substance from a transdermal  
863 system and affect the efficacy or safety of the product. Therefore skin irritation and sensitization  
864 should be assessed.

865 To fully evaluate the equivalence of a generic transdermal product to the reference product similarity  
866 has also to be shown for skin irritation and sensitization unless otherwise justified by e.g. very similar  
867 quantitative and qualitative composition.

868 The strength chosen for the test is determined by considering the following factors:

- 869
- previous human experience
  - previous sensitisation/irritation tests in animals
- 870

871 **Overall Study Design for a generic application**

872 The study suggested has an active- and placebo-controlled, multiple-dose, three-phase, parallel-group  
873 design.

874 Screening evaluations are performed within a 14-day period prior to application of the patches.

875 Screening evaluations should consist of a medical history, complete physical examination, 12-lead  
876 electrocardiogram (ECG), laboratory evaluations (including serum chemistry, hematology, and  
877 urinalysis), and urine drug screen.

878 Subjects are assigned to one of two analysis groups (Group 1 and Group 2) and are evaluated for both  
879 cumulative dermal irritation and contact sensitization. Test, reference and placebo transdermal patches  
880 should be applied to randomly assigned test areas on the backs of subjects in the two groups.  
881 Application areas are upper left back, upper right back, or left back below according to a randomization  
882 scheme within each subject. Skin reactions have to be evaluated by a trained observer blinded to the  
883 treatment.

884 Criteria for discontinuation of the test should be mentioned in order to avoid excessive reaction.

885 Each subject participates in the following three consecutive study phases.

886 **Induction/Cumulative Irritation Phase**

887 Group 1 subjects apply test, reference, and placebo patches to randomly assigned treatment areas for  
888 21 consecutive days.

889 Group 2 subjects apply test, reference, and placebo patches to randomly assigned treatment areas  
890 three times weekly over a period of 21 days (a total of nine applications). In Group 2, the patches  
891 remain in place for 48 hours (on weekdays) and 72 hours (on weekends). The new patch should be  
892 applied to the same site as the previous patch.

893 **Rest Phase**

894 Following the Induction/Cumulative Irritation Phase, each subject enters a 2-week Rest Phase. No  
895 patches are applied during the Rest Phase.

896 **Challenge Phase**

897 Following the Rest Phase, patches are applied to new skin sites within the designated areas for 48  
898 hours.

899 In addition to dermal assessments at 0.5 and 24 hours after patch removal, subjects participating in  
900 the Challenge Phase also return for examination on Days 40 and 41 for additional dermal assessments  
901 at 48 and 72 hours after removal of the last patch.

902 To minimize the effect of inter-subject variability, each study participant receives all three treatments  
903 simultaneously. In addition, to control for the unlikely possibility of a treatment-by-site-interaction, the  
904 three treatments should be randomly assigned to three application areas so that each treatment  
905 occupied each application area with approximately equal frequency throughout the panel of study  
906 participants.

<b>Group 1</b>	<b>Cumulative Irritation Phase</b>				
	Test, Reference Placebo	One patch of each drug applied daily to the back of each subject for 21 days			
	<b>Induction of Contact Sensitization</b>		<b>Rest Phase</b>	<b>Challenge Phase</b>	
Test, Reference Placebo	One patch of each drug applied daily to the back of each subject for 21 days	No patches applied for 2 weeks	Test, Reference Placebo	One patch of each drug applied to the back of each subject; patch removed after 48 hours	
<b>Group 2</b>	<b>Induction of Contact Sensitization</b>		<b>Rest Phase</b>	<b>Challenge Phase</b>	
	Test, Reference Placebo	One patch of each drug applied to the back of each subject three times a week over a period of 21 days	No patches applied for 2 weeks	Test, Reference Placebo	One patch of each drug applied to the back of each subject; patch removed after 48 hours

907 Dermal response has to be assessed for all subjects in Group 1 and Group 2. Application sites for both  
908 groups are evaluated for skin irritation 30 minutes after patch removal (dermal response and other  
909 effects scores determined), and new patches are applied 1 hour after removal every time that the  
910 patch is removed during the Induction/Cumulative Irritation Phase.

911 To evaluate contact sensitization during the Challenge Phase, test, reference, and placebo patches are  
912 applied simultaneously for 48 hours to previously unused sites on Group 1 and Group 2 subjects.  
913 Application sites were evaluated at 0.5, 24, 48, and 72 hours after patch removal.

