

INTERNATIONAL CONCIL FOR HARMONISATION OF TECHNICAL  
REQUIREMENTS FOR PHARMACEUTICALS FOR HUMAN USE

**ICH HARMONISED GUIDELINE**

**BIOPHARMACEUTICS CLASSIFICATION SYSTEM-BASED**

**BIOWAIVERS**

**M9**

Draft version

Endorsed on 7 June 2018

*Currently under public consultation*

*At Step 2 of the ICH Process, a consensus draft text or guideline, agreed by the appropriate ICH Expert Working Group, is transmitted by the ICH Assembly to the regulatory authorities of the ICH regions for internal and external consultation, according to national or regional procedures.*

**M9**  
**Document History**

<b>Code</b>	<b>History</b>	<b>Date</b>
M9	Endorsement by the Members of the ICH Assembly under <i>Step 2</i> and release for public consultation (document dated 6 June 2018).	7 June 2018

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# ICH HARMONISED GUIDELINE

## BIOPHARMACEUTICS CLASSIFICATION SYSTEM-BASED

### BIOWAIVERS

#### M9

##### ICH Consensus Guideline

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## 1 INTRODUCTION

2 **1.1. Background and Objective**

3 Two drug products containing the same active substance are considered bioequivalent if their  
4 bioavailabilities (rate and extent of drug absorption) after administration in the same molar  
5 dose lie within acceptable predefined limits. These limits are set to ensure comparable *in vivo*  
6 performance, i.e., similarity in terms of safety and efficacy. In *in vivo* bioequivalence studies,  
7 the pivotal pharmacokinetic parameters AUC (the area under the concentration time curve),  
8 and  $C_{max}$  (the maximum concentration), are generally used to assess the rate and extent of  
9 drug absorption.

10 The BCS (Biopharmaceutics Classification System)-based biowaiver approach is intended to  
11 reduce the need for *in vivo* bioequivalence studies i.e., it can provide a surrogate for *in vivo*  
12 bioequivalence. *In vivo* bioequivalence studies may be exempted if an assumption of  
13 equivalence in *in vivo* performance can be justified by satisfactory *in vitro* data. The BCS is a  
14 scientific approach based on the aqueous solubility and intestinal permeability characteristics  
15 of the drug substance. The BCS categorizes drug substances into one of four BCS classes as  
16 follows:

17 Class I: high solubility, high permeability

18 Class II: low solubility, high permeability

19 Class III: high solubility, low permeability

20 Class IV: low solubility, low permeability

21 This guidance will provide recommendations to support the biopharmaceutics classification of  
22 drug substances and the BCS-based biowaiver of bioequivalence studies for drug products.

23 **1.2 Scope**

24 BCS-based biowaivers may be used to demonstrate bioequivalence for example between  
25 products used in early clinical development through commercialization, for line extensions of  
26 the same pharmaceutical form of innovator products, in applications for generic drug products,  
27 and post-approval changes that would otherwise require *in vivo* bioequivalence evaluation, in  
28 accordance with regional regulations.

29 The BCS-based biowaiver is only applicable to immediate release, solid orally administered  
30 dosage forms or suspensions designed to deliver drug to the systemic circulation. Drug  
31 products having a narrow therapeutic index are excluded from consideration for a BCS-based  
32 biowaiver in this guidance. Fixed-dose combination (FDC) products are eligible for a  
33 BCS-based biowaiver when all drug substances contained in the combination drug product

34 meet the criteria as defined in sections 2 and 3 of this guidance.

35

## 36 **2. BIOPHARMACEUTICS CLASSIFICATION OF THE DRUG SUBSTANCE**

37 BCS-based biowaivers are applicable to drug products where the drug substance exhibits high  
38 solubility and, either high permeability (BCS Class I) or low permeability (BCS Class III).

39

40 A biowaiver is only applicable when the drug substance(s) in test and reference products are  
41 identical. For example, a biowaiver is not applicable when the drug substance in the test  
42 product is a different salt, ester, isomer, or mixture of isomers from that in the reference  
43 product. Pro-drugs may be considered for a BCS-based biowaiver when absorbed as the  
44 pro-drug.

45

### 46 **2.1. Solubility**

47 A drug substance is classified as highly soluble if the highest single therapeutic dose is  
48 completely soluble in 250 ml or less of aqueous media over the pH range of 1.2 – 6.8 at  $37 \pm$   
49  $1^\circ\text{C}$ . In cases where the highest single therapeutic dose does not meet this criterion but the  
50 highest strength of the reference product is soluble under the aforementioned conditions,  
51 additional data should be submitted to justify the BCS-based biowaiver approach.

