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4 **Guideline on equivalence studies for the demonstration of**
5 **therapeutic equivalence for products that are locally**
6 **applied, locally acting in the gastrointestinal tract as**
7 **addendum to the guideline on the clinical requirements**
8 **for locally applied, locally acting products containing**
9 **known constituents.**
10 Draft

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12 This guideline builds upon the existing 'The Note for guidance on the clinical requirements for locally
13 applied, locally acting products containing known constituents' (CPMP/EWP/239/95).

14 Comments should be provided using this [template](#). The completed comments form should be sent to
PKWPsecretariat@ema.europa.eu

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23 **Table of contents**

24 **Executive summary 3**

25 **1. Introduction (background) 3**

26 **2. Scope..... 3**

27 **3. Legal basis and relevant guidelines 4**

28 **4. Main guideline text 4**

29 4.1. Types of locally acting, locally applied gastrointestinal products4

30 4.2. General requirements for demonstration of equivalence 5

31 4.3. Equivalence requirements in specific situations6

32 4.3.1. Products acting locally in the mouth and/or throat 6

33 4.3.2. Products acting locally in the stomach8

34 4.3.3. Products acting locally in the intestine.....9

35 4.3.4. Products acting locally in the rectum 11

36 4.4. Requirements for additional strengths..... 12

37

38

39 **Executive summary**

40 This guideline defines the requirements that need to be fulfilled to waive clinical trials with clinical or
41 pharmacodynamic endpoints in the demonstration of therapeutic equivalence for locally applied, locally
42 acting gastrointestinal products. It also defines the *in vivo* bioequivalence studies and *in vitro*
43 equivalence tests that are necessary.

44 **1. Introduction (background)**

45 This guideline refers to medicinal products that are applied locally and intended to exert their effect
46 locally within the gastrointestinal (GI) tract. The assumption is that systemic action, if any, would be
47 considered as an undesired effect.

48 The Note for guidance on the clinical requirements for locally applied, locally acting products containing
49 known constituents (CPMP/EWP/239/95) provides general recommendations on the clinical
50 requirements for medicinal products with known active substances. According to this guideline, in order
51 to demonstrate therapeutic equivalence, clinical trials are in principle considered necessary, but other
52 models may be used or developed. Depending on the situation, human pharmacodynamic (PD) studies,
53 local availability studies or, where appropriate, even animal or *in vitro* studies may be considered,
54 provided that the respective methods/models are adequately qualified.

55 During recent years the assessment of locally applied and locally acting products has evolved. It has
56 been shown that alternative models (including *in vitro* and *in vivo* methods) may have a higher
57 sensitivity than traditional clinical and PD endpoints to detect possible differences between medicinal
58 products containing the same active substance. Also based on the experience with some of these
59 alternative models, either individually or in combination, it is possible to compare directly or indirectly
60 concentrations at the site of action. Therefore, therapeutic equivalence of locally applied, locally acting
61 GI products could be demonstrated using these alternative models, provided they have been proven to
62 be able to accurately reflect *in vivo* drug release and availability at the site of action. Furthermore, it
63 has been recognised that the similarity of drug release and availability at the site of action are the
64 major factors determining similar clinical responses for locally applied, locally acting medicinal products
65 containing the same active substance. Therefore, in those cases where the *in vitro* tests or
66 pharmacokinetic (PK) studies reflect *in vivo* drug release and availability at the site of action, clinical
67 trials could be waived.

68 The type of studies required to demonstrate equivalence should be decided taking into account the
69 different characteristics of the different types of dosage forms acting in the GI tract.

70 **2. Scope**

71 This guideline focuses on the choice of *in vitro* equivalence tests and PK bioequivalence studies as
72 suitable models for the demonstration of therapeutic equivalence for locally applied, locally acting GI
73 products with immediate or modified release containing the same chemical entity. The choice has to be
74 fully justified.

75 The design of PD studies and therapeutic equivalence clinical trials depends on the respective
76 therapeutic field. The corresponding guidelines should be taken into consideration and these types of
77 studies and trials are outside of the scope of this guideline.

78 The scope is limited to chemical entities. Recommendations for biologicals can be found in guidelines
79 on similar biological medicinal products.

80 **3. Legal basis and relevant guidelines**

81 This guideline applies mainly to Marketing Authorisation Applications for human medicinal products
82 submitted in accordance with the Directive 2001/83/EC as amended, under Art. 10(3) (hybrid
83 applications). It may also be applicable to Marketing Authorisation Applications for human medicinal
84 products submitted under Art. 8(3) (full applications), Art.10b (fixed combination), Art.10a (well-
85 established use applications) of the same Directive, and for extension and variation applications in
86 accordance with Commission Regulations (EC) No 1084/2003 and 1085/2003.

