Prague

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BIOWAIVERS
LOCALLY APPLIED LOCALLY ACTING IN GIT

Training materials prepared by J-M. Cardot

INTRODUCTION

GENERAL SCHEME IN VIVO BIOWAIVER

Local Action on targetted receptors

Drug Dosage Form

Release of API

Dissolution of API

Dissolved API: solution of API

Absorption permeation

Efflux protein: pGp

Absorbed API

First pass

Liver, hepatic first pass effect

Entero hepatic recycling

Excretion ; renal, bile, etc.

Distribution

Systemic blood flow ; central compartment

Peripheric compartment if any

Elimination

Metabolisation

Therapeutic response

Action on targetted receptors

Formulated drug

kd

Solubilized drug

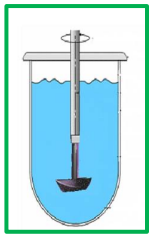
Kdd Or Kr

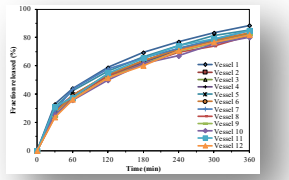
kid

Drug particle

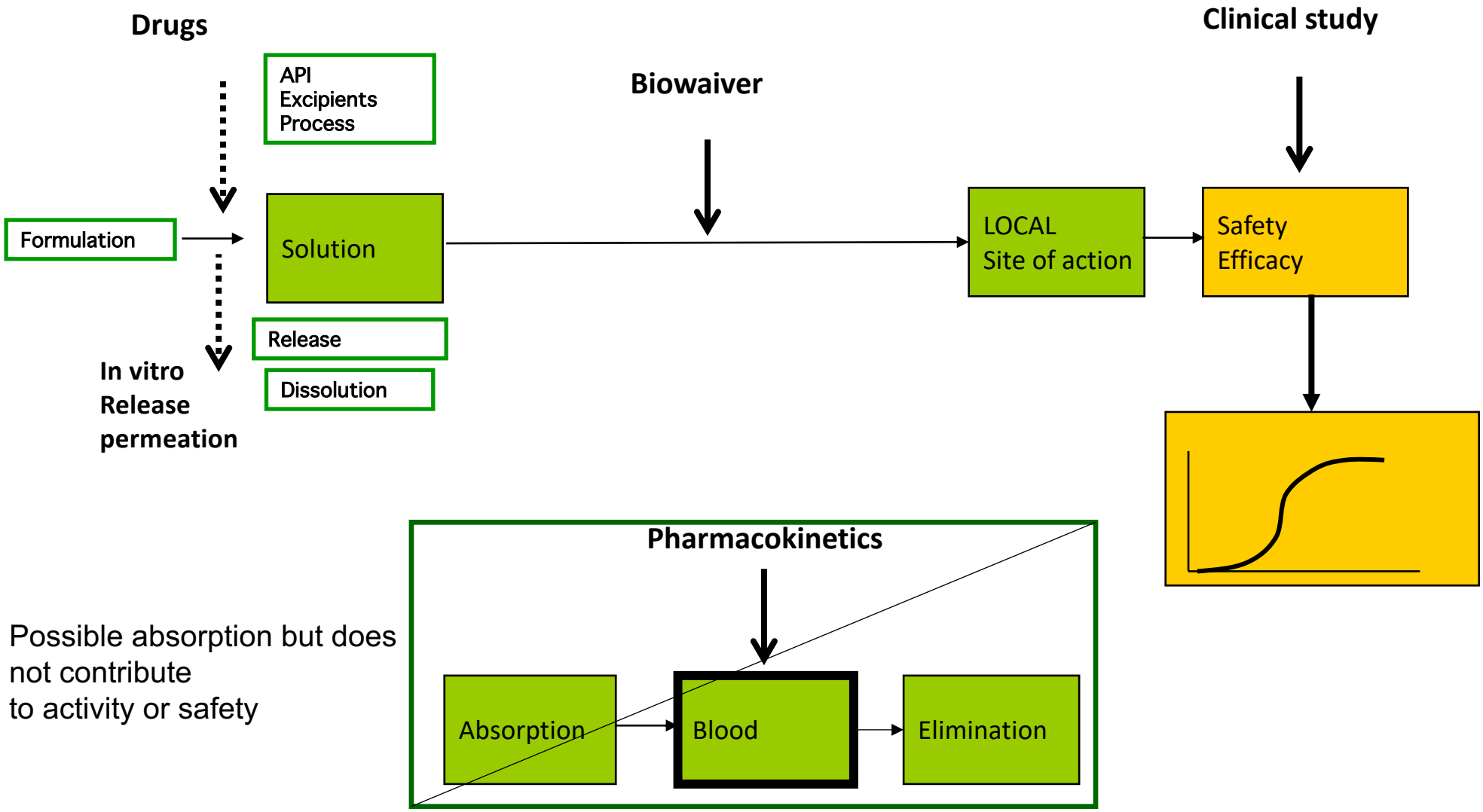
Or release

in vitro tests





LOACALLY ACTING



Possible absorption but does not contribute to activity or safety

DEFINITION OF BIOAVAILABILITY

"Bioavailability means the rate and extent to which the active substance or active moiety is absorbed from the pharmaceutical form and becomes available **at the site of action** … (in the general circulation)"

EMEA CPMP/EWP/QWP 1401/88 rev 1

DEFINITION OF BIOWAIVER

Waiver of evidence of in vivo bioavailability or bioequivalence
Reduce in vivo bioequivalence studies, i.e., it may represent a surrogate for in vivo bioequivalence.

In vivo bioequivalence studies may be exempted if the equivalence in the in vivo performance can be justified by satisfactory in vitro data.

Bioequivalence => same bioavailability.

FOR LOCALLY APPLIED LOCALLY ACTING