52

53 The applicant is expected to establish experimentally the equilibrium saturated solubility of  
54 the drug substance over the pH range of 1.2 – 6.8 at  $37 \pm 1^\circ\text{C}$  using a shake-flask technique or  
55 an alternative method, if justified. At least three buffers within this range, including buffers at  
56 pH 1.2, 4.5 and 6.8, should be evaluated. In addition, solubility at the pKa of the drug  
57 substance should be evaluated if it is within the specified pH range. The pH for each test  
58 solution should be measured after the addition of the drug substance and at the end of the  
59 equilibrium solubility study to ensure the solubility measurement is conducted under the  
60 specified pH. The pH should be adjusted if necessary. The lowest measured solubility over the  
61 pH range of 1.2 – 6.8 will be used to classify the drug substance.

62

63 A minimum of three replicate determinations at each solubility condition/pH is necessary to  
64 demonstrate solubility using a validated stability-indicating method, with appropriate  
65 compendial references for the media employed.

66

67 In addition, adequate stability of the drug substance in the solubility media should be  
68 demonstrated. In cases where the drug substance is not stable with  $>10\%$  degradation over  
69 the extent of the solubility assessment, solubility cannot be adequately determined and thus  
70 the drug substance cannot be classified. In this case a BCS-based biowaiver cannot be applied.

71 In addition to experimental data, literature data may be provided to substantiate and support

72 solubility determinations, keeping in mind that peer reviewed articles may not contain the  
73 necessary details of the testing to make a judgement regarding the quality of the studies.

74

## 75 **2.2. Permeability**

76 The assessment of permeability should preferentially be based on the extent of absorption  
77 derived from human pharmacokinetic studies, e.g., absolute bioavailability or mass balance.

78

79 High permeability can be concluded when the absolute bioavailability is  $\geq 85\%$ . High  
80 permeability can also be concluded if  $\geq 85\%$  of the administered dose is recovered in urine as  
81 unchanged (parent drug), or as the sum of parent drug, Phase 1 oxidative and Phase 2  
82 conjugative metabolites. Regarding metabolites in feces only oxidative and conjugative  
83 metabolites can be considered. Metabolites produced through reduction or hydrolysis should  
84 not be included, unless it can be demonstrated that they are not produced by microbial action  
85 within the gastrointestinal tract. Unchanged drug in feces cannot be counted toward the extent  
86 of absorption, unless appropriate data supports that the amount of parent drug in feces to be  
87 accounted for absorbed drug material is from biliary excretion, intestinal secretion or  
88 originates from an unstable metabolite, e.g., glucuronide, sulphate, N-oxide that has been  
89 converted back to the parent by the action of microbial organisms.

90

91 Human *in vivo* data derived from published literature (for example, product knowledge and  
92 previously published bioavailability studies) may be acceptable, keeping in mind that peer  
93 reviewed articles may not contain the necessary details of the testing to make a judgement  
94 regarding the quality of the results.

95

96 Permeability can be also assessed by validated and standardized *in vitro* methods using  
97 Caco-2 cells(see Annex I). The results from Caco-2 permeability assays should be discussed  
98 in the context of available data on human pharmacokinetics. *In vitro* cell permeability assays  
99 (Caco-2) used in support of high permeability should be appropriately validated and  
100 standardized as outlined in Annex 1. If high permeability is inferred by means of an *in vitro*  
101 cell system, permeability independent of active transport should be proven as outlined in  
102 Annex I, “Assay Considerations”.

103

104 If high permeability is not demonstrated, the drug substance is considered to have low  
105 permeability (e.g. BCS class III).

106

## 107 Instability in the Gastrointestinal Tract

108 If mass balance studies or *in vitro* Caco-2 studies are used to demonstrate high permeability,  
109 additional data to document the drug’s stability in the gastrointestinal tract should be provided,

110 unless  $\geq 85\%$  of the dose is recovered as unchanged drug in urine. Stability in the  
111 gastrointestinal tract may be documented using compendial and simulated gastric and  
112 intestinal fluids or, with suitable justification, other relevant methods. Drug solutions should  
113 be incubated at 37°C for a period that is representative of the *in vivo* contact of the drug  
114 substance with these fluids, i.e., one hour in gastric fluid and three hours in intestinal fluid.  
115 Drug concentrations should then be determined using a validated stability indicating assay  
116 method. Significant degradation (>10 percent) of a drug in this study could suggest potential  
117 instability.

