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Guideline on equivalence studies for the demonstration of therapeutic equivalence for products that are locally applied, locally acting in the gastrointestinal tract as addendum to the guideline on the clinical requirements for locally applied, locally acting products containing known constituents.

Draft

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

Comments should be provided using this template. The completed comments form should be sent to PKWPsecretariat@ema.europa.eu

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30 Churchill Place● Canary Wharf ● London E14 5EU● United Kingdom
Telephone +44 (0)20 36606000 **Facsimile** +44 (0)20 3660 5555
Send a question via our website www.ema.europa.eu/contact

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Executive summary

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

1. Introduction (background)

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

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

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

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

2. Scope

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

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

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

3. Legal basis and relevant guidelines

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

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

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

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

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

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

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

4. Main guideline text

4.1. Types of locally acting, locally applied gastrointestinal products

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

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

b. Drugs that have a target in the lumen or at the membrane surface

2. According to their mechanism of action, e.g.:

a) Chelating compounds of the GI fluids/milieu or binding to targets in the lumen (e.g. phosphate or bile).

b) Adding endogenous compounds (e.g. pancreatin)

c) Changing physicochemical conditions (e.g. antacids)

d) Exerting a physical effect (e.g. osmotic / bulking agents)

e) Binding to receptors or targets in the intestinal mucosa (e.g. loperamide, corticosteroids, 5-ASA)

3. According to their biopharmaceutical and PK properties:

a) Absorbable drugs

b) Non-absorbable drugs

4. According to their pharmaceutical form:

a) Immediate release formulations

a) solutions

b) non-solutions

b) Modified release formulations

5. According to the state of the drug in the dosage form:

a) A solute in solution (e.g. solution, gel)

b) A solute in solid pharmaceutical form (e.g. lozenge)

c) A solid in liquid (e.g. cream, ointment, suspension)

d) A solid in solid pharmaceutical form (e.g. tablet)

4.2. General requirements for demonstration of equivalence

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

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

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

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

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

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

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

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

4.3. Equivalence requirements in specific situations

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

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

Solutions

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

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

immediate release oral dosage form, equivalence studies are required.

Non-solutions

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

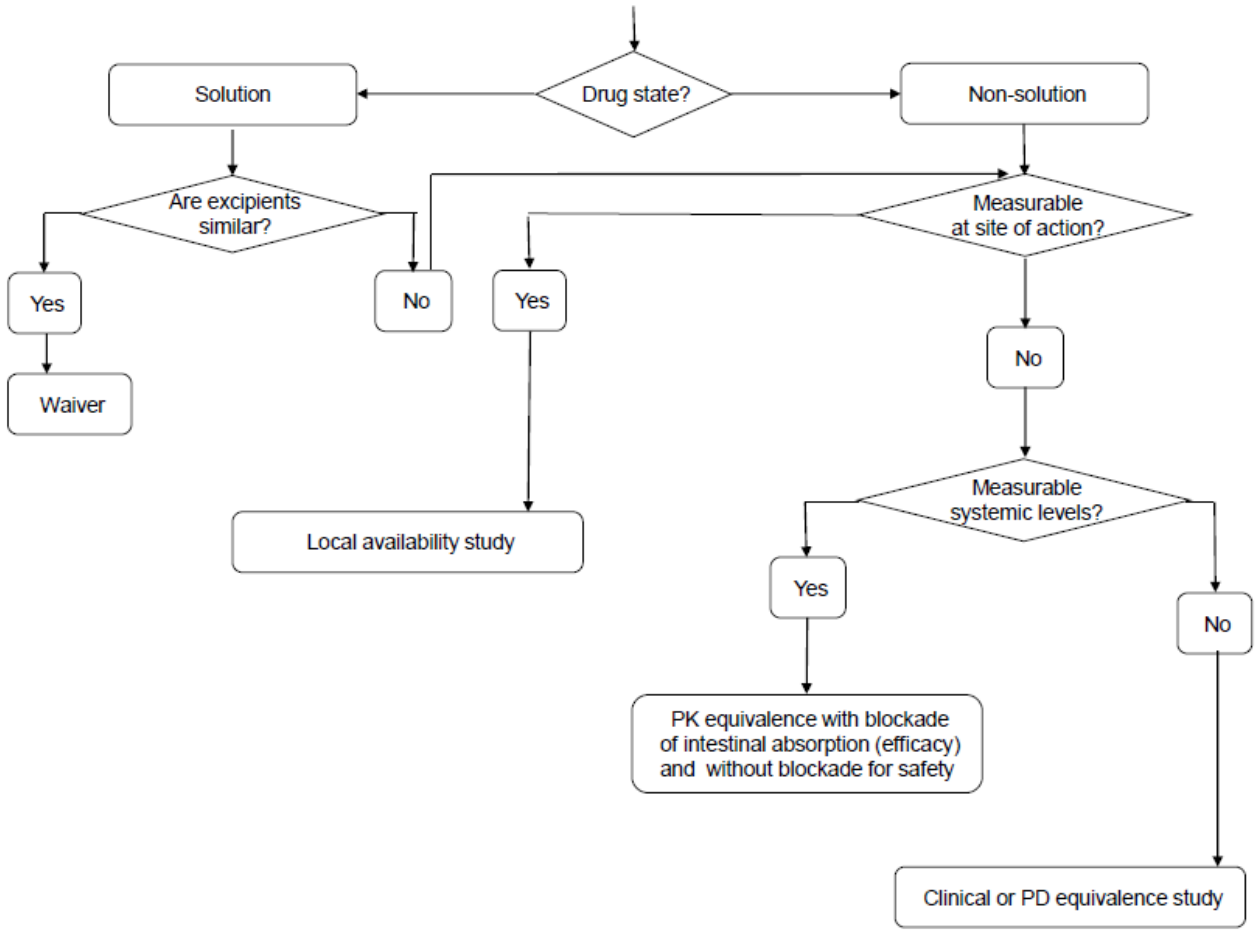
In those cases where it is justified that the drug is released from the dosage form as a solution due to its high solubility and not as a suspension, it is possible to assess indirectly the local availability or the amount released by assessing the amount remaining in the dosage form at selected time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

