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Guideline on equivalence studies for the demonstration of therapeutic equivalence for locally applied, locally acting products in the gastrointestinal tract[†]

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[†]This guideline is an addendum to the 'Note for guidance on the clinical requirements for locally applied, locally acting products containing known constituents' (CPMP/EWP/239/95).

*On page 4, section 3 EC regulations No. 1084/2003 and No. 1085/2003 have been replaced with (EC) No. 1234/2008.

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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

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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 at specific sites(s) in 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 substances. 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 specific sites 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 sites of action. Furthermore, it has been recognised that the similarity of drug release and availability at the sites 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 local availability at the sites of action, clinical trials could be waived.

The type of studies required to demonstrate equivalence should be determined by careful consideration of the product characteristics, mechanism of action, underlying disease being treated, validity of any in vitro or in vivo studies, the effects of any excipients and differences in dose delivery systems. The absence of clinical studies needs to be justified.

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 considering all relevant parameters having an impact on the in vivo release and local availability.

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 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 Regulation (EC) No. 1234/2008.

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

- Note for guidance on the 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 (EMA/CHMP/EWP/192217/2009);
- Reflection paper on statistical methodology for the comparative assessment of quality attributes in drug development. Draft (EMA/CHMP/138502/2017).

Many of the scientific principles described in the Guideline on 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) are applicable also in this area.

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.

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 sites of action, e.g.:
 - a) In the mouth and/or throat (e.g. local analgesics or anaesthetics);
 - b) In the oesophagus and/or stomach (e.g. antacids);
 - c) In the proximal or distal sections of the small intestine, in the colon or in the rectum (e.g. anti-inflammatory and anti-motility agents).

2. According to the location of the target:
 - a) Drugs that have a pharmacological, intracellular target;
 - b) Drugs that have a target in the lumen or at the membrane surface;
 - c) Drugs acting at multiple sites.
3. 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-aminosalicylic acid).
4. According to their biopharmaceutical and PK properties:
 - a) Absorbable drugs;
 - b) Non-absorbable drugs.
5. According to their pharmaceutical form:
 - a) Immediate release formulations
 - a. solutions
 - b. non-solutions
 - b) Modified release formulations.
6. According to the state of the drug substance in the dosage form, e.g.:
 - a) Dissolved in a liquid pharmaceutical form (e.g. solution);
 - b) Dissolved in a solid pharmaceutical form (e.g. lozenge);
 - c) Undissolved in liquid or semisolid (e.g. gel or suspension);
 - d) Undissolved 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 an abridged application 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, taking into consideration all parameters with relevant impact on in vivo transit, release and dissolution. *In vitro* test(s)/model(s) 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. The results of the test method should be robust, reproducible, sensitive and specific for the purpose for which it is intended.

In order to claim that an alternative model to clinical and PD endpoints is reflecting *in vivo* drug release and availability at the sites of action, the applicant should justify the relevance for the therapeutic effect and the higher or similar sensitivity to detect differences between formulations, in comparison with clinical and/or PD data, 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.

In general, the following hierarchy 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;
- pharmaceutical quality data + *in vitro* model + *in vivo* PK data.

The approach taken should be fully justified with regard to reflecting all relevant parameters in the *in vivo* situation in patients. 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 therapeutic equivalence is demonstrated with a PD approach, data on the extent of absorption may be required in line with the 'Guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/ Corr **)'.

In certain cases a PK bioequivalence study in humans may also be indicative of therapeutic equivalence (e.g. drugs that are mainly absorbed from the sites 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 others may be submitted, if justified by taking into account all parameters of the *in vivo* situation that are relevant for transit, release and dissolution.

Gamma scintigraphy and other imaging techniques are useful tools to capture *in vivo* disintegration and distribution along the GI tract. Therefore, they can be useful where there is no *in vivo* dissolution step. Imaging techniques in combination with PK sampling can also be used to show the GI distribution for the test formulation and to relate systemic exposure (partial areas) towards location in the GI tract.

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, 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 as topical products and buccal sprays as similar to nasal sprays).

Solutions

If the test product is a solution at the time of administration and contains an active substance in the same concentration as an approved reference 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. If there are differences in excipients, an equivalence study should be conducted, unless the differences in the qualitative and/or quantitative composition of these excipients can be adequately justified by reference to other data and taking into account of Appendix II of the 'Guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/ Corr **)'.