914 Skin reactions can be examined and graded using the numerical and letter scores outlined in Table 1  
915 (dermal response) and Table 2 (other effects).

916 Each application site receives a separate dermal response score and other effects score. Dermal  
 917 response scores require that at least 25% or more of the patch area demonstrate an observable  
 918 response. During the Challenge Phase (contact sensitization evaluation), only combined dermal  
 919 response scores  $\geq 2$  are considered a positive response.

<b>Table 1</b>	<b>Dermal Response Score</b>
<b>Score</b>	<b>Definition</b>
0	No evidence of irritation
1	Minimal erythema, barely perceptible
2	Definite erythema, readily visible; minimal edema or minimal papular response
3	Erythema and papules
4	Definite edema
5	Erythema, edema, and papules
6	Vesicular eruption
7	Strong reaction spreading beyond test site

920

<b>Table 2</b>	<b>Dermal Response Score</b>
<b>Score</b>	<b>Definition</b>
0	None observed
1	Slight glazed appearance
2	Marked glazing
3	Glazing with peeling and cracking
4	Glazing with fissures Film of dried serous exudates covering all or part of the patch site Small petechial erosions and/or scabs

921 "Strong" reaction to the test patch are defined as a dermal response score of 3-7 or any dermal score  
 922 combined with another effects rating of 4.

<b>Group</b>	<b>Phase</b>	<b>Evaluation by observer</b>	<b>Assessment of Test, Reference and Placebo</b>
Group 1	Cumulative Irritation Phase	Dermal Response Score Other Effects Score	<ul style="list-style-type: none"> <li>• Mean Irritation Score = average of Dermal Response Scores</li> <li>• Total Cumulative Irritation Score sum of Dermal Response Scores</li> <li>• Combined Dermal Response Score sum of Dermal Response Score and Other Effects Score</li> <li>• Mean Combined Dermal Response Score</li> </ul>
Group 1 + 2	Challenge Phase (Contact Sensitization)	Dermal Response Score Other Effects Score	-Combined Dermal Response Score 2:2

923 The primary analysis compares the test and reference treatments for the mean irritation scores  
 924 (average numeric dermal response over the observations) and the total cumulative irritation scores  
 925 (sum of the numeric dermal response scores over the observations). The two one-sided t-test method  
 926 should be used to compare the irritation scores between treatments. For each parameter, least squares  
 927 means for each treatment are derived from an ANOVA model where subject and treatment are fixed  
 928 effects. The ratio of the least squares means of the test treatment to the reference treatment has to be  
 929 calculated, along with its 90% confidence interval. A 90% confidence interval that falls completely  
 930 within the interval 0.8 to 1.25 leads to the conclusion that the two treatments are equivalent.

931 The assessment of contact sensitization consists of tabulations of dermal response scores  $\geq 2$  during  
932 the Challenge Phase. No statistical analysis has to be performed on these data.  
933

## 934 **Appendix II (In vitro in vivo correlation):**

### 935 **1 Introduction**

936 An *in vitro in vivo correlation* (IVIVC) is a mathematical model describing the relationship between an  
937 *in vitro* property of a dosage form (mainly dissolution or drug release) and a relevant *in vivo* response  
938 (mainly drug plasma concentration or amount absorbed).

939 When a modified release formulation is developed, it is highly recommended to establish an IVIVC:

940 a) to quantify *in vivo* release and formulation related effect on absorption,

941 b) to establish the clinical relevance of *in vitro* dissolution tests and associated dissolution  
942 specifications

943 c) to support biowaiver claims in later phases of clinical development or post-authorisation if there are  
944 changes in formulation.

945 Historically different levels of IVIVC relationships have been described; including levels A, B and C (see  
946 Annex 2, Guideline on quality of oral modified release products EMA/CHMP/QWP/467527/2012). Level  
947 A IVIVCs, in contrast to levels B and C, predict the entire concentration-time profile and for this reason  
948 are highly encouraged. Where an IVIVC is used to support regulatory decisions such as dissolution  
949 specification or biowaiver, a validated level A correlation is a prerequisite.

950 The usefulness of an IVIVC depends on how accurately it can predict resultant plasma concentrations  
951 from any given set of *in vitro* data. This in turn is heavily dependent on the design of the *in vitro* and *in vivo*  
952 studies used to develop and validate the IVIVC.