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

- 89 – Clinical requirements for locally applied, locally acting products containing known constituents
90 (CPMP/EWP/239/95).
- 91 – Pharmacokinetic studies in man (Eudralex, Volume 3, 3CC3a).
- 92 – Guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/ Corr **).
- 93 – Guideline on the pharmacokinetic and clinical evaluation of modified release dosage forms
94 (EMA/CPMP/EWP/280/96 Corr1).
- 95 – Guideline on bioanalytical method validation (EMA/CHMP/EWP/192217/2009).
- 96 – Requirements for clinical documentation for orally inhaled products (OIP) including the
97 requirements for demonstration of therapeutic equivalence between two inhaled products for
98 use in the treatment of Asthma and Chronic Obstructive Pulmonary Disease (COPD)
99 (CPMP/EWP/4151/00 rev 1).

100 The guideline should also be read in conjunction with relevant guidelines on pharmaceutical quality.

101 The test products used in the equivalence study must be prepared in accordance with GMP regulations
102 including Eudralex volume 4.

103 Equivalence trials conducted in the EU/EEA have to be carried out in accordance with Directive
104 2001/20/EC. Trials conducted outside of the Union and intended for use in a Marketing Authorisation
105 Application in the EU/EEA have to be conducted to the standards set out in Annex I of the community
106 code, Directive 2001/83/EC as amended.

107 Companies may apply for CHMP Scientific Advice for specific queries and in particular, in case of
108 narrow therapeutic index drugs.

109 **4. Main guideline text**

110 ***4.1. Types of locally acting, locally applied gastrointestinal products***

111 For the purpose of this guideline locally applied, locally acting products can be classified:

- 112 1. According to the site of action, e.g.:
 - 113 a) In the mouth and/or throat (e.g. local analgesics or anaesthetics).
 - 114 b) In the stomach (e.g. antacids)
 - 115 c) In the intestine (e.g. anti-inflammatory and anti-motility agents)
 - 116 a. Drugs that have a pharmacological, intracellular target

- 117 b. Drugs that have a target in the lumen or at the membrane surface
- 118 2. According to their mechanism of action, e.g.:
- 119 a) Chelating compounds of the GI fluids/milieu or binding to targets in the lumen (e.g. phosphate
120 or bile).
- 121 b) Adding endogenous compounds (e.g. pancreatin)
- 122 c) Changing physicochemical conditions (e.g. antacids)
- 123 d) Exerting a physical effect (e.g. osmotic / bulking agents)
- 124 e) Binding to receptors or targets in the intestinal mucosa (e.g. loperamide, corticosteroids, 5-
125 ASA)
- 126 3. According to their biopharmaceutical and PK properties:
- 127 a) Absorbable drugs
- 128 b) Non-absorbable drugs
- 129 4. According to their pharmaceutical form:
- 130 a) Immediate release formulations
- 131 a) solutions
- 132 b) non-solutions
- 133 b) Modified release formulations
- 134 5. According to the state of the drug in the dosage form:
- 135 a) A solute in solution (e.g. solution, gel)
- 136 b) A solute in solid pharmaceutical form (e.g. lozenge)
- 137 c) A solid in liquid (e.g. cream, ointment, suspension)
- 138 d) A solid in solid pharmaceutical form (e.g. tablet)

139 **4.2. General requirements for demonstration of equivalence**

140 General assessment of equivalence applies to locally applied, locally acting GI products to be approved
141 either as a generic/hybrid or as a reformulated product, i.e. therapeutic equivalence should ensure
142 equivalence in terms of efficacy and safety. In principle, clinical trials with clinical endpoints are
143 considered necessary to demonstrate therapeutic equivalence, but alternative approaches may be used
144 provided they have a sound justification and appropriate qualification. *In vitro* test(s)/model(s) should
145 be validated (e.g. in line with ICH Q2 (R1)) before use and they should reflect the particular (unique)
146 characteristics of the pharmaceutical form for which equivalence is being claimed. A comprehensive
147 and sound justification for the chosen *in vitro* test(s)/model(s) should be provided.

148 In order to claim that an alternative model is reflecting *in vivo* drug release and availability at the site
149 of action, the applicant should justify the relevance for the therapeutic effect and the higher or similar
150 sensitivity based on their own experimental data or literature data.

151 The sensitivity of the PK endpoints/*in vitro* methods following administration of different doses of the
152 reference product should be well established, e.g. based on literature data or on a pilot study.

153 Alternatively, it could be addressed as part of the study designed to demonstrate bioequivalence with
154 the use of additional groups with different doses of the reference formulation to ensure that the dose
155 used for the bioequivalence comparison is sensitive and sufficiently discriminative to detect potential
156 differences between formulations.