Demonstrate equivalence of quantity / nature of drug available at site of action!

REMARK PLASMA CONCENTRATION FOR LALA

Plasma concentration is more seen as marker of possible side effect when drug is dedicated to local action.

Either equivalence could be demonstrated via BE (LALA acting in GI Tract)
Or
BE study is used for safety: results T/R must be below the 125.00% limits.

OUTCOME

Biowaiver mainly described and defined for:

- Drug dissolved in single vehicle,
- Same concentration of API as reference,
- Same qualitative-quantitative composition as reference in excipient, some differences accepted (if non influencing behavior), limits cited ± 5%, exceptional ± 10% of amount in reference,
- Product acting at the “surface”,
- Valid in vitro tests could be used to support biowaiver.

GUIDELINE ON EQUIVALENCE STUDIES FOR THE DEMONSTRATION OF THERAPEUTIC EQUIVALENCE FOR PRODUCTS THAT ARE LOCALLY APPLIED, LOCALLY ACTING IN THE GASTROINTESTINAL TRACT AS ADDENDUM

CLEARLY SEPARATE ACCORDING TO

Site of action

- In the mouth and/or throat (e.g. local analgesics or anesthetics).
- In the stomach (e.g. antacids)
- In the intestine (e.g. anti-inflammatory and anti-motility agents)
  - Drugs that have a pharmacological, intracellular target
  - Drugs that have a target in the lumen or at the membrane surface

mechanism of action, e.g.:

- Chelating compounds of the GI fluids/milieu or binding to targets in the lumen (e.g. phosphate or bile).
- Adding endogenous compounds (e.g. pancreatin)
- Changing physicochemical conditions (e.g. antacids)
- Exerting a physical effect (e.g. osmotic / bulking agents)
- Binding to receptors or targets in the intestinal mucosa (e.g. loperamide, corticosteroids, ASA)