### 953 **2 Study Design Considerations**

954 Generally, two or more formulations with sufficiently different dissolution profiles and an appropriate  
955 reference formulation (for the purpose of deconvolution) with fast drug release (e.g., oral solution or  
956 immediate release formulation) are administered in a crossover study in healthy volunteers. For  
957 modified release products, the IVIVC study is normally conducted in the fasted state, even when the  
958 product is recommended to be taken with food. Parent drug levels are quantified as a function of time  
959 in blood or plasma.

960 Extrapolation beyond the range of formulations used in IVIVC development and validation is not  
961 acceptable for regulatory applications (e.g. specification setting and biowaiver requests). Thus, the  
962 choice of formulations requires careful consideration. This is further discussed in the Guideline on  
963 quality of oral modified release products (EMA/CHMP/QWP/467527/2012). As the sensitivity of the  
964 plasma concentration-time profile for a given drug will depend on its particular disposition properties, it  
965 is advisable to base IVIVC formulation selection on expected plasma concentration-time profiles  
966 (simulated using an assumed IVIVC relationship or range of possible relationships and the known  
967 disposition characteristics of the drug).

968 While it is acceptable to use different dosage strengths to establish an IVIVC or for external validation,  
969 it should be noted that different dosage strengths of the same formulation would generally not be  
970 considered to represent “different” release rates. For this reason, judgement of whether the dissolution  
971 profiles for different formulations are “different” is normally based on % of labelled (or actual) content.

#### 972 **2.1 Role and Choice of Reference Formulation**

973 A reference formulation is a fast-releasing formulation included in IVIVC studies to allow calculation of  
974 the *in vivo* release of drug as a function of time for each MR formulation (see section 3.2). The *in vivo*

975 release-time profile is normally obtained by deconvolution and truly reflects drug release in vivo only  
976 when the reference formulation is an oral solution (and there is no precipitation from this solution in  
977 the stomach or GI tract). Immediate release formulations can be used as reference products in IVIVC  
978 studies and will also allow adequate approximation of the in vivo drug release from the MR  
979 formulations as long as the rate of dissolution from the IR formulation is fast relative to its absorption  
980 (which is normally the case for the drugs that are chosen as suitable for MR product development).  
981 Sometimes IV product is used as the reference for IVIVC. This will also allow adequate approximation  
982 of in vivo drug release as long as absorption is fast (i.e. for drugs with high permeability).

983 A reference formulation should be included in any study where the data will be used to support the  
984 development and internal or external validation of the IVIVC.

## 985 **2.2 Sampling Times**

986 Considerations for the choice of in vitro sampling times are discussed in the Guideline on quality of oral  
987 modified release products (EMA/CHMP/QWP/467527/2012). Although discussed separately, an  
988 integrated approach to the design of the IVIVC study (including in vitro dissolution and in vivo  
989 blood/plasma sampling times) is encouraged.

990 Sampling time decisions for blood/plasma are best made based on simulations using the actual (or  
991 modelled) in vitro release data for the clinical batches manufactured for the IVIVC study. If the in vitro  
992 dissolution is pH or rotation-speed dependent, it is useful to do simulations using the range of in vitro  
993 dissolution profiles in order to design a sampling regimen to cover the range of potential in vivo  
994 behaviours. Also, if there is some *a priori* understanding of the likely IVIVC relationship this is best  
995 built into the initial simulation. For example, for injectable controlled release formulations, in vitro  
996 release testing is often designed to be complete within 24-48 h, while the in vivo delivery is designed  
997 to continue for 1-2 months. Thus, a time-scaling factor (or range of factors) can be anticipated *a priori*  
998 and built into the model to provide a more realistic picture of the expected in vivo behaviour and better  
999 choose appropriate sampling times for the test formulations.

## 1000 **2.3 Number of Subjects**

1001 The number of subjects to be included in an IVIVC study is dependent, as for the design of BE studies,  
1002 on the variability of the drug product. Although no firm guidance can be given, a pragmatic approach  
1003 would be to use no fewer than 12 in a crossover IVIVC study.

## 1004 **3 IVIVC Development and Validation**

### 1005 **3.1 General Considerations**

1006 The overall goal of IVIVC is to be able to reliably predict the entire time course of plasma concentration  
1007 from a modified release formulation based on in vitro release data. In principle any methodology that  
1008 is scientifically sound can be used for this. Although a few are discussed below, methodology will  
1009 continue to evolve and this list should not be considered to be exhaustive. As the purpose of the IVIVC  
1010 is to be able to predict without in vivo testing the plasma concentration resulting from a modified  
1011 formulation with different in vitro release data, it is a prerequisite that a single IVIVC relationship is  
1012 applicable to all formulations used in its development and validation.