157 In general, the following hierarchy from simpler to more complex bodies of data required to
158 demonstrate equivalence should be followed: pharmaceutical quality data alone, pharmaceutical
159 quality data + *in vitro* model, pharmaceutical quality data + *in vivo* PK data and pharmaceutical quality
160 data + *in vitro* model + *in vivo* PK data. The approach taken should be fully justified. In order to use
161 these alternative methods, it should be taken into account that product quality (as critical quality
162 attributes) is an essential part, as is the method of administration. For instance, the requirements for
163 demonstration of *in vivo* PK bioequivalence may be waived under a specific set of circumstances when,
164 for example, the test and reference products are a solution, the products possess similar critical quality
165 attributes and are qualitatively and quantitatively similar, and the method of administration is the
166 same. In order to address systemic safety, even if clinical equivalence is demonstrated with a PD
167 approach, data on the extent of absorption may be required, or their lack should be justified. If this
168 requires a bioequivalence study, then the 90% confidence interval range for the ratio test/reference of
169 the PK parameters of interest should not exceed the upper limit of the acceptance range as described
170 in the guideline on the investigation of bioequivalence.

171 In certain cases a PK bioequivalence study may also be indicative of therapeutic equivalence (e.g.
172 drugs that are mainly absorbed from the site of action). In these cases the usual acceptance criteria
173 for bioequivalence should be applied.

174 Local safety and tolerability should be addressed. Ideally, the same excipients and amounts used in the
175 reference products should be selected for the test products. Differences in inactive ingredients,
176 whether known or unknown, may require additional comparative tolerability studies.

177 The list of *in vitro* models included in this guideline is not exhaustive and other may be submitted, if
178 justified.

179 **4.3. Equivalence requirements in specific situations**

180 **4.3.1. Products acting locally in the mouth and/or throat**

181 A large variety of dosage forms can be administered for local action in the mouth and/or the throat,
182 e.g. solutions, suspensions, elixirs, powders, tablets, lozenges, troches, gels, ointments, buccal sprays,
183 etc. The general principles outlined in this guideline are applicable to all these products. Further
184 detailed guidance can be obtained in other guidelines that may be more applicable to certain dosage
185 forms (e.g. gels and ointments as topical products and buccal sprays as similar to nasal sprays).

186 Solutions

187 If the test product is a solution at time of administration and contains an active substance in the same
188 concentration as an approved solution, studies supporting equivalent efficacy and safety may be
189 waived. However, excipient composition should be critically reviewed since excipients may affect local
190 residence time (e.g. palatability, surface tension, viscosity, etc.), *in vivo* solubility (e.g. co-solvents) or
191 *in vivo* stability of the active substance. An equivalence study should be conducted, unless the
192 differences in the amounts of these excipients can be adequately justified by reference to other data
193 and taking account of Appendix II of the guideline on the investigation of bioequivalence.

194 In those cases where the test product is an oral solution that is intended to be equivalent to another

195 immediate release oral dosage form, equivalence studies are required.

196 Non-solutions

197 If the test product is not a solution (e.g. solid dosage form), demonstration of equivalent availability at
198 the site of action by means of C_{max} and AUC of saliva concentration-time profiles can be considered as
199 a surrogate of therapeutic equivalence. Local availability studies are feasible because direct sampling in
200 the site of action is often possible (i.e. saliva). Therefore, a comparative local *in vivo* availability study
201 with sampling of saliva is a possible approach despite its inherent variability. In accordance with the
202 standard accepted methods of assessment of bioequivalence the maximum concentration (C_{max}), the
203 area under the curve (AUC) and the time to C_{max} (T_{max}) should be compared. Equivalence may be
204 concluded if the 90 % confidence interval for each parameter lies within the acceptance range of 80.00
205 to 125.00%.

206 In those cases where it is justified that the drug is released from the dosage form as a solution due to
207 its high solubility and not as a suspension, it is possible to assess indirectly the local availability or the
208 amount released by assessing the amount remaining in the dosage form at selected time points. In
209 addition, in those cases where it is justified that the drug is dispersed homogeneously in the dosage
210 form, the amount remaining in the dosage form can be estimated by weight. Equivalence may be
211 concluded as for *in vitro* dissolution tests as outlined in Appendix 1 of the guideline on the investigation
212 of bioequivalence. Dissolution profile similarity should be assessed based on an acceptance range of
213 $\pm 10\%$ in accordance to the acceptance range (≥ 50) of the f_2 similarity factor.