biopharmaceutical and PK properties

- Absorbable drugs
- Non-absorbable drugs

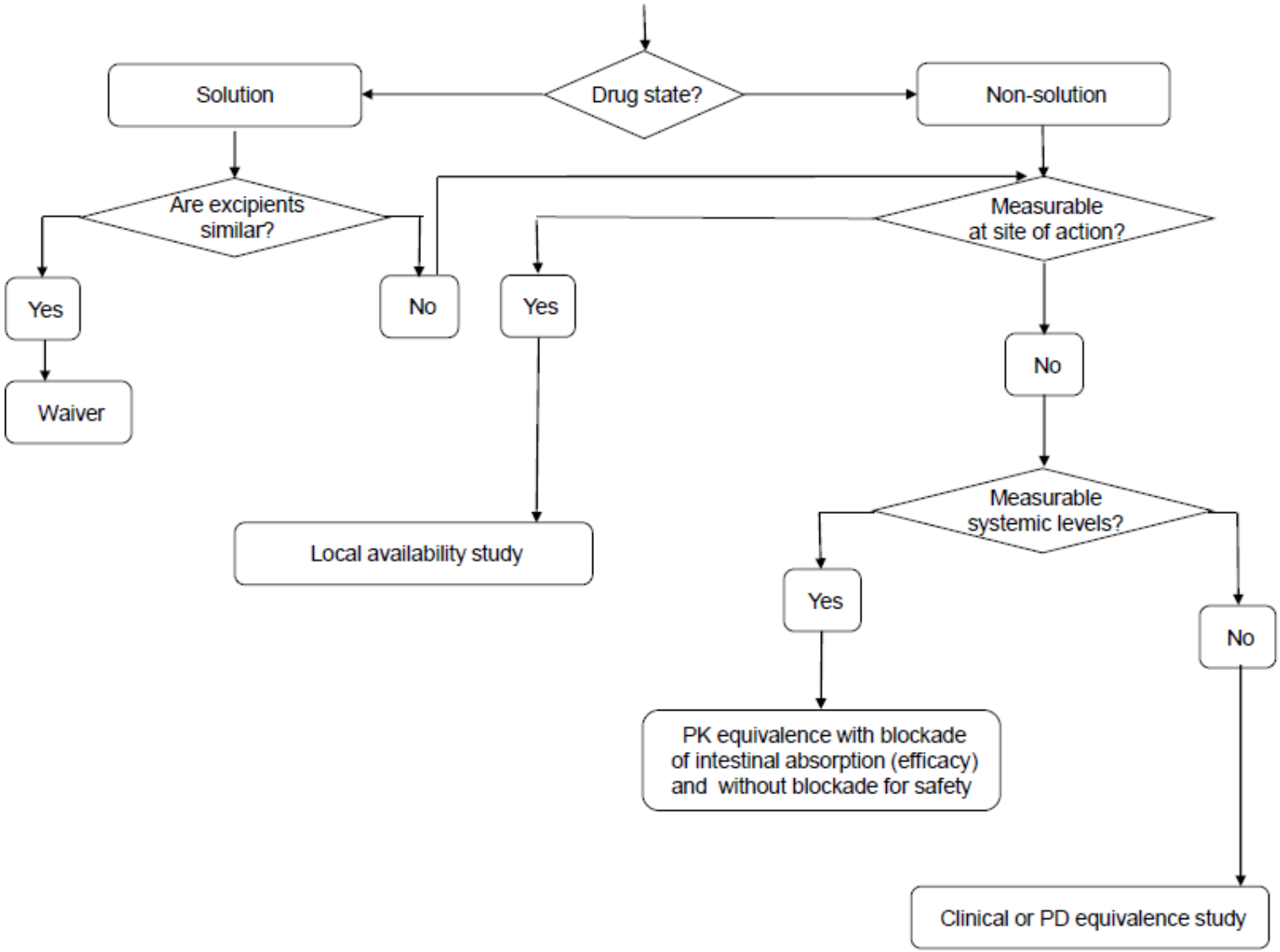
pharmaceutical form:

- Immediate release formulations : solutions, non-solutions
- Modified release formulations

state of the drug in the dosage form:

- A solute in solution (e.g. solution, gel)
- A solute in solid pharmaceutical form (e.g. lozenge)
- A solid in liquid (e.g. cream, ointment, suspension)
- A solid in solid pharmaceutical form (e.g. tablet)