In those cases where the test product is an oral solution that is intended to be equivalent to another immediate release oral dosage form, therapeutic 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 sites of action by means of C_{max} and AUC of saliva concentration-time profiles can be considered as a surrogate of therapeutic equivalence. Local availability studies are feasible because direct sampling at the sites 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 (C_{max}), the area under the curve (AUC) and the time to C_{max} (T_{max}) should be compared. Equivalence may be concluded if the 90 % confidence interval of the ratio of geometric means 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 an *in vivo* study. 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 (CPMP/EWP/QWP/1401/98 Rev. 1/ Corr **)'.

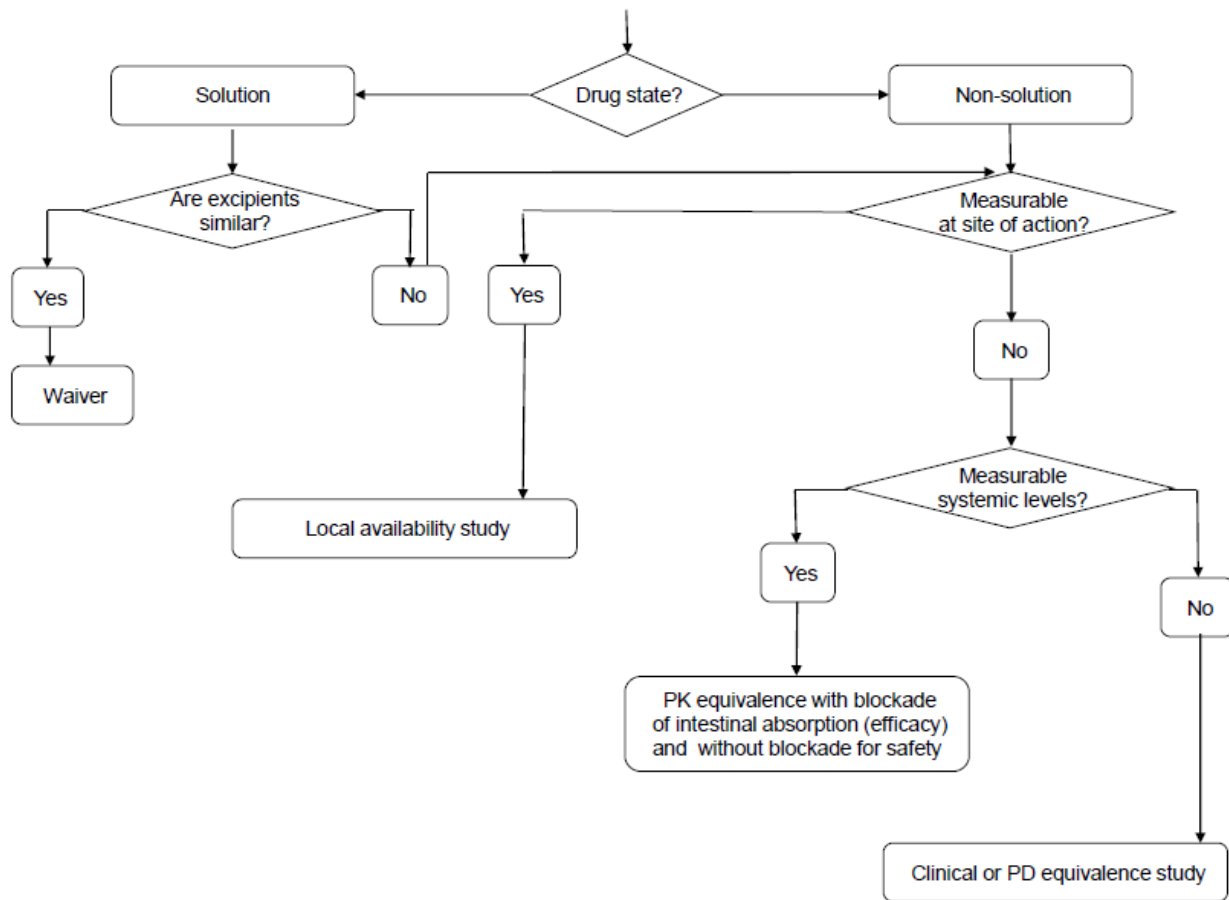
Dissolution profile similarity should be assessed based on an acceptance range of $\pm 10\%$ in accordance to the acceptance range (≥ 50) of the f_2 similarity factor.

