Regulatory Year in Review

New Draft Guidelines

Vit Perlik

Updated "Guidelines"

- **19 updated guidelines or guidance documents**
  - 11 w/o veterinary and pharmacovigilance topics, mainly related to ICH guidelines and quality

Document title	Language	Status	First published	Last update
NEW ICH guideline Q4B Annex 1 on evaluation and recommendation of pharmacopoeial texts for use in the ICH regions on residue on ignition/sulphated ash - Step 5	(English only)	adopted	01.11.2007	13.07.2017
ICH guideline Q4B Annex 10 on evaluation and recommendation of pharmacopoeial texts for use in the ICH regions on polyacrylamide gel electrophoresis - general chapter - Step 5	(English only)	adopted	11.02.2013	13.07.2017
ICH guideline Q4B annex 2 on evaluation and recommendation of pharmacopoeial texts for use in the ICH regions on test for extractable volume of parenteral preparations general chapter - Step 5	(English only)	adopted	01.12.2008	13.07.2017
ICH guideline Q4B Annex 3 on evaluation and recommendation of pharmacopoeial texts for use in the ICH regions on test for particulate contamination: sub-visible particles general chapter - Step 5	(English only)	adopted	01.12.2008	13.07.2017
ICH guideline Q4B Annex 4A on evaluation and recommendation of pharmacopoeial texts for use in the ICH regions on micro enumeration - Step 5	(English only)	adopted	01.06.2009	13.07.2017
ICH guideline Q4B Annex 4B on evaluation and recommendation of pharmacopoeial texts for use in the ICH regions on Tests for specified micro-organisms - Step 5	(English only)	adopted	01.06.2009	13.07.2017
ICH guideline Q4B Annex 4C on evaluation and recommendation of pharmacopoeial texts for use in the ICH regions on acceptance criteria for pharmaceutical preparations and substances for pharmaceutical use - Step 5	(English only)	adopted	01.06.2009	13.07.2017
ICH guideline Q4B Annex 5 on evaluation and recommendation of pharmacopoeial texts for use in the ICH regions on disintegration test - general chapter - Step 5	(English only)	adopted	11.02.2013	13.07.2017
ICH guideline Q4B Annex 8 on evaluation and recommendation of pharmacopoeial texts for use in the ICH regions sterility test - general chapter - Step 5	(English only)	adopted	11.02.2013	13.07.2017
ICH guideline Q4B Annex 9 on evaluation and recommendation of pharmacopoeial texts for use in the ICH regions on tablet friability - general chapter - Step 5	(English only)	adopted	11.02.2013	13.07.2017
Reflection paper on the requirements for selection and justification of starting materials for the manufacture of chemical active substances	(English only)	adopted	10.10.2014	06.07.2017

New "Guidelines"

- 44 new guidelines or guidance documents including product specific guidelines
  - 29 w/o veterinary and pharmacovigilance topics
  - 15 new product specific guidelines

Document title	Language	Status	First published	Last update
NEW Abiraterone tablets 250 mg product-specific bioequivalence guidance	(English only)	adopted	03.03.2017	
Addendum to the guideline on the evaluation of medicinal products indicated for treatment of bacterial infections to address the clinical development of new agents to treat pulmonary disease due to Mycobacterium tuberculosis - Revision 1	(English only)	adopted	03.08.2017	
Crizotinib hard capsules 200 mg and 250 mg product-specific bioequivalence guidance	(English only)	adopted	10.07.2017	
NEW Elvitegravir film-coated tablets 85 mg and 150 mg product-specific bioequivalence guidance	(English only)	adopted	10.07.2017	
Elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil film-coated tablets 150 mg/150 mg/200 mg/245 mg product-specific bioequivalence guidance	(English only)	adopted	10.07.2017	
Emtricitabine/rilpivirine/tenofovir disoproxil film-coated tablets 200 mg/25 mg/245 mg product-specific bioequivalence guidance	(English only)	adopted	10.07.2017	
Everolimus tablets 0.25 mg, 0.5 mg, 0.75 mg and 1 mg; 2.5 mg, 5 mg and 10 mg, dispersible tablets 0.1 mg and 0.25 mg; 2 mg, 3 mg and 5 mg product-specific bioequivalence guidance	(English only)	adopted	03.01.2017	
Exenatide powder and solvent for prolonged-release suspension for injection, 2 mg, and powder and solvent for prolonged-release suspension for injection in pre-filled pen, 2 mg product-specific bioequivalence guidance	(English only)	adopted	03.03.2017	
Fingolimod