MOUTH AND/OR THROAT



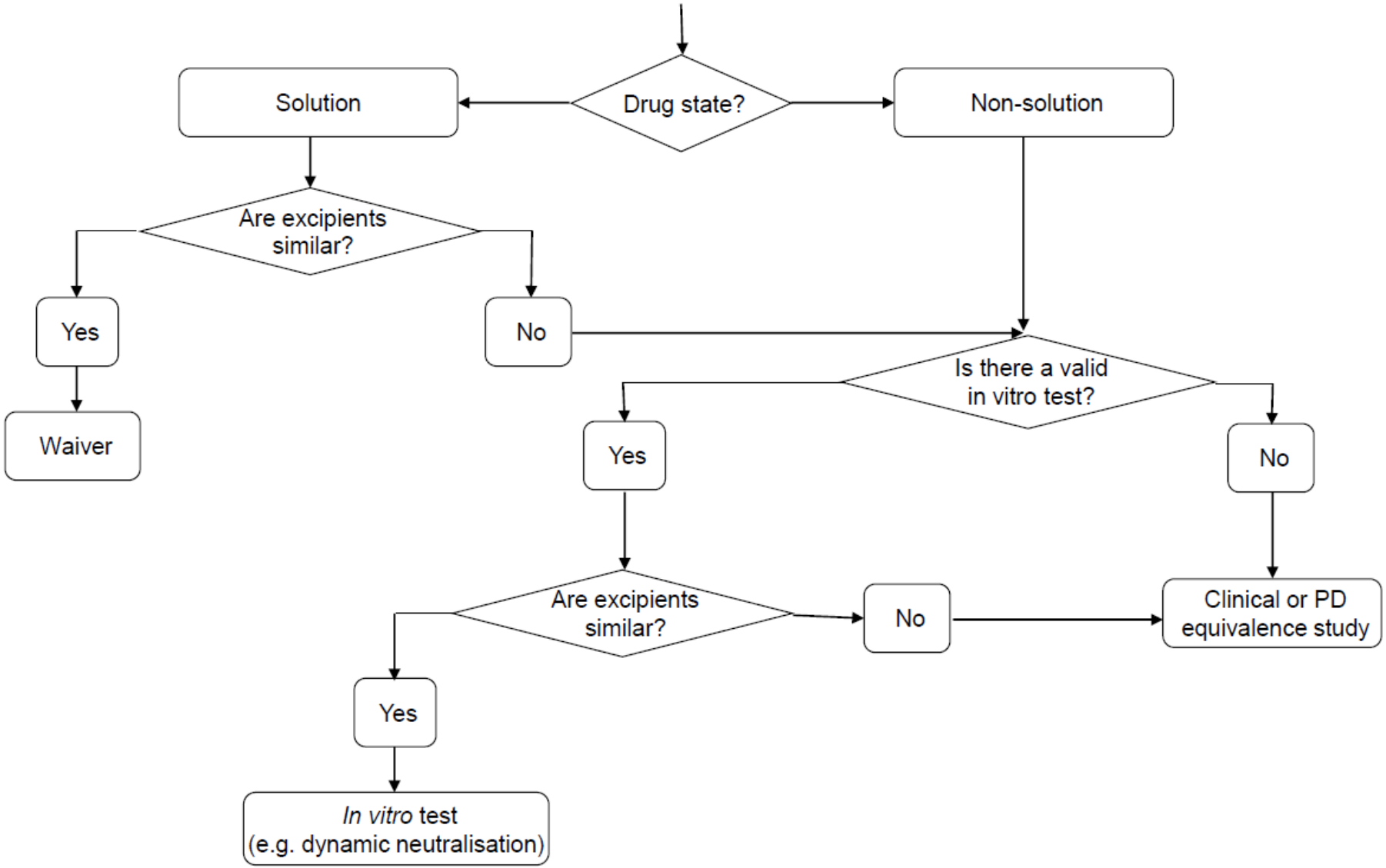
CLINICAL PHARMACOLOGY AND PHARMACOKINETICS: QUESTIONS AND ANSWERS 3.10 LOZENGES

For products acting locally in the mouth and/or throat, the guideline on equivalence studies for the demonstration of therapeutic equivalence for locally applied, locally acting products in the gastrointestinal tract (CPMP/EWP/239/95 Rev. 1, Corr.1) states that in those cases where it is justified that the drug is released from the dosage form as a solution due to its high solubility, 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. The guideline does however not mention to what extent the active substance must be released to ensure a conclusive result.