118

### 119 **3. SUPPORT OF THE ELIGIBILITY OF A DRUG PRODUCT FOR A BCS-BASED** 120 **BIOWAIVER**

121 A drug product is eligible for a BCS-based biowaiver provided that the drug substance(s)  
122 satisfy the criteria regarding solubility and permeability (BCS Class I and III), the drug  
123 product is an immediate-release oral dosage form with systemic action, and the drug product  
124 is a dosage form that is pharmaceutically equivalent to the reference product. In cases where  
125 the highest single therapeutic dose does not meet the high solubility criterion but the highest  
126 strength of the reference product is soluble under the required conditions, BCS-based  
127 biowaivers can be supported based on additional data. An example of such additional data is  
128 demonstration of dose proportional pharmacokinetics (i.e. AUC and  $C_{\max}$ ) over a dose range  
129 that includes the highest therapeutic dose.

130

131 Drug products with buccal or sublingual absorption are not eligible for a BCS-based  
132 biowaiver application. As such, an orodispersible product is eligible for a biowaiver  
133 application only if there is no buccal or sublingual absorption and the product is labelled to be  
134 taken with water only.

135

136 In order for a drug product to qualify for a BCS-based biowaiver, criteria with respect to the  
137 composition (excipients) and *in vitro* dissolution performance of the drug product should be  
138 satisfied. The drug product acceptance criteria are described in sections 3.1 and 3.2 below.

139

#### 140 **3.1. Excipients**

141 Excipient differences between the proposed test and the reference products should be assessed  
142 for their potential to affect *in vivo* absorption. This should include consideration of the drug  
143 substance properties as well as excipient effects. To be eligible for a BCS-based biowaiver,  
144 the applicant should justify why the proposed excipient differences will not affect the  
145 absorption profile of the drug substance under consideration, i.e., rate and extent of absorption,  
146 using a mechanistic and risk-based approach. The decision tree for performing such an  
147 assessment is outlined in Figures 1 and 2 in Annex II.

148

149 The possible effects of excipients on aspects of *in vivo* absorption such as solubility,  
150 gastrointestinal motility, transit time and intestinal permeability including transporter  
151 mechanisms, should be considered. Excipients that may affect absorption include  
152 sugar-alcohols, e.g., mannitol, sorbitol, and surfactants, e.g., sodium lauryl sulfate. The risk  
153 that a given excipient will affect the absorption of a drug substance should be assessed  
154 mechanistically by considering

- 155 • the amount of excipient used,
- 156 • the mechanism by which the excipient may affect absorption,
- 157 • absorption properties (rate, extent and mechanism of absorption) of the drug  
158 substance.

159

160 The amount of excipients that may affect absorption in the test and reference formulations  
161 should be addressed during product development, such that excipient changes are kept to a  
162 minimum. Small amounts included in the tablet coating or levels below documented  
163 thresholds of effect for the specific drug substance are of less concern.

164

165 By definition, BCS Class I drugs are highly absorbed, and have neither solubility nor  
166 permeability limited absorption. Therefore they generally represent a low risk group of  
167 compounds in terms of the potential for excipients to affect absorption, compared to other  
168 BCS classes. Consideration of excipient effects for BCS Class I drug products should focus on  
169 potential changes in the rate or extent of absorption. For example, if it is known that the drug  
170 has high permeability due to active uptake, excipients that can inhibit uptake transporters are  
171 likely to be of concern. For BCS Class I drugs that exhibit slow absorption, the potential for a  
172 given excipient to increase absorption rate should also be considered.

173

174 For BCS Class I drugs, qualitative and quantitative differences in excipients are permitted,  
175 except for excipients that may affect absorption, which should be qualitatively the same and  
176 quantitatively similar, i.e., within  $\pm 10.0\%$  of the amount of excipient in the reference product.

177

178 BCS Class III drug substances are considered to be more susceptible to the effects of  
179 excipients. These drugs are poorly permeable and may have site-specific absorption, so there  
180 are a greater number of mechanisms through which excipients can affect their absorption than  
181 for BCS Class I drugs. For BCS Class III drugs, all of the excipients should be qualitatively  
182 the same and quantitatively similar (except for film coating or capsule shell excipients). This  
183 is defined in Table 1. Examples of acceptable differences in excipients are shown in Annex II.