In those cases where concentrations are not measured directly at the sites 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.

In many cases plasma levels cannot be used directly as a surrogate for therapeutic equivalence because it is necessary to distinguish between plasma levels obtained from local absorption at the sites of action in the upper digestive tract (e.g. mouth) and those due to absorption in 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 sites 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 sites of action. In these cases, a bioequivalence study without blockage of the gastrointestinal absorption is required in order to address systemic safety.

Currently, 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 oesophagus or the stomach

Solutions

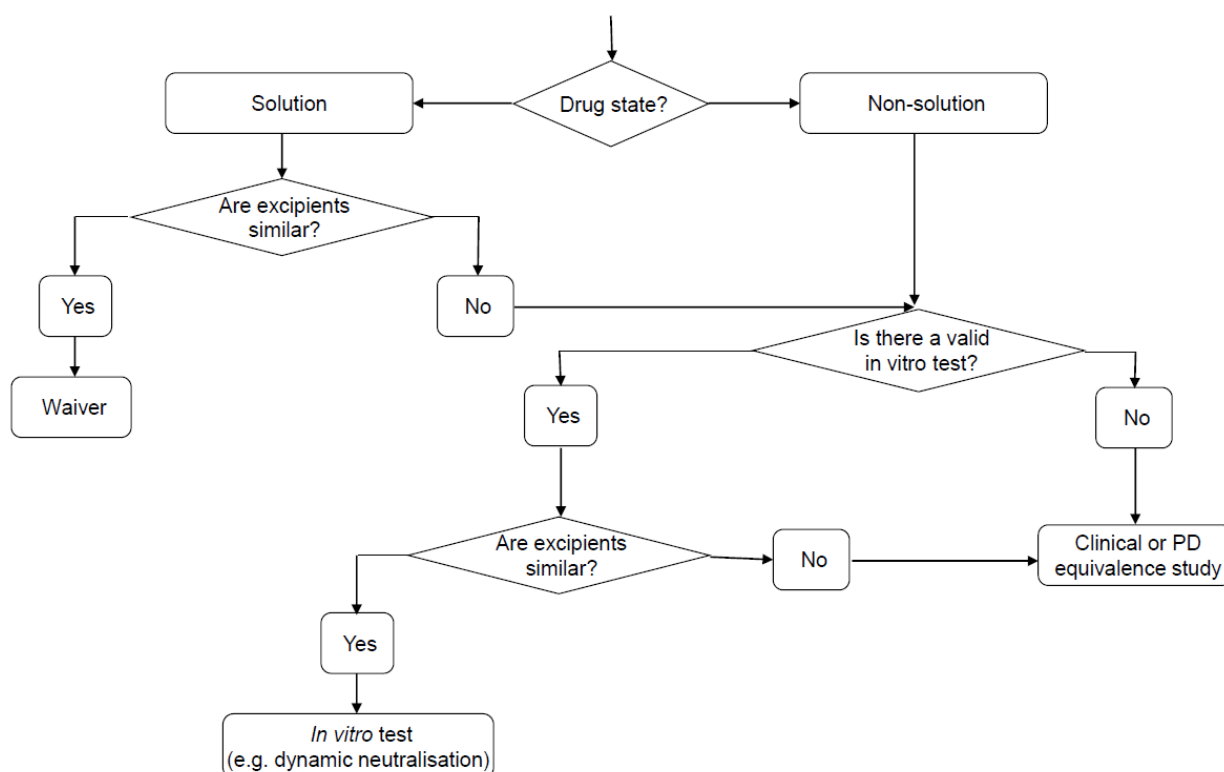
See Section 4.3.1. In addition, particular consideration should be given to the amount and type of excipients that may affect gastric emptying (for products acting in the stomach) or residence time in the oesophagus (e.g. viscosity, surface tension, etc.), absorption (e.g. pH), *in vivo* solubility (e.g. 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 $\pm 10\%$ acceptance range, unless otherwise justified.