The Pharmacokinetics Working Party (PKWP) is of the opinion that if equivalence is evaluated with this type of study, the lozenges (test and reference) are expected to be completely dissolved during the study time. Given the limited experience at the current time for this type of *in vivo* study, the PKWP considers that a recovery of >85% is expected, unless otherwise justified.

When the study is designed, consider providing an instruction to the subjects on how to suck the lozenge in order to achieve sufficient release during a reasonable study time.

STOMACH



EXAMPLE SOLUTION

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. cosolvents) or in vivo stability of the active substance

drug substance BCS classification should be considered.

EXAMPLE ANTI ACID

in vitro methodology based on dynamic and static neutralizing tests

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.

EXAMPLE RIET-NALES METHOD

ELSEVIER

European Journal of Pharmaceutics and Biopharmaceutics 53 (2002) 217–225

European Journal of Pharmaceutics and Biopharmaceutics

www.elsevier.com/locate/ejphabio

Research paper

An improved in vitro method for the evaluation of antacids with in vivo relevance☆

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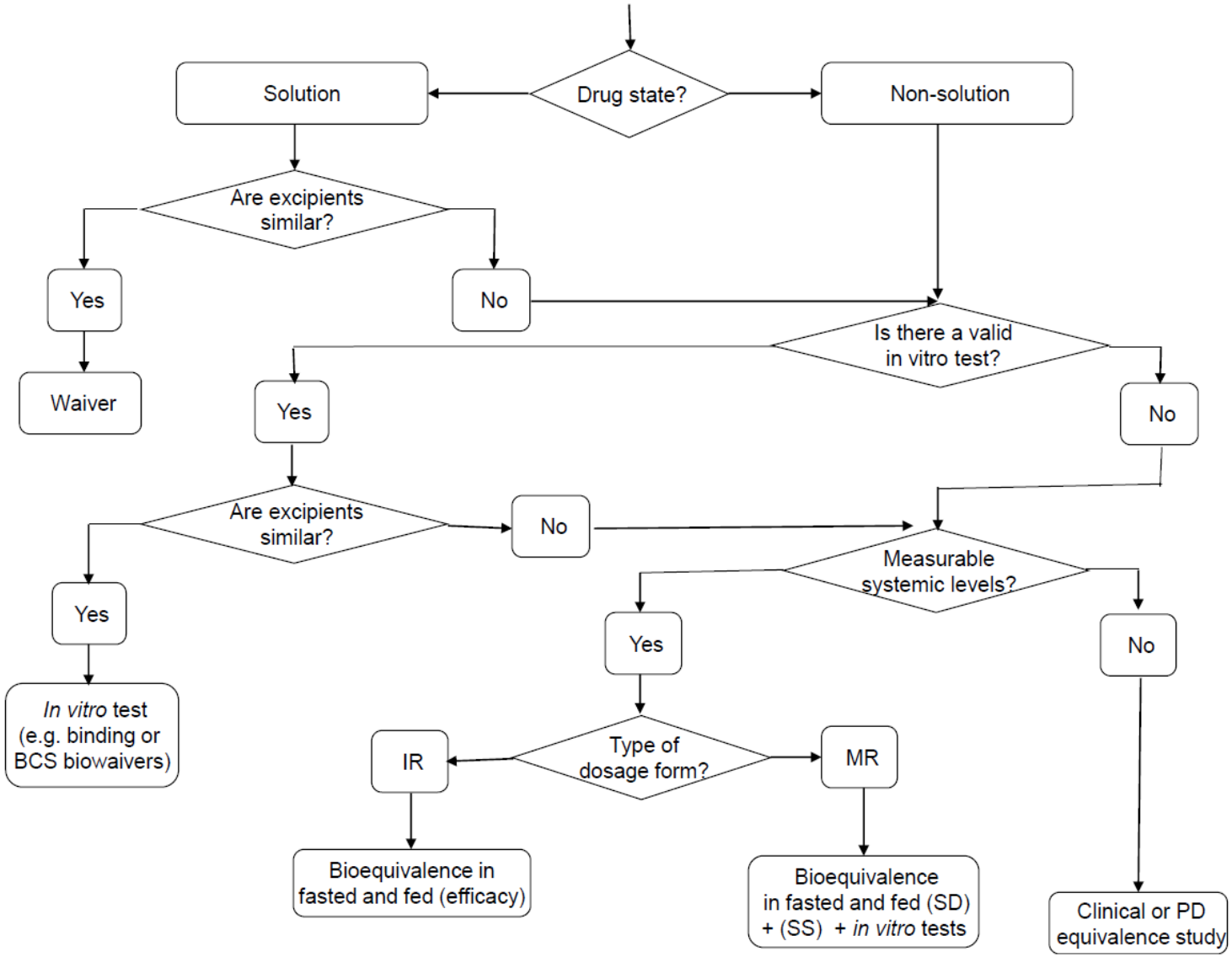
Abstract