184



185  
186  
187

**Table 1: Allowable differences in excipients for drug products containing BCS Class III drugs.**

Excipient class	Percent of the amount of excipient in the reference	Percent difference relative to core weight (w/w)
<b>Excipients which may affect absorption:</b>	<b>± 10.0%</b>	
<b>All excipients:</b>		
<b>Filler</b>	± 10.0%	
<b>Disintegrant</b>		
<b>Starch</b>	± 6.0%	
<b>Other</b>	± 2.0%	
<b>Binder</b>	± 1.0%	
<b>Lubricant</b>		
<b>Ca or Mg stearate</b>	± 0.5%	
<b>Other</b>	± 2.0%	
<b>Glidant</b>		
<b>Talc</b>	± 2.0%	
<b>Other</b>	± 0.2%	
<b>Total % change permitted:</b>		<b>10.0%</b>

188 Note: Core does not include tablet film coat or capsule shell

189

190 For FDC formulations containing only BCS Class I drugs, criteria regarding excipients should  
191 follow that for a BCS Class I drug. For FDC formulations containing only BCS Class III  
192 drugs, or BCS Class I and BCS Class III drugs, criteria regarding excipients should follow  
193 that for a BCS Class III drug. This is applicable to FDCs which are pharmaceutically  
194 equivalent.

195

196 **3.2. In vitro Dissolution**

197 When applying the BCS based biowaiver approach, comparative *in vitro* dissolution tests  
198 should be conducted using one batch representative of the proposed commercial  
199 manufacturing process for the test product relative to one batch of the reference product. The  
200 test product should originate from a batch of at least 1/10 of production scale or 100,000 units,  
201 whichever is greater, unless otherwise justified. During a (clinical) development phase,

202 smaller batch sizes may be acceptable, if justified. The comparative *in vitro* dissolution  
 203 experiments should use compendial apparatuses and validated analytical methods.

204

205 The following conditions should be employed in the comparative dissolution studies to  
 206 characterize the dissolution profile of the product:

- 207 • Apparatus: paddle or basket
- 208 • Volume of dissolution medium: 900 ml or less (it is recommended to use the volume  
 209 selected for the QC test)
- 210 • Temperature of the dissolution medium:  $37 \pm 1^\circ\text{C}$
- 211 • Agitation: paddle apparatus - 50 rpm  
 212 basket apparatus - 100 rpm
- 213 • At least 12 units of reference and test product should be used for each dissolution  
 214 profile determination.
- 215 • Three buffers: pH 1.2, pH 4.5, and pH 6.8. Pharmacopoeial buffers should be  
 216 employed. Additional investigation may be required at the pH of minimum solubility  
 217 (if different from the buffers above). Purified water may be used as an additional  
 218 dissolution medium in some regions.
- 219 • Organic solvents are not acceptable and no surfactants should be added.
- 220 • Samples should be filtered during collection
- 221 • For gelatin capsules or tablets with gelatin coatings where cross-linking has been  
 222 demonstrated, the use of enzymes may be acceptable, if appropriately justified.

223

224 When high variability or coning is observed in the paddle apparatus at 50 rpm, the use of the  
 225 basket apparatus at 100 rpm is recommended. Additionally, use of sinkers in the paddle  
 226 apparatus to overcome issues such as coning may be considered with justification.

227

228 To qualify for a BCS-based biowaiver for BCS Class I drug substances both the test product  
 229 and reference product should display either very rapid ( $\geq 85$  for the mean percent dissolved in  
 230  $\leq 15$  minutes) or rapid ( $\geq 85$  for the mean percent dissolved in  $\leq 30$  minutes) and similar *in vitro*  
 231 dissolution characteristics under all of the defined conditions. In cases where one product has  
 232 rapid dissolution and the other has very rapid dissolution, statistical similarity of the profiles  
 233 should be demonstrated as below.

234

235 For the comparison of dissolution profiles, where applicable, the similarity factor  $f_2$  should be  
 236 estimated by using the following formula:

237

$$238 \quad f_2 = 50 \cdot \log \{ [1 + (1/n) \sum_{t=1}^n (R_t - T_t)^2]^{-0.5} \cdot 100 \}$$

239

240 In this equation  $f_2$  is the similarity factor,  $n$  is the number of time points,  $R(t)$  is the mean  
 241 percent reference drug dissolved at time  $t$  after initiation of the study;  $T(t)$  is the mean percent  
 242 test drug dissolved at time  $t$  after initiation of the study.