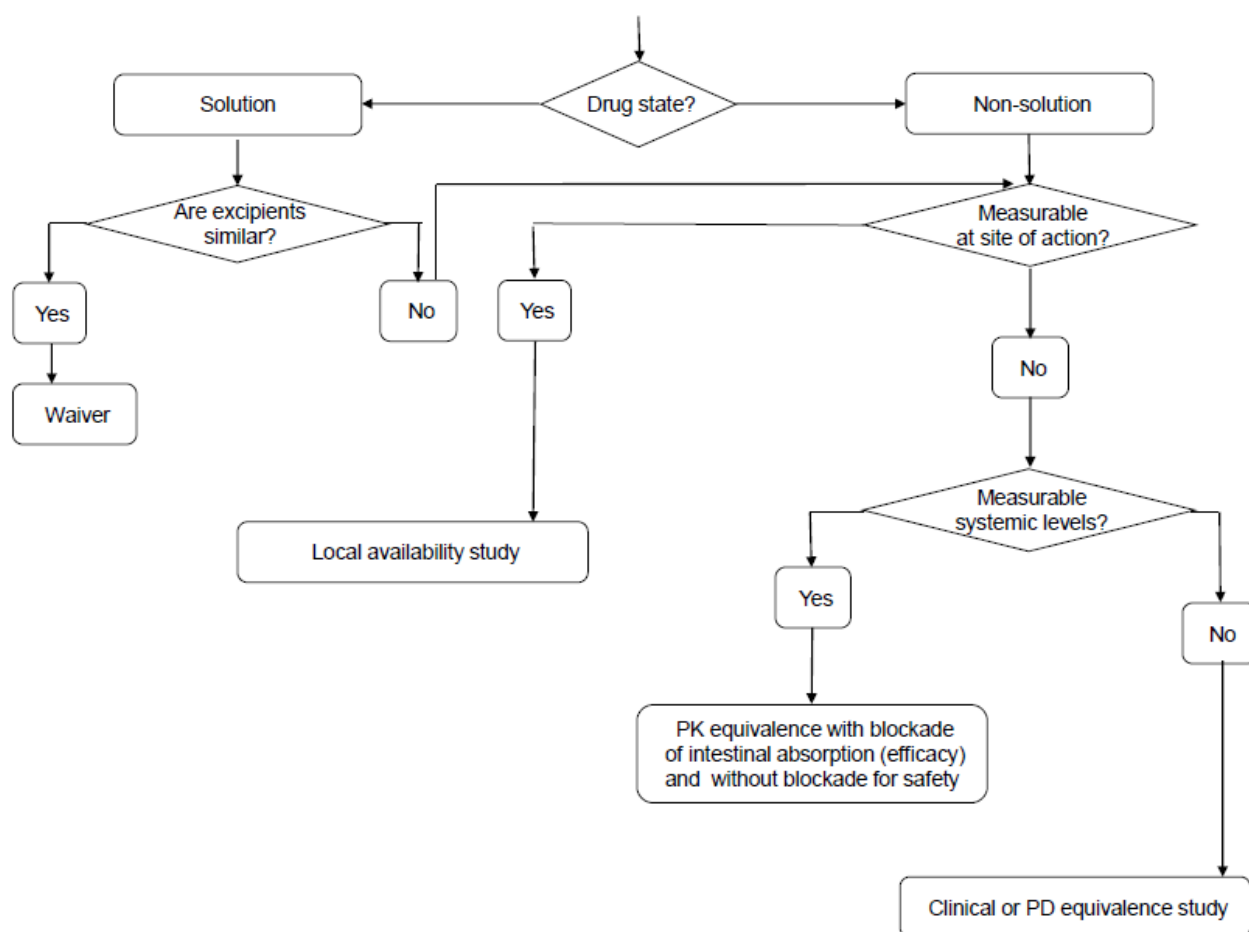
214 In those cases where concentrations are not measured directly at the site of action (e.g.
215 concentrations in saliva), it is necessary to review critically the excipient composition to ensure that
216 differences in excipients do not affect local residence time (e.g. palatability, surface tension, viscosity,
217 etc.), *in vivo* solubility (e.g. co-solvents) and/or *in vivo* stability of the active substance.

218 Plasma levels cannot in many cases be used directly as a surrogate of therapeutic equivalence because
219 it is necessary to distinguish between plasma levels obtained from local absorption at the site of action
220 in the upper digestive tract (e.g. mouth) and those due to absorption in the other parts of the GI tract
221 (e.g. the intestine). Only if absorption in other parts of the GI tract can be disregarded (e.g. by use of
222 activated charcoal), can the plasma levels be considered as reflective of the concentrations at the site
223 of action and would be acceptable. However, it should be ensured that activated charcoal is able to
224 block absorption from the intestine to negligible levels with respect to the systemic levels obtained by
225 absorption through the site of action.

226 For the time being, usual comparative *in vitro* dissolution methodology is not considered indicative of
227 *in vivo* dissolution in the mouth and/or throat.