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, unless otherwise justified. 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 (CPMP/EWP/QWP/1401/98 Rev. 1/Corr***)'. Plasma levels cannot be used, in principle, as a surrogate of equivalence in efficacy for products acting locally in the stomach exclusively because the sites of action in the stomach are reached first and are different to the sites of absorption in the intestine. Hypothetically, two products with a different release and dissolution and consequently different time of contact with the site of action, 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. Therefore, pharmacokinetic bioequivalence studies are not considered as a valid methodology to demonstrate therapeutic equivalence in this case.

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 the amount and type of 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 the efficacy and safety of 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 (as appropriate) 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 $\pm 10\%$ 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 (CPMP/EWP/QWP/1401/98 Rev. 1/Corr**)'. However, in case of drugs without systemic bioavailability (i.e. BCS class III) very rapid dissolution is not essential and similarly 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 sites of action is the site of absorption for drugs acting inside the GI 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). When the rate and extent of absorption of the drug is comparable, distribution of drug within the different zones of the intestine are expected to be 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.

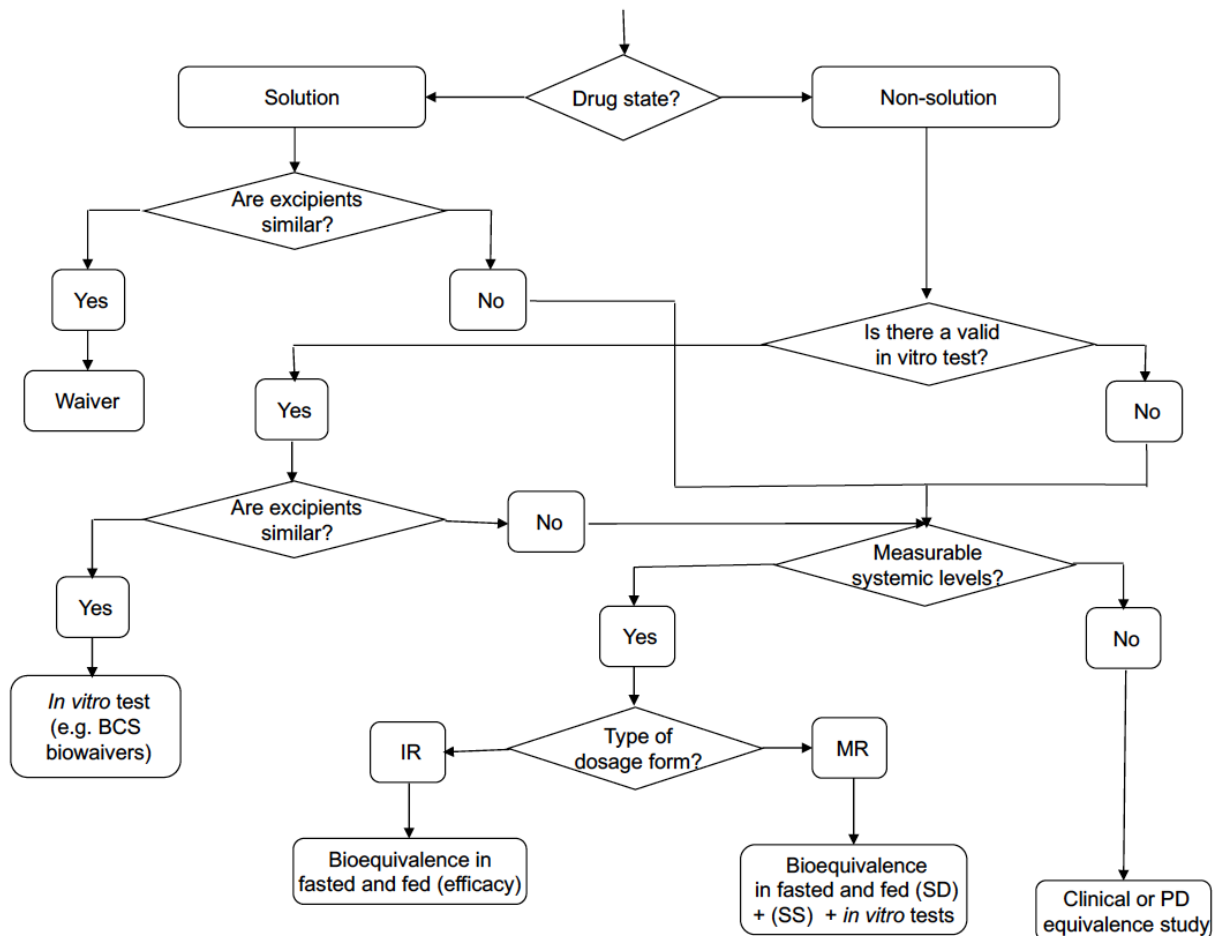
For modified release products containing a drug being absorbed and showing systemic bioavailability, bioequivalence studies based on plasma levels could also be used as a surrogate of equivalence in efficacy and systemic safety if the systemic absorption starts at a similar site and absorption kinetics are equivalent, because the systemic absorption occurs at the sites of release. Partial AUC assessment can help to distinguish absorption caused by an early release and absorption from release at the sites 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, ionic buffer strength, physiological buffer composition, mechanical stress 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 (EMA/CPMP/EWP/280/96 Corr1)' 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. Comparison of drug levels in faeces may be necessary in certain cases.