An improved in vitro method for the evaluation of antacids for use with standard equipment is described. The method is a modification of an older method (RIGO method) and has in vivo relevance. The improved method uses USP dissolution test apparatus 2 with a stirring rate of 125 rpm in combination with a computerized automatic burette. The test solution is 250 ml 0.02 M HCl. A total of 20 min after addition of an antacid to the test solution titration starts at a constant speed of 2.0 ml/min 0.1 M HCl. The proposed acceptance criteria for a waiver for clinical studies are: pH after 4 min not less than 2.5 to ensure a rapid onset of effect, pH after 20 min not exceeding 7.0 to ensure that the pH in the stomach remains within physiological values, buffering capacity between pH 2.5 and 4.5 not less than 8 meq/dose and neutralizing capacity not less than 10 meq/dose to ensure sufficient efficacy within the physiological range. The improved method has been validated with respect to robustness to variations in sample preparation, repeatability and intermediate precision and has been cross-validated versus the RIGO method. The improved method has been found to be rather insensitive to variations in sample pretreatment and at least equivalent to the RIGO method.

Keywords: Antacids; In vitro/in vivo; Neutralizing capacity; Buffering capacity; USP dissolution test apparatus; Acceptance criteria

INTESTINE



EXAMPLE BINDING TO COMPONENTS OF THE GI MILIEU

Cholestyramine, colestipol, calcium acetate, sevelamer, etc… In vitro studies based on their binding capacity (e.g. in-vitro equilibrium and dynamic binding studies)

Excipients not critical and disintegration and dissolution profiles in the physiological pH range (as appropriate) are similar.

In vitro similarity should be assessed with a ±10% acceptance range, unless otherwise justified.

EXAMPLE BULKING

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.

Excipients not critical and disintegration and dissolution profiles in the physiological pH range (as appropriate) are similar.

EXAMPLE OF PRODUCT SPECIFIC RECOMMANDATION: FERIC CITRATE

HTTPS://WWW.EMA.EUROPA.EU/EN/HUMAN-REGULATORY/RESEARCH-DEVELOPMENT/SCIENTIFIC-GUIDELINES/CLINICAL-PHARMACOLOGY-PHARMACOKINETICS/CLINICAL-PHARMACOLOGY-PHARMACOKINETICS-QUESTIONS-ANSWERS#6.-BIOWAIVERS-SECTION POINT 4.9

This guideline should be read in conjunction with the guideline on 'Equivalence studies for the demonstration of therapeutic equivalence for locally applied, locally acting products in the gastrointestinal tract' .

The iron component in ferric citrate coordination complex reacts with dietary phosphate in the gastrointestinal (GI) tract and precipitates phosphate as ferric phosphate. This compound is insoluble and is excreted in the stool thereby reducing the amount of phosphate that is absorbed from the GI tract. The scope of the present guidance is to provide possible options to establish therapeutic equivalence of products containing ferric citrate coordination complex.