228

229 **Decision tree for products acting locally in the mouth and/or throat**



230

231 **4.3.2. Products acting locally in the stomach**

232 Solutions

233 See Section 4.3.1. In addition, particular consideration should be given to excipients that may affect
 234 gastric emptying, absorption (e.g. pH), *in vivo* solubility (e.g. co-solvents) or *in vivo* stability of the
 235 active substance (e.g. pH). In general, Appendix II of the guideline on the investigation of
 236 bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/Corr**) and the drug substance BCS classification
 237 should be considered.

238 Non-solutions

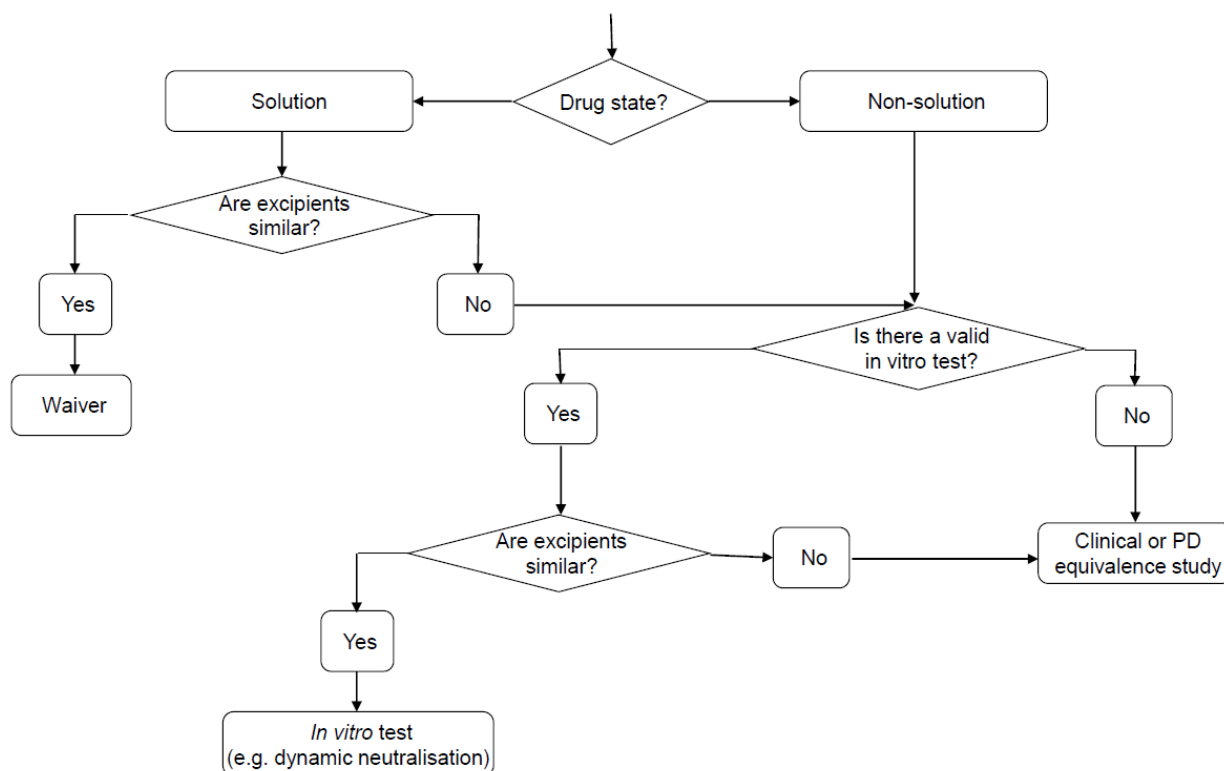
239 For antacids, *in vitro* methodology based on dynamic and static neutralizing tests is considered a
 240 surrogate methodology for therapeutic equivalence demonstration. It is anticipated that a number of
 241 different *in vitro* methods may be used to demonstrate similarity between the reference and test
 242 products. The Applicant should justify the selected dynamic and static neutralizing tests, along with the
 243 *in vitro* parameters, especially that the proposed end-points are clinically relevant. The *in vitro*
 244 methods should use widely accepted apparatus or, if a new method is used, should be suitably
 245 validated. *In vitro* similarity should be assessed with a $\pm 10\%$ acceptance range, unless otherwise
 246 justified (e.g. by assessing the difference between batches of the reference product).

247 In those cases where some degree of drug absorption and systemic bioavailability is observed, a
 248 bioequivalence study is required in order to address systemic safety. The systemic safety

249 bioequivalence study could be waived if a BCS biowaiver were applicable according to the criteria
 250 described in the guideline on the investigation of bioequivalence. Plasma levels cannot be used, in
 251 principle, as a surrogate of equivalence in efficacy for products acting locally in the stomach exclusively
 252 because the site of action in the stomach is different to the site of absorption in the intestine.
 253 Hypothetically, two products with a different release and dissolution, but within the gastric residence
 254 time, may exhibit a similar plasma concentration – time profile since the gastric emptying is the rate-
 255 limiting factor for absorption.