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

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

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

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



4.3.2. Products acting locally in the stomach

Solutions

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

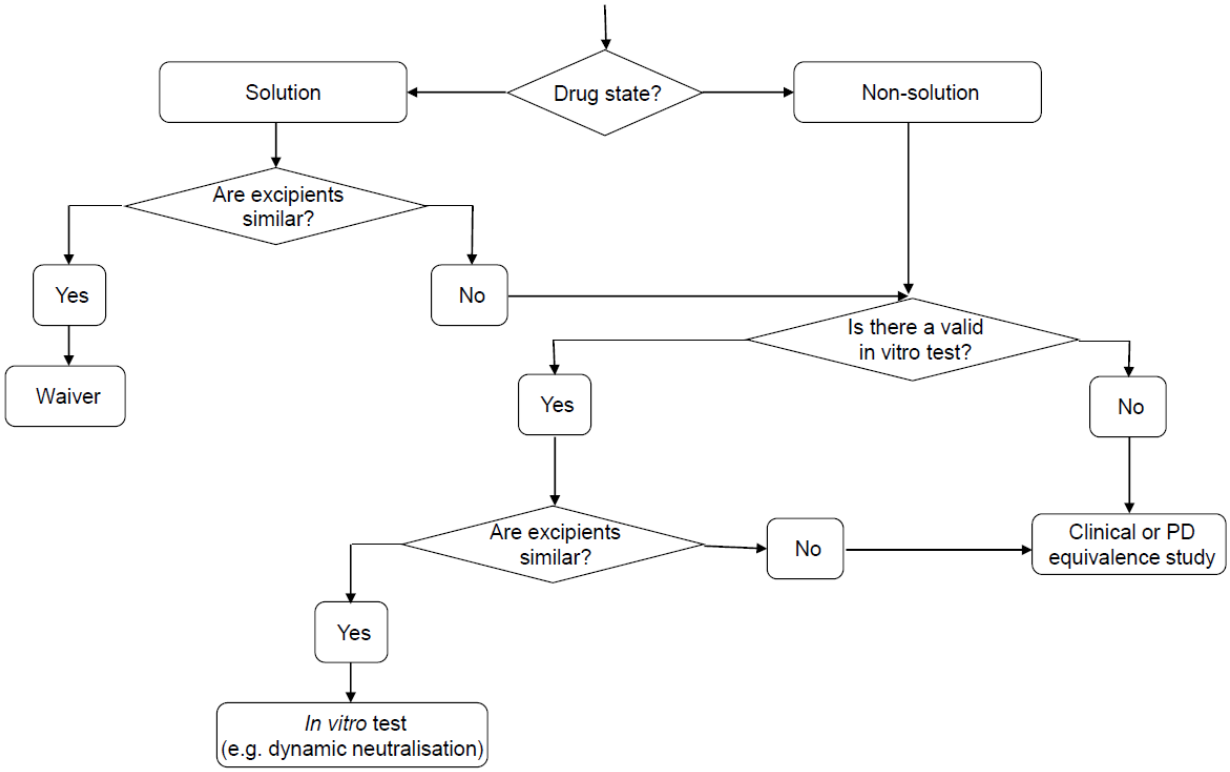
Non-solutions

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

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

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

Decision tree for products acting locally in the stomach



4.3.3. Products acting locally in the intestine