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 the amount and type of 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

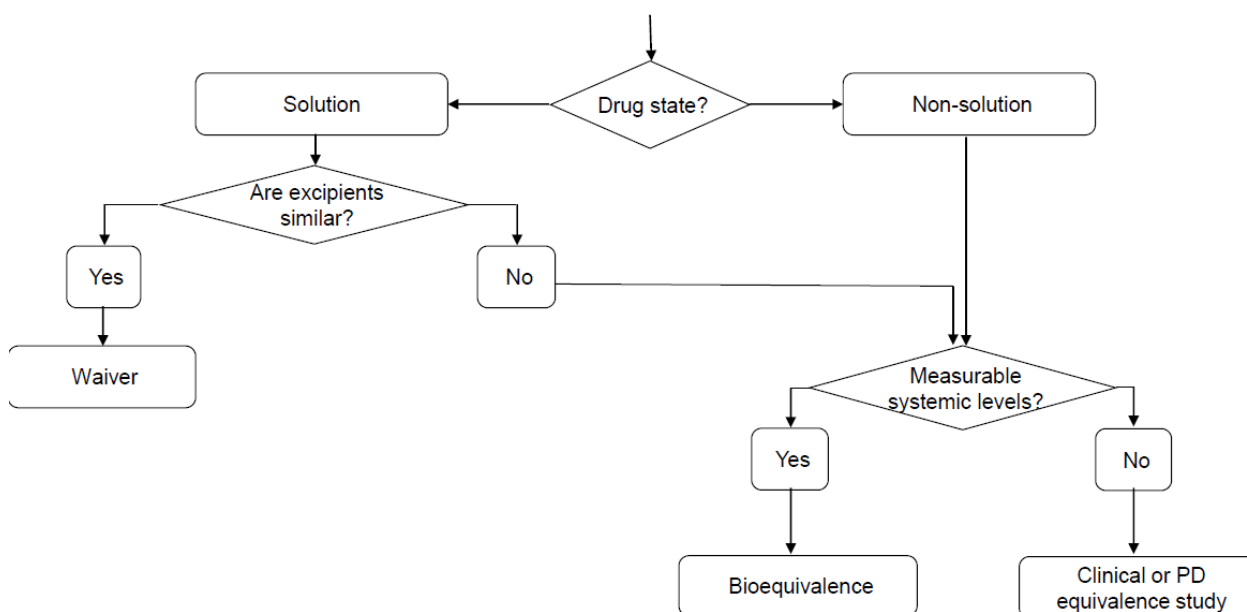
If the test product is not a solution (e.g. solid dosage form), demonstration of equivalent drug release and availability at the sites of action can be considered as surrogate of therapeutic equivalence.

In those cases where systemic bioavailability is observed, a PK bioequivalence study is required in order to address systemic safety, unless otherwise justified. 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 sites of action. Then, plasma levels reflect the drug release and availability close to the sites of action. Comparison of drug levels in faeces may be necessary.

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 (CPMP/EWP/QWP/1401/98 Rev. 1/Corr**)' and the Guideline on the pharmacokinetic and clinical evaluation of modified release dosage forms (EMA/CPMP/EWP/280/96 Corr1).

In those cases where the reference product has different strengths and equivalence is shown by means of *in vivo* studies (e.g. human 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 (CPMP/EWP/QWP/1401/98 Rev. 1/Corr**)' and the 'Guideline on the pharmacokinetic and clinical evaluation of modified release dosage forms (EMA/CPMP/EWP/280/96 Corr1)'.

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.