Similarity of the drug substance

As ferric citrate coordination complex is a relatively complex drug substance with standardized molar ratio, which is important for the action of the drug, similarity of the drug substance should be established between the test and the reference product based on comparative physico-chemical characterizations. Based on the data generated from the characterization, the applicant should define and prove the chemical structure and molecular formula of the test drug substance in comparison to the reference drug substance. At least three batches of the test drug substance and at least three batches of the extracted reference drug substance should be characterized to assess drug substance similarity.

- *Option 1 Biowaiver based on BCS classification*

Ferric citrate coordination complex is a highly soluble substance with very low (<1%) systemic absorption and can be considered as a BCS class III substance. As such, a biowaiver can be established according to BCS classification in line with the requirements of Appendix III of the 'Guideline on the investigation of bioequivalenceCPMP/EWP/QWP/1401/98 Rev.1/Corr**)'.

However, in BCS III drugs that are without or with very low systemic bioavailability, such as ferric citrate coordination complex, very rapid dissolution is not essential and similar rapid dissolution is also acceptable.

- *Option 2 In vitro studies*

In case a biowaiver based on BCS classification, as mentioned above, is not possible, in vitro phosphate binding studies comparing the test and reference products are considered acceptable surrogates for the assessment of efficacy, as ferric citrate coordination complex acts locally in the GI tract:

Phosphate Binding Studies

Two studies are required to compare the rate and extent of phosphate binding: (a) a comparative in vitro equilibrium binding study (**pivotal**) and (b) a comparative in vitro kinetic binding study.

1. Comparative in vitro equilibrium binding study pH Range: 1.2, 3.0, and 7.5.

Strength to be tested: 1 g of ferric citrate coordination complex (equivalent to 210 mg of ferric iron). Whole tablets should be used.

Phosphate concentrations to be used: Test and reference products should be incubated with at least 8 phosphate concentrations at each pH level. Maximum phosphate binding (attainment of plateau) should be clearly demonstrated prior to selecting these eight phosphate concentrations for the study. Phosphate concentrations should be spaced until the maximum binding is clearly established.

Incubation conditions: All incubations should be conducted at 37°C. Wait at least one hour until equilibrium pH has been reached. The pH should be monitored and adjusted every 15 minutes if needed. Data should be provided demonstrating that the length of time selected for incubation with the phosphate-containing medium yields maximum binding.

Additional Data: Each binding study should be repeated at least 12 times (12 replicates at each pH at each concentration level).

Results Evaluation: The Langmuir binding constants k1 and k2 should be determined in the equilibrium binding study. The test/reference ratio should be calculated for k1. The 90% confidence interval should be calculated for k2, with acceptance criteria of 90% to 111.11%.

2. Comparative in vitro kinetic binding study pH range: 1.2, 3.0, and 7.5.

Strength to be tested: 1 g of ferric citrate coordination complex (equivalent to 210 mg of ferric iron). Whole tablets should be used.

Phosphate concentrations to be used: the lowest concentration, the mid concentration (approximately 50% of the highest concentration) and the highest concentration of the corresponding equilibrium binding study should be used to incubate whole tablets at each pH level.

Incubation conditions: All incubations should be conducted at 37°C under constant gentle shaking, and each binding study should be repeated at least 12 times (12 tablets at each concentration).

Evaluation of results: Ferric citrate-phosphate binding should be monitored as a function of time. At least eight time points should be chosen up to 24 hours that adequately address binding under each condition. The test/reference bound phosphate ratios at the various times should be compared but not subjected to the 90% confidence interval criteria.