Solutions

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

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

Non-solutions

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

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

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

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

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

a) absorption is not saturated at the relevant dose (shown e.g. by means of a dose-proportionality study for all the PK parameters of interest);

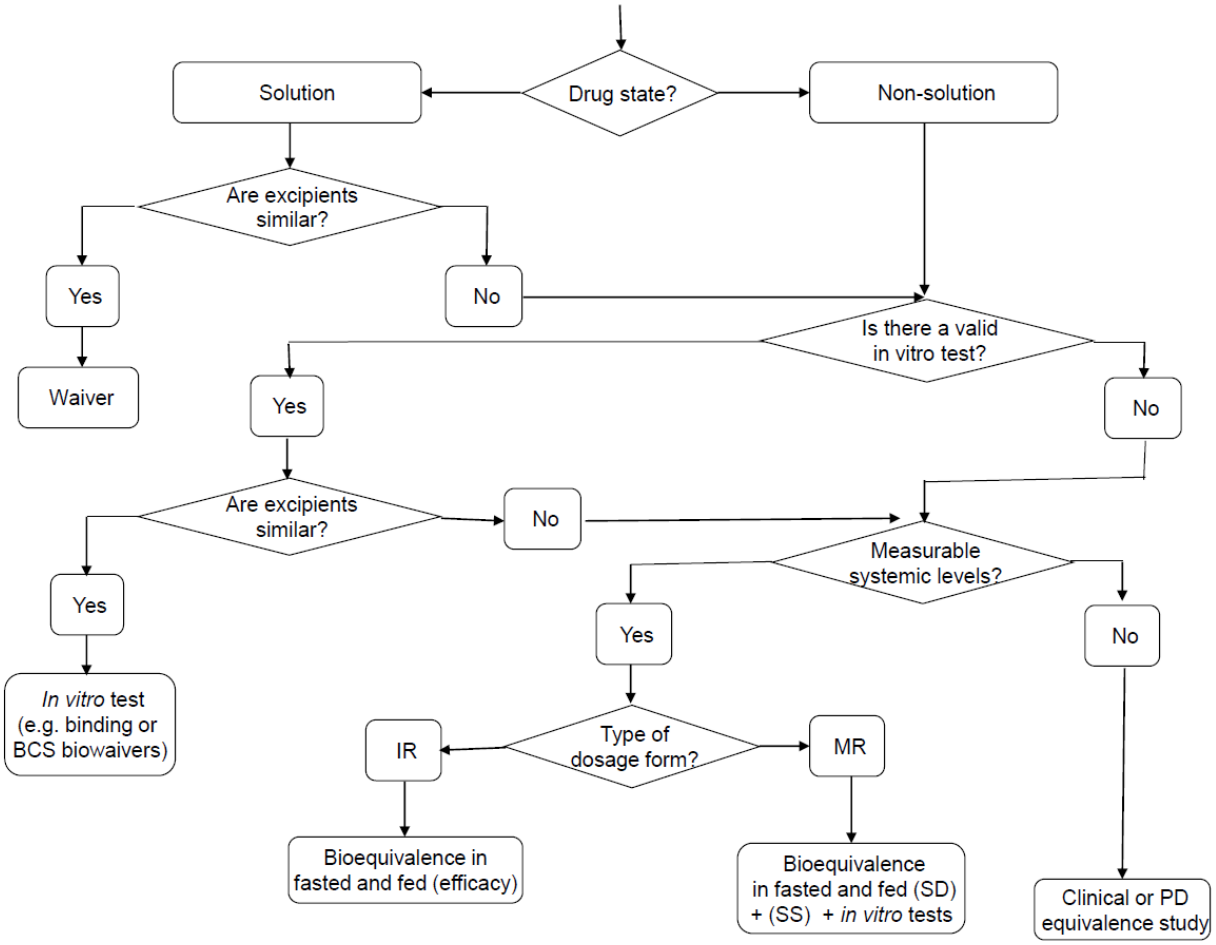
b) test and reference are the same dosage form;