### 1013 **3.2 Acceptable Methods of Data Analysis**

1014 Two general categories of mathematical approaches to IVIVC modelling are one- and two-stage  
1015 methods. The two-stage method is deconvolution-based. One stage approaches include convolution-  
1016 based and differential equation-based methods.

1017 Deconvolution-based methods involve two stages of data analysis. The first stage employs  
1018 deconvolution to estimate the time course of in vivo absorption. Noncompartmental methods of  
1019 deconvolution are preferred. The second stage establishes the relationship between cumulative in vivo  
1020 absorption and in vitro drug release. A linear relationship between in vivo absorption and in vitro  
1021 release, although desirable, is not necessary and there are many physiological and physicochemical  
1022 factors that make this less likely. In principle, any relationship that is applicable to all IVIVC  
1023 formulations is acceptable including sigmoidal, Hill, incorporation of time-scaling and time-shifting  
1024 parameters and approaches to account for incomplete absorption (absorption cut-off time, nonlinear  
1025 absorption functions) with justification based on an understanding of the formulation, physicochemical,  
1026 pharmacokinetic and physiological factors controlling drug release in vitro and vivo. Different time  
1027 scales for each formulation points to the absence of a single relationship for the IVIVC formulations.  
1028 Deconvolution-based methods are particularly helpful for exploratory data analysis during the model  
1029 building process, as they provide graphical output (cumulative amount absorbed in vivo versus  
1030 cumulative amount released in vitro and Levy plots: time for a specific %of dose absorbed in vivo  
1031 versus time for a specific % of dose released in vitro) that can be used to identify appropriate models  
1032 for the IVIVC relationship and provide appropriate initial parameter estimates necessary for one-stage  
1033 modelling methods.

1034 Convolution-based and differential equation-based methods are classified as single stage because  
1035 modelling involves utilising the observed data directly without transformation (i.e. through  
1036 deconvolution). Single stage approaches offer a number of advantages over deconvolution based  
1037 methods, as the model predicts directly the plasma concentration-time course; modelling focuses on  
1038 the ability to predict measured quantities, not indirectly calculated quantities such as the cumulative  
1039 amount absorbed; and the results are more readily interpreted in terms of the effect of the in vitro  
1040 release on conventional bioequivalence metrics. Additionally, the compartmental approach allows for  
1041 non-linear (e.g. Michaelis-Menten) disposition kinetics, whereas the convolution-based method  
1042 assumes linear disposition. Although both convolution-based and differential-based methods are single  
1043 stage, they differ in the form of the relationship between in vitro release and plasma drug  
1044 concentration. The convolution-based approach uses an integral transform, such as:

$$1045 \quad C(t) = r(t) * C_{\delta} = \int_0^t C_{\delta}(t - \tau)r(\tau)d\tau$$

1046 where C is plasma concentration, r is the in vivo input rate,  $C_{\delta}$  is the unit impulse response (i.e. the  
1047 plasma concentration profile resulting from instantaneous absorption of a unit dose of drug) and \* is  
1048 the convolution operator.

1049 The differential equation-based approach utilises a traditional compartmental model framework for  
1050 drug disposition and incorporates an input function.

1051 In both cases, an IVIVC equation quantifies the relationship between drug release in vitro [ $r_{dis}(t)$ ] and  
1052 drug absorption in vivo [ $r(t)$ ]. The simplest relationship is where drug dissolution reflects its rate of  
1053 drug absorption. In this case:

$$1054 \quad r(t) = r_{dis}(t)$$

1055 Various more complex functions that account for time lags for absorption, different time scales for in  
1056 vitro dissolution and in vivo absorption and changing permeability through the gastrointestinal tract  
1057 can be incorporated into the IVIVC equation. For example, the following equation includes a lag time  
1058 ( $t_0$ ), a time scaling factor ( $s_1$ ), a time-dependent multiplying factor [ $\varphi_{abs}(t)$ ] that accounts for  
1059 changing permeability and a scaling factor ( $s_r$ ) that allows incomplete absorption or utilisation of  
1060 different units between in vitro dissolution and in vivo absorption.