256
 257

Decision tree for products acting locally in the stomach



258

259 **4.3.3. Products acting locally in the intestine**

260 Solutions

261 See Section 4.3.2. In addition, particular consideration should be given to excipients that may affect GI
 262 transit (e.g. sorbitol, mannitol, etc.), absorption (e.g. surfactants or excipients that may affect
 263 transport proteins), *in vivo* solubility (e.g. co-solvents) or stability of the active substance.

264 Bioequivalence studies based on systemic exposure might be employed to compare test and reference
 265 products if some degree of systemic bioavailability is observed.

266 Non-solutions

267 For those products with a mechanism of action based on binding to components of the GI milieu
 268 through the whole intestine (e.g. cholestyramine, colestipol, calcium acetate, sevelamer) *in vitro*
 269 studies based on their binding capacity (e.g. *in-vitro* equilibrium and dynamic binding studies) are
 270 considered acceptable surrogates for the assessment of efficacy, as long as excipients are not critical
 271 and disintegration and dissolution profiles in the physiological pH range are similar. Similarly, for those

272 products with a bulking effect demonstration of similarity by means of *in vitro* tests (e.g. swelling,
273 viscosity) is considered as demonstration of therapeutic equivalence. *In vitro* similarity should be
274 assessed with a $\pm 10\%$ acceptance range, unless otherwise justified.

275 For immediate release products containing a highly soluble drug, a BCS biowaiver is possible based on
276 the criteria defined in Appendix III of the guideline on the investigation of bioequivalence. However, in
277 those drugs without systemic bioavailability (i.e. BCS class III) very rapid dissolution is not essential
278 and rapid dissolution may be acceptable.

279 If the conditions to apply for a BCS biowaiver are not fulfilled and some degree of systemic
280 bioavailability is observed, bioequivalence studies based on plasma levels usually in fed and fasting
281 state could be used as a surrogate of equivalence in efficacy and systemic safety because the site of
282 action is the site of absorption for drugs acting inside the gastrointestinal membrane. For drugs acting
283 in the lumen or the luminal side of the membrane bioequivalence studies based on plasma levels
284 usually in fasting and fed state could also be used as a surrogate of equivalence, if absorption is not
285 saturated (demonstrated e.g. by means of a dose-proportionality study). It can be assumed that when
286 the rate and extent of absorption of the drug is comparable, distribution of drug within the different
287 zones of the intestine is comparable. Bioequivalence studies in fasting and fed state are usually
288 required, even for products that are recommended to be taken in fasting state only, because locally
289 acting drugs generally have low permeability and remain in the intestinal lumen for a prolonged period.
290 Therefore, they are expected to interact with food during their intestinal transit.

291 For modified release products containing a drug being absorbed and showing systemic bioavailability,
292 bioequivalence studies based on plasma levels could also be used as a surrogate of equivalence in
293 efficacy and systemic safety because the systemic absorption occurs at the site of release. Partial AUC
294 assessment can help to distinguish absorption caused by an early release and absorption from release
295 at the site of action, if:

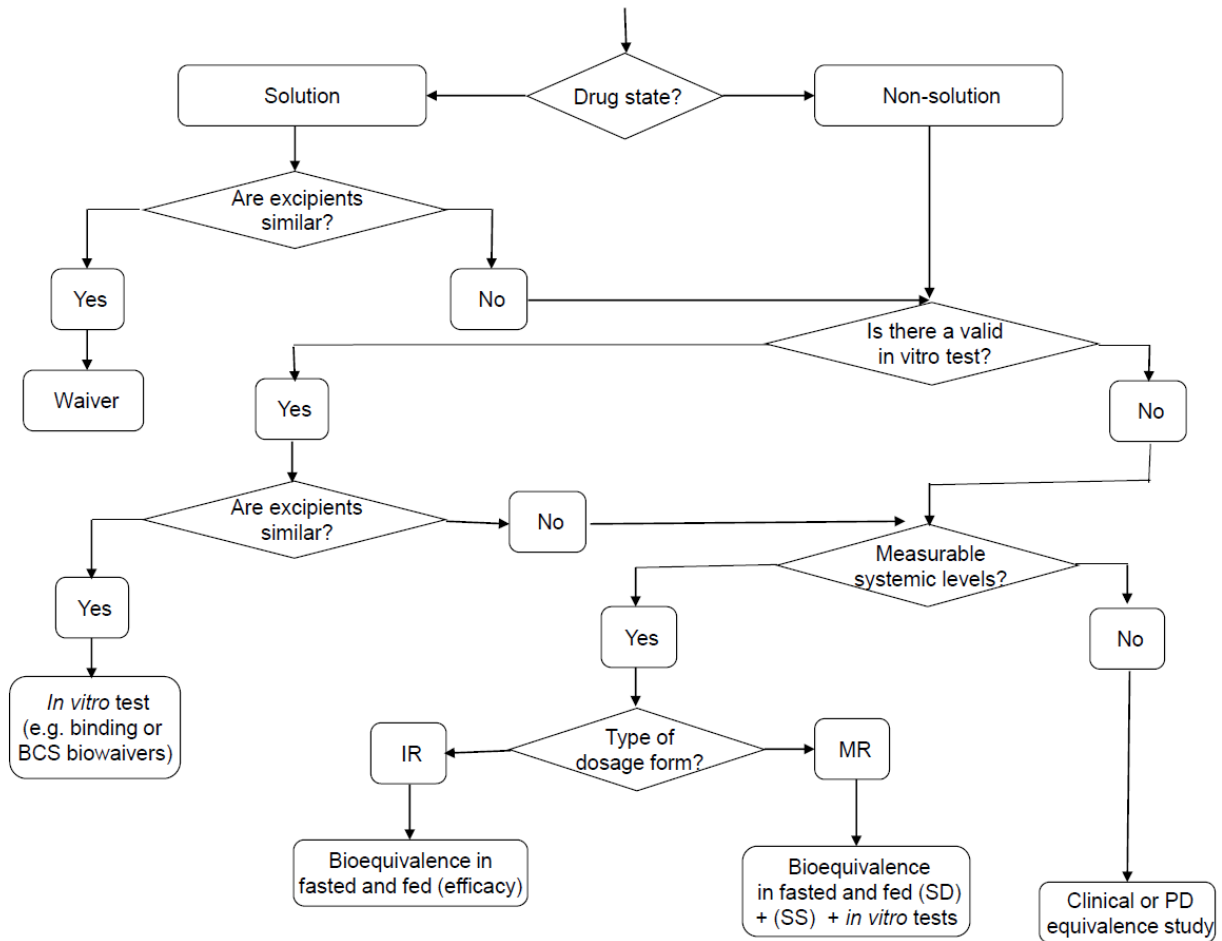
- 296 a) absorption is not saturated at the relevant dose (shown e.g. by means of a dose-proportionality
297 study for all the PK parameters of interest);
- 298 b) test and reference are the same dosage form;
- 299 c) test and reference exhibit similar *in vitro* dissolution profiles in a battery of state-of-the-art
300 experiments (not only in the QC media and buffers at pH 1.2, 4.5 and 6.8, but also *in vitro*
301 methods simulating intraluminal pH-conditions and residence times in the human GI tract, e.g.
302 tests in the reciprocating cylinder apparatus simulating "average" fasted subjects and also a range
303 of "patient-specific" patterns of pH-conditions and passage times with continuous and
304 discontinuous passage through the small intestine);
- 305 d) partial exposures and their corresponding absorption sites are well justified.

306 The requirements defined in the 'Guideline on the Pharmacokinetic and Clinical Evaluation of Modified
307 Release Dosage Forms' should be applied. Bioequivalence should be demonstrated in single dose
308 studies in fasting and fed state and, in case of prolonged release products with significant
309 accumulation, also in a multiple dose study. Partial AUCs (early and late partial AUCs as defined by
310 predefined, well justified cut-off points) should be used as primary PK endpoint in both types of single
311 dose studies, even in case of significant accumulation when a multiple dose study is required.

312

313

Decision tree for products acting locally in the intestine



314

4.3.4. Products acting locally in the rectum

316 A large variety of dosage forms can be administered for local action in the rectum, e.g. enemas in
317 solution or suspension, suppositories, gels, foams, etc. The general principles outlined in this guideline
318 are applicable to all these products. Further detailed guidance can be obtained in other guidelines that
319 may be more applicable to certain dosage forms (e.g. gels and foams as topical products).

320 Solutions

321 See section 4.3.1. In addition, particular consideration should be given to excipients that may affect
322 local tolerance, local residence time (e.g. surface tension, viscosity, etc.) *in vivo* solubility (e.g. co-
323 solvents) or *in vivo* stability of the active substance.