c) test and reference exhibit similar *in vitro* dissolution profiles in a battery of state-of-the-art experiments (not only in the QC media and buffers at pH 1.2, 4.5 and 6.8, but also *in vitro* methods simulating intraluminal pH-conditions and residence times in the human GI tract, e.g. tests in the reciprocating cylinder apparatus simulating “average” fasted subjects and also a range of “patient-specific” patterns of pH-conditions and passage times with continuous and discontinuous passage through the small intestine);

d) partial exposures and their corresponding absorption sites are well justified.

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

Decision tree for products acting locally in the intestine



4.3.4. Products acting locally in the rectum

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

Solutions

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

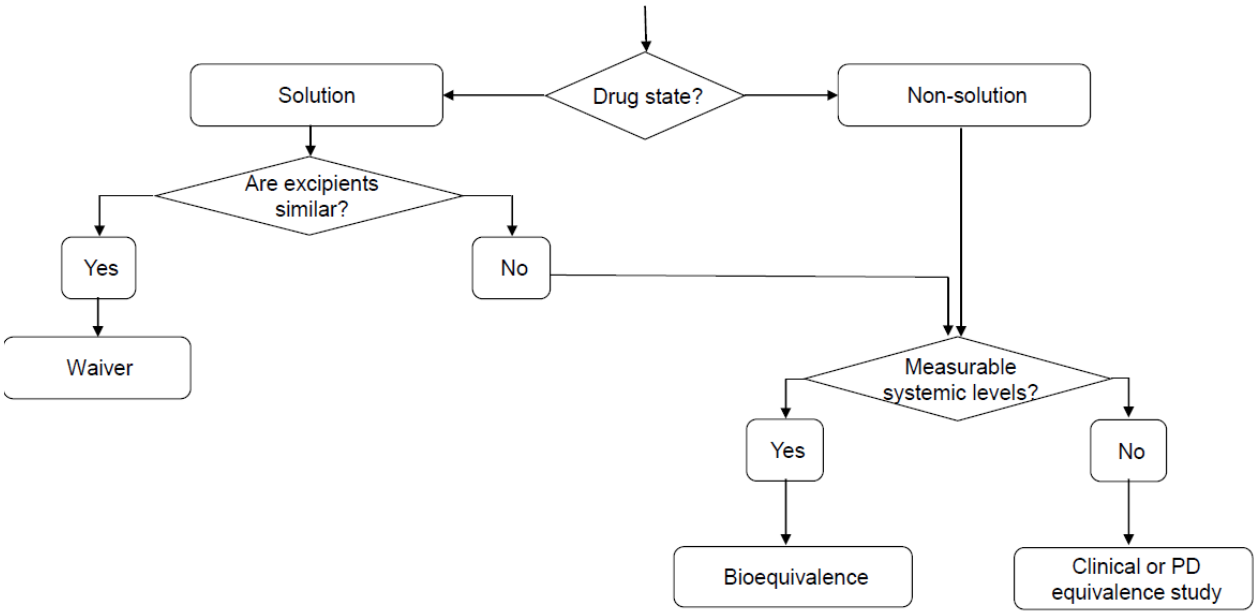
Non-solutions

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

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

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

Decision tree for products acting locally in the rectum



4.4. Requirements for additional strengths

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

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

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

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

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