1061  $r(t) = \varphi_{abs}(t) s_r r_{dis}(t_0 + s_1 t)$

1062 Most IVIVC analyses use averaged in vitro dissolution to predict an averaged in vivo concentration-  
1063 time profile. This approach does not address adequately random variation in vitro, but more  
1064 importantly, in vivo. From this point of view the one stage approaches offer the advantage that they  
1065 are amenable to a nonlinear mixed effects analysis framework, which allows individual variability to be  
1066 incorporated into the model, potentially improving the reliability of the model for inferences regarding  
1067 the bioequivalence metrics of new formulations.

1068 Where a two-stage approach is utilised, the average absorption profile should be derived from  
1069 averaging of the individual subject absorption profiles (i.e. from individual deconvolution), rather than  
1070 by deconvolution of the average concentration-time profiles.

### 1071 **3.3 IVIVC Model Qualification and Predictability Assessment**

1072 Model selection should be based on an understanding of the physicochemical properties of the drug, its  
1073 absorption characteristics, the dissolution test characteristics and criteria for assessing goodness of fit  
1074 (e.g. posterior predictive check). General requirements for model evaluation within the nonlinear  
1075 mixed effects context are outlined in detail in the Guideline on reporting the results of population  
1076 pharmacokinetic analyses (CHMP/EWP/185990/06). The purpose of the model is to be able to predict  
1077 with adequate accuracy the expected plasma concentration-time curve from an in vitro dissolution data  
1078 for a modified formulation. This is demonstrated by a graphical comparison of predicted and observed  
1079 concentrations and calculation of prediction errors for summary parameters including at least  $C_{max}$ ,  
1080  $AUC_{0-t}$  and  $partialAUC$  (see section 6.8.1).

1081 An IVIVC model is generally accepted as adequately accurate if from visual inspection the entire  
1082 concentration-time curve is well predicted and the prediction errors are within acceptable limits.  
1083 Internal predictability is assessed using the IVIVC model to predict the concentration-time profile from  
1084 the respective dissolution data for each formulation. The summary parameters ( $C_{max}$ , etc.) are  
1085 calculated from the predicted concentration-time curve and compared to the respective summary  
1086 parameters for the observed data. The prediction error (PE), defined as  $\%PE = [(observed\ value -$   
1087  $predicted\ value) / observed\ value] \times 100$ , is calculated for each of the summary parameters.  
1088 The absolute value of the prediction error for all summary parameters should be less than 15% for  
1089 each formulation and on average for all formulations included in IVIVC development should be less  
1090 than 10% for each summary parameter. Where an individual formulation is found to be inadequately  
1091 predicted by the IVIVC, it is acceptable to redevelop the IVIVC excluding the outlier formulation,  
1092 resulting in a narrower range of dissolution data included in the IVIVC. However, this will then  
1093 determine the range over which the IVIVC is accepted as predictive, impacting on the potential for  
1094 specification and biowaiver justification.

1095 In addition to evaluation of internal predictability utilising the batches included in a formal IVIVC study,  
1096 it is encouraged to continue to demonstrate the applicability of the IVIVC with additional development  
1097 batches (e.g. large scale batches used in pivotal studies, additional dosage strengths, any later  
1098 formulation changes that were studied in vivo, etc.). The procedure for external predictability analysis  
1099 is as described above utilising the IVIVC previously developed. The concentration-time profiles are  
1100 predicted based on the reference immediate release product pharmacokinetics observed in the study  
1101 used for external validation purposes and the in vitro dissolution data for the particular external  
1102 validation batch. The absolute value of the prediction error for all summary parameters should be less  
1103 than 10% for each formulation used for external validation.

### 1104 **3.4 Reporting**

1105 The IVIVC report should include a listing of all in vivo studies available for the modified release  
1106 formulation and a rationale for the selection of data included in IVIVC analysis. Data listings should  
1107 include: individual data and summary statistics for in vitro dissolution data, plasma concentration-time  
1108 data, derived pharmacokinetic parameters and cumulative amount absorbed (derived from  
1109 deconvolution, even if a one stage method is used for model development) for all batches used in  
1110 model development.

1111 Graphical displays should include in vitro dissolution versus time (highlighting batches of clinical  
1112 significance, such as the to-be-marketed formulation, etc.), cumulative amount absorbed versus time,  
1113 absorption rate versus time, overlay of dissolution and absorption time courses (to judge different time  
1114 frames, time lags between in vitro and in vivo data) and cumulative amount absorbed in vivo versus  
1115 amount released at same time in vitro (with overlay of 1:1, regression lines as helpful/appropriate) for  
1116 all formulations included in IVIVC analysis. A Levy plot (time for a specific fraction released in vivo  
1117 versus the time for the same fraction in vitro) may also be a useful graphical display where an obvious  
1118 time difference exists between time courses of in vitro release and in vivo absorption.