243

244 The evaluation of the similarity factor is based on the following conditions:

- 245 • A minimum of three time points (zero excluded)
- 246 • The time points should be the same for the two products
- 247 • Mean of twelve individual values for every time point for each product.
- 248 • Not more than one mean value of  $\geq 85\%$  dissolved for any of the products.
- 249 • To allow the use of mean data, the coefficient of variation should not be more than  
 250 20% at early time-points (up to 10 minutes), and should not be more than 10% at  
 251 other time points.

252

253 Two dissolution profiles are considered similar when the  $f_2$  value is  $\geq 50$ . When both test and  
 254 reference products demonstrate that  $\geq 85\%$  of the label amount of the drug is dissolved in 15  
 255 minutes, comparison with an  $f_2$  test is unnecessary and the dissolution profiles are considered  
 256 similar. In case the coefficient of variation is too high,  $f_2$  calculation is considered not  
 257 accurate and reliable and a conclusion on similarity in dissolution cannot be made.

258

259 To qualify for a BCS-based biowaiver for BCS Class III drug substances both the test product  
 260 and reference product should display very rapid ( $\geq 85$  for the mean percent dissolved in  $\leq 15$   
 261 minutes) *in vitro* dissolution characteristics under the defined conditions.

262

263 For FDC formulations, dissolution profiles should meet the criteria for all drug substances in  
 264 the FDC to be considered. For FDC formulations containing only BCS I drugs, criteria  
 265 regarding dissolution should follow that for a BCS Class I drug. For FDC formulations  
 266 containing only BCS Class III drugs, criteria regarding dissolution should follow that for a  
 267 BCS Class III drug. For FDCs containing both BCS Class I and BCS Class III drugs the  
 268 dissolution criteria for the applicable BCS class for each component should be applied.

269

270 For products with more than one strength the BCS approach should be applied for each  
 271 strength, i.e., it is expected that test and reference product dissolution profiles are compared at  
 272 each strength.

273

#### 274 4. DOCUMENTATION

275 The applicant should provide complete information on the critical quality attributes of the test  
 276 drug substance and drug product and as much information as possible for the reference  
 277 product, including, but not limited to: polymorphic form and enantiomeric purity; and any

278 information on bioavailability or bioequivalence problems with the drug substance or drug  
279 product, including literature surveys and applicant derived studies. All study protocols  
280 including standards, quality assurance and testing methods should be appropriately detailed  
281 and validated according to current regulatory guidance's and policies.

282 The reporting format should include tabular and graphical presentations showing individual  
283 and mean results and summary statistics. The tabular presentation should include standard  
284 deviation and coefficient of variation.

285 The report should include all excipients, their qualitative and, if possible, quantitative  
286 differences between the test and reference products.

287 A full description of the analytical methods employed, including validation, e.g. method  
288 linearity, accuracy and precision, should be provided. A detailed description of all test  
289 methods and media, including test and reference batch information [unit dose (milligram  
290 and %), batch number, manufacturing date and batch size where known, expiry date, and any  
291 comments] should also be provided. The dissolution report should include a thorough  
292 description of experimental settings and analytical methods, including information on the  
293 dissolution conditions such as apparatus, de-aeration, filtration during sampling, volume, etc.

294 In addition, complete information with full description of the methods applied should be  
295 provided for the Caco-2 cell permeability assay method, if applicable (see Annex I).

296

## 297 **5. GLOSSARY**

298 AUC: Area under the concentration versus time curve

299 BCS: Biopharmaceutics Classification System

300  $C_{max}$ : Maximum concentration

301 FDC: Fixed-dose combination

302 Pharmaceutically equivalent: Medicinal products containing the same amount of the same  
303 active substance(s) in the same dosage forms.

304 pKa: Acid dissociation constant at logarithmic scale

305 rpm: rotation per minute

306

**307 ANNEX I: Caco-2 CELL PERMEABILITY ASSAY METHOD CONSIDERATIONS**

308 Permeability assays employing cultured Caco-2 epithelial cell monolayers derived from a  
309 human colon adenocarcinoma cell line are widely used to estimate intestinal drug absorption  
310 in humans. Caco-2 cells undergo spontaneous morphological and biochemical enterocytic  
311 differentiation, and express cell polarity with an apical brush border, tight intercellular  
312 junctions, and several active transporters as in the small intestine. Due to a potential for low  
313 or absent expression of efflux (e.g., P-gp, BCRP, MRP2) and uptake (e.g., PepT1, OATP2B1,  
314 MCT1) transporters, the use of Caco-2 cell assays in support of high permeability for BCS  
315 classification is limited to passively transported drugs (for definition see Assay  
316 Considerations).