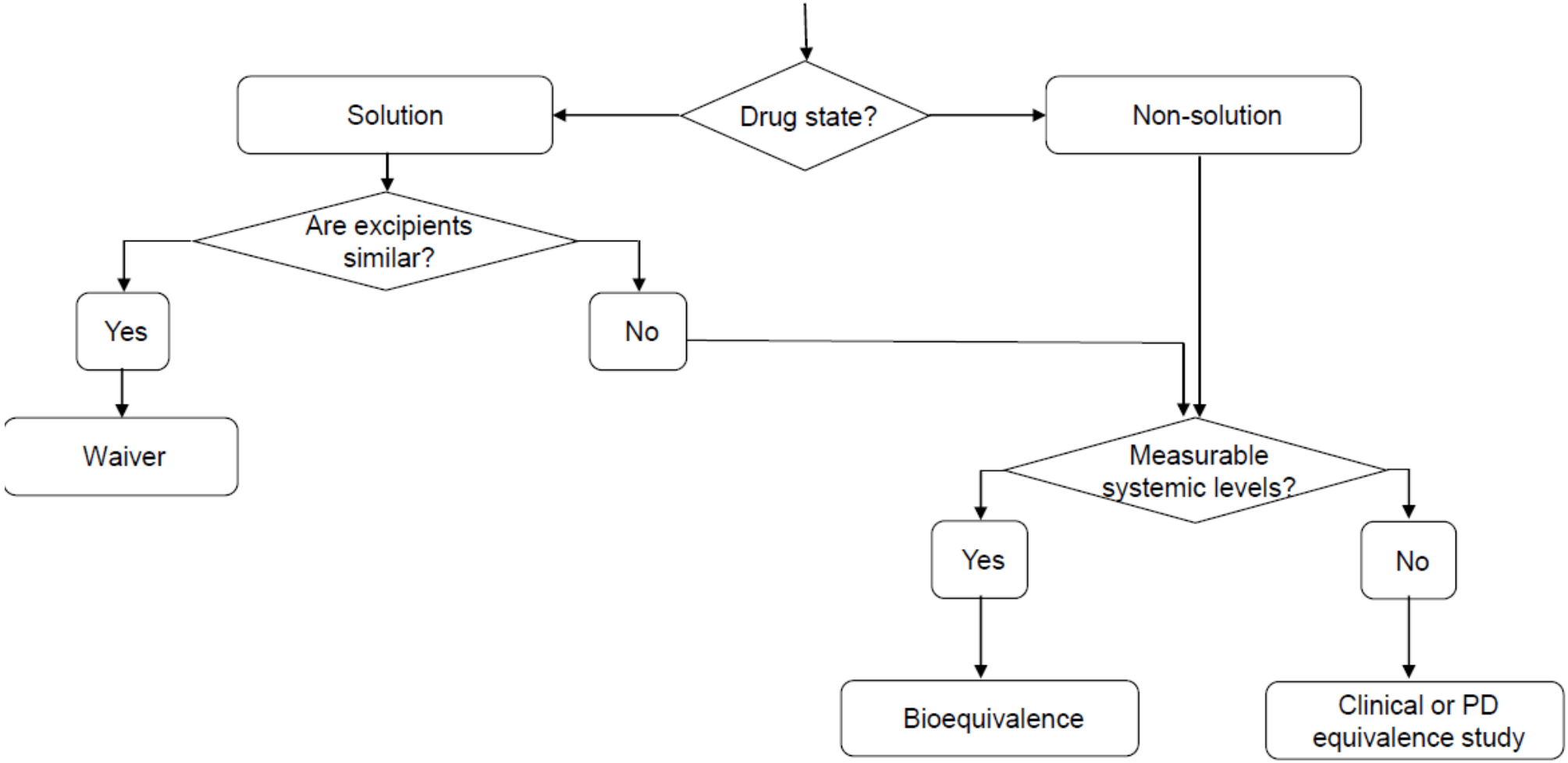
Analytical Method Considerations: The ferric citrate complex is achiral and therefore an enantioselective analytical method is not required. The analyte will be the unbound phosphate in filtrate in order to calculate phosphate bound to ferric citrate in the relevant biological fluid

REMARKS

Limits are 0.9-1.11 => tighten vs US FDA

More than one option is proposed

RECTUM



REMARKS

In case of in vitro tests or waivers

- particular consideration to excipients that may affect
- local tolerance,
- local residence time (e.g. surface tension, viscosity, etc.)
- in vivo solubility (e.g. co-solvents)
- in vivo stability of the active substance.

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THANK YOU

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