1119 The dissolution test method should be described and a justification of its appropriateness given the  
1120 physicochemical properties of the drug, etc. should be included.

1121 A full description of the modelling methodology and software employed and basis of decisions should  
1122 be included, supported by a discussion of the formulation, physicochemical, pharmacokinetic and  
1123 physiological factors controlling drug release in vitro and vivo. Where a compartmental deconvolution  
1124 method is used (e.g. Wagner-Nelson or Lou-Riegelman), the appropriateness of the approach should  
1125 be discussed.

1126 Plots evaluating goodness of fit, appropriate to the modelling methodology employed, should be  
1127 included as well as final parameter estimates for all fitted data (e.g. in vitro dissolution and in vivo  
1128 absorption in case a model is used for interpolation, as well for the IVIVC model itself).

1129 The final IVIVC model predicted plasma concentration-time data, derived parameters and associated  
1130 prediction error should be included in a table. Graphical comparison of predicted and observed  
1131 concentration-time profiles should be provided.

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1149

1150 **Appendix III: Summary of study recommendations for**  
 1151 **abridged applications:**

1152 **Prolonged release single unit formulation (SmPC recommends intake under fasting or**  
 1153 **fasting and fed conditions)**

Strength	Single dose fasting study**	Single dose fed Study	Multiple dose study*
high	yes	yes	yes
middle	yes	waiver	waiver
low	yes	waiver	waiver

1154 \* see criteria for necessity in section 6.1

1155 \*\* bracketing approach possible if criteria (see section 6.6) are met

1156 **Prolonged release single unit formulation (SmPC recommends intake under fed conditions)**

Strength	Single dose fasting study	Single dose fed Study**	Multiple dose study*
high	yes	yes	yes
middle	waiver	yes	waiver
low	waiver	yes	waiver

1157 \* see criteria for necessity in section 6.1

1158 \*\* bracketing approach possible if criteria (see section 6.6) are met

1159  = if criteria (see section 6) are met, waivers to some strengths or bracketing  
 1160 approach are possible

1161

1162 **Prolonged release multiple unit formulation (SmPC recommends intake under fasting or**  
 1163 **fasting and fed conditions)**

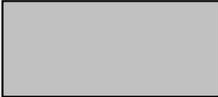
Strength	Single dose fasting study	Single dose fed Study	Multiple dose study*
high	yes	yes	yes
middle	waiver	waiver	waiver
low	waiver	waiver	waiver

1164 \* see criteria for necessity in section 6.1

1165 **Prolonged release multiple unit formulation (SmPC recommends intake fed conditions)**

Strength	Single dose fasting study	Single dose fed Study	Multiple dose study*
high	yes	yes	yes
middle	waiver	waiver	waiver
low	waiver	waiver	waiver

1166 \* see criteria for necessity in section 6.1

1167  = if criteria (see section 6) are met, waivers to some strengths or bracketing  
 1168 approach are possible

1169

1170 **Delayed release single unit formulation (SmPC recommends intake under fasting or fasting**  
 1171 **and fed conditions)**

Strength	Single dose fasting study**	Single dose fed Study
high	yes	yes
middle	yes	waiver
low	Yes	waiver

1172 \*\* bracketing approach possible if criteria (see section 6.6) are met

1173 **Delayed release single unit formulation (SmPC recommends intake under fed conditions)**

Strength	Single dose fasting study	Single dose fed Study**
high	Yes	yes
middle	waiver	yes
low	waiver	yes

1174 \*\* bracketing approach possible if criteria (see section 6.6) are met

1175  = if criteria (see section 6) are met, waivers to some strengths or bracketing  
 1176 approach are possible

1177

1178 **Delayed release multiple unit formulation (SmPC recommends intake under fasting or**  
 1179 **fasting and fed conditions)**

Strength	Single dose fasting study	Single dose fed Study
high	yes	yes
middle	waiver	waiver
low	waiver	waiver

1180 **Delayed release multiple unit formulation (SmPC recommends intake under fed conditions)**

Strength	Single dose fasting study	Single dose fed Study
high	yes	yes
middle	waiver	waiver
low	waiver	waiver

1181  = if criteria (see section 6) are met, waivers to some strengths or bracketing  
 1182 approach are possible