324 Non-solutions

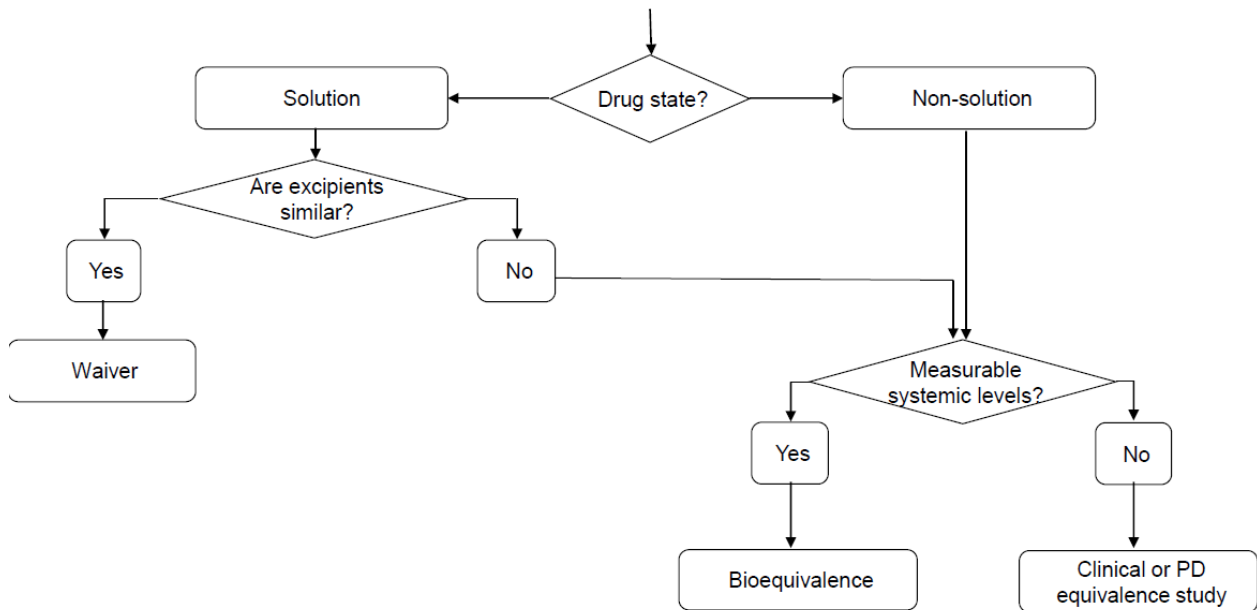
325 If the test product is not a solution (e.g. solid dosage form), demonstration of equivalent drug release
326 and availability at the site of action can be considered as surrogate of therapeutic equivalence.

327 In those cases where systemic bioavailability is observed, a PK bioequivalence study is required in
328 order to address systemic safety. In such cases plasma levels could also be used as a surrogate of
329 equivalence in efficacy for products acting locally in the rectum and the colon (e.g. enemas) if the drug
330 is absorbed from the site of action. Then, plasma levels reflect the drug release and availability close to
331 the site of action.

332 In any case, excipient composition should be critically reviewed since excipients may affect tolerability,
333 systemic absorption, local residence time (e.g. surface tension, viscosity, etc.), *in vivo* solubility (e.g.
334 co-solvents) or *in vivo* stability of the active substance. An equivalence study should be conducted,
335 unless the differences in the amounts of these excipients can be adequately justified by reference to
336 other data.

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339

Decision tree for products acting locally in the rectum



340

341 4.4. Requirements for additional strengths

342 The conditions that additional strengths have to fulfil in order to be waived depend on the type of
343 product (e.g. immediate release or modified release oral dosage forms). In principle these
344 requirements are similar to those for systemically acting products as described in the guideline on the
345 investigation of bioequivalence and the guideline on the pharmacokinetic and clinical evaluation of
346 modified release dosage forms.

347 In those cases where the reference product has different strengths and equivalence is shown by means
348 of *in vivo* studies (e.g. bioequivalence PK studies, i.e. pharmaceutical quality data + *in vivo* PK data),
349 bioequivalence should be shown with the most sensitive strength to detect possible differences.
350 Additional strengths may be waived from this *in vivo* demonstration ("additional strength biowaiver") if
351 certain conditions are met as described in the 'Guideline on the investigation of bioequivalence'.

352 In those cases where the reference product has different strengths and equivalence is shown by means
353 of pharmaceutical quality data (e.g. comparison of excipient composition) or pharmaceutical quality
354 data + *in vitro* data (e.g. comparative dissolution profiles in a BCS biowaiver for a class III containing
355 product), equivalence should be shown for each individual strength of the test product with respect to
356 the corresponding strength of the reference product, instead of using the "additional strength
357 biowaiver", i.e. a comparison between the different strengths of the test product.

358 In those cases where the reference product has different strengths and equivalence is shown by means
359 of pharmaceutical quality data + *in vitro* data + *in vivo* PK data (e.g. prolonged release solid oral

360 dosage form), additional strengths may be waived from the *in vivo* demonstration ("additional strength
361 biowaiver") if certain conditions are met as described above, but, in addition, equivalence to the
362 corresponding strength of the reference product in the pharmaceutical quality data and the *in vitro*
363 data should be shown for each individual strength.