317

**318 Method validation**

319 The suitability of the Caco-2 cell assays for BCS permeability determination should be  
320 demonstrated by establishing a rank-order relationship between experimental permeability  
321 values and the extent of drug absorption in human subjects using zero, low (<50%), moderate  
322 (50 – 84%), and high ( $\geq 85\%$ ) permeability model drugs. A sufficient number of model drugs  
323 are recommended for the validation to characterize the full permeability range (a minimum 5  
324 for each permeability category, high, moderate and low is recommended; examples are  
325 provided in Table 1). Further, a sufficient number (minimum of 3) of cell assay replicates  
326 should be employed to provide a reliable estimate of drug permeability. The established  
327 relationship should permit differentiation between low, moderate and high permeability drugs.

328

329 Caco-2 cell monolayer integrity should be confirmed by comparing transepithelial electrical  
330 resistance (TEER) measures and/or other suitable indicators, prior to and after an experiment.  
331 In addition, cell monolayer integrity should be demonstrated by means of compounds with  
332 proven zero permeability.

333

334 Reporting of the method validation should include a list of the selected model drugs along  
335 with data on extent of absorption in humans (mean, standard deviation, coefficient of  
336 variation) used to establish suitability of the method, permeability values for each model drug  
337 (mean, standard deviation, coefficient of variation), permeability class of each model drug,  
338 and a plot of the extent of absorption as a function of permeability (mean  $\pm$  standard deviation  
339 or 95 percent confidence interval) with identification of the high permeability class boundary  
340 and selected high permeability internal standard used to classify the test drug substance.

341

342 In addition, a description of the study method, drug concentrations in the donor fluid,  
343 description of the analytical method, equation used to calculate permeability, and where

344 appropriate, information on efflux potential, e.g., bidirectional transport data should be  
345 provided for a known substrate.

346

### 347 **Assay considerations**

348 As noted above, the use of Caco-2 cell assays in support of BCS permeability determination is  
349 limited to passively transported drugs. A passive transport mechanism can be inferred when  
350 the pharmacokinetics of the drug (assessed as AUC and  $C_{max}$  parameters) are dose  
351 proportional over the relevant clinical dose range. Alternatively, the absence of an active  
352 transport mechanism may be verified using a suitable assay system that expresses known  
353 efflux transporters, e.g., by demonstrating independence of measured *in vitro* permeability on  
354 initial drug concentration, e.g., 0.01, 0.1, and 1 times the highest strength dissolved in 250 ml,  
355 or on transport direction (efflux ratio, i.e., ratio of apparent permeability ( $P_{app}$ ) between the  
356 basolateral-to-apical and apical-to-basolateral directions  $<2$  for the selected drug  
357 concentrations).

$$358 \text{Efflux ratio} = P_{appBL \rightarrow AP} / P_{appAP \rightarrow BL}.$$

359 Functional expression of efflux transporters should be verified by using bidirectional transport  
360 studies demonstrating asymmetric permeability of selected efflux transporter substrates, e.g.,  
361 digoxin, vinblastine, rhodamine 123, at non-saturating concentrations.

362

363 The test drug substance concentrations used in the permeability studies should be justified. A  
364 validated Caco-2 method used for drug permeability determinations should employ conditions  
365 established during the validation, and include a moderate and a high permeability model drug  
366 as internal standards to demonstrate consistency of the method, i.e., included in the donor  
367 fluid along with the test drug. The choice of internal standards should be based on  
368 compatibility with the test drug, i.e., they should not exhibit any significant physical,  
369 chemical, or permeation interactions. The permeability of the internal standards may be  
370 determined following evaluation of the test drug in the same monolayers or monolayers in the  
371 same plate, when it is not feasible to include internal standards in the same cell culture well as  
372 the test drug permeability evaluation. The permeability values of the internal standards should  
373 be consistent between different tests, including those conducted during method validation.  
374 Acceptance criteria should be set for the internal standards and model efflux drug. Mean drug  
375 and internal standards recovery at the end of the test should be assessed. For recoveries  $<80\%$ ,  
376 a mass balance evaluation should be conducted including measurement of the residual amount  
377 of drug in the membrane.

378

379 Evaluation of the test drug permeability for BCS classification may be facilitated by selection  
380 of a high permeability internal standard with permeability in close proximity to the  
381 moderate/high permeability class boundary. The test drug is considered highly permeable

382 when its permeability value is equal to or greater than that of the selected internal standard  
 383 with high permeability.

384

385 Information to support high permeability of a test drug substance (mean, standard deviation,  
 386 coefficient of variation) should include permeability data on the test drug substance, the  
 387 internal standards, *in vitro* gastrointestinal stability information, and data supporting passive  
 388 transport mechanism.

389

390 **Table 2. Examples of model drugs for permeability assay method validation**

Group	Drug
High Permeability ( $f_a \geq 85$ percent)	Antipyrine Caffeine Ketoprofen Naproxen Theophylline Metoprolol Propranolol Carbamazepine Phenytoin Disopyramide Minoxidil
Moderate Permeability ( $f_a = 50$ -84 percent)	Chlorpheniramine Creatinine Terbutaline Hydrochlorothiazide Enalapril Furosemide Metformin Amiloride Atenolol Ranitidine
Low Permeability ( $f_a < 50$ percent)	Famotidine Nadolol Sulpiride Lisinopril Acyclovir Foscarnet Mannitol

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Group	Drug
	Chlorothiazide Polyethylene glycol 400 Enalaprilat
Zero Permeability	FITC-Dextran Polyethylene glycol 4000 Lucifer yellow Inulin Lactulose
Efflux Substrates	Digoxin Paclitaxel Quinidine Vinblastine

391

392

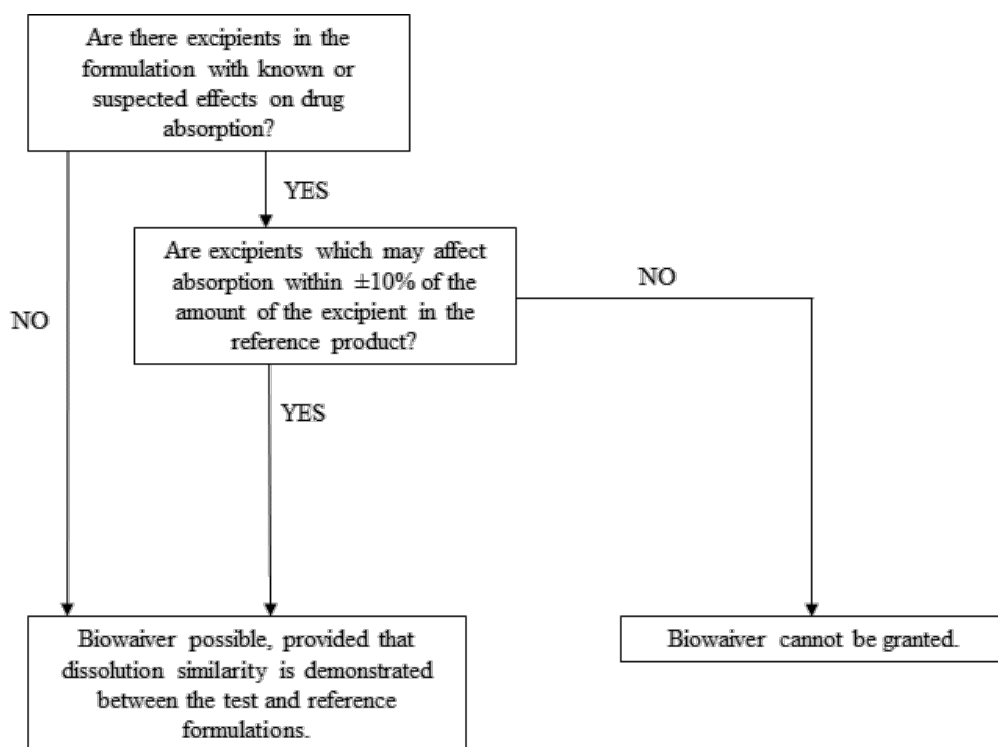
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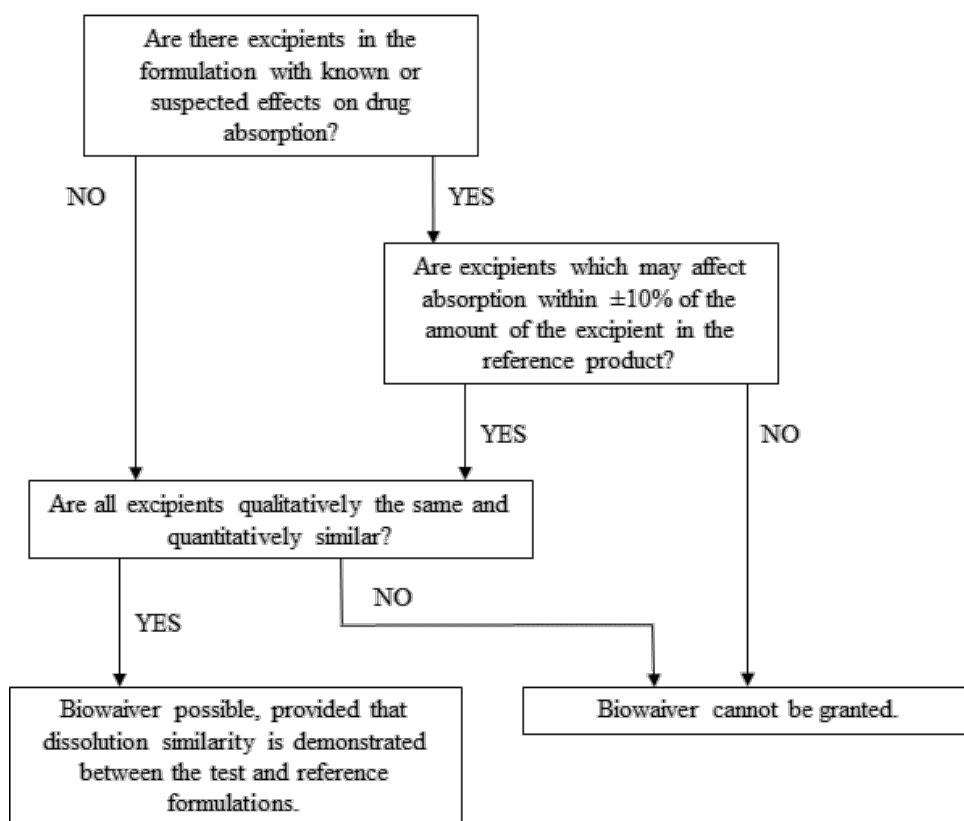
395 ANNEX II: FURTHER INFORMATION ON THE ASSESSMENT OF EXCIPIENT  
 396 DIFFERENCES

397 Figure 1. BCS Class I Drug Substances



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400 Figure 2. BCS Class III Drug Substances



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403 **EXAMPLES OF ACCEPTABLE DIFFERENCES IN EXCIPIENTS**404 **Example 1: BCS Class I Biowaiver**

405 The amount of sorbitol (an excipient that affects absorption) in the test formulation is different  
406 from the reference formulation. The permitted range is 45 mg to 55 mg of sorbitol based on  
407 the amount in the reference formulation (50 mg  $\pm$  10.0%).

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<b>Component</b>	<b>Amount (mg) reference</b>	<b>Amount (mg) test</b>
Drug substance	100	100
Microcrystalline cellulose (filler)	100	95
HPMC (binder)	10	10
Talc	5	5
Sorbitol (filler)	50	55
Total	265	265

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412 **Example 2: BCS Class III Biowaiver**

413 The test formulation is qualitatively the same as the reference formulation. The amount of  
 414 sorbitol (an excipient that affects absorption) in the test formulation is different from the  
 415 reference formulation. The permitted range is 9 mg to 11 mg of sorbitol based on the amount  
 416 in the reference formulation (10 mg  $\pm$  10.0%). For the other excipients the differences were  
 417 within the criteria provided in Table 1.

Component	Reference Product		Test Product		Absolute percent difference relative to core weights
	Composition (mg)	Proportion relative to core weight (%w/w)	Composition (mg)	Proportion relative to core weight (%w/w)	
Drug substance	100	49.3%	100	46.5%	--
Lactose monohydrate (filler)	85	41.9%	97	45.1%	3.2%
Croscarmellose sodium (disintegrant)	6	3.0%	7	3.3%	0.3%
Magnesium stearate	2	1.0%	2	0.9%	0.1%
Sorbitol (filler)	10	4.9%	9	4.2%	0.7%
Total	203	100%	215	100%	
<b>Total change:</b>					<b>4.3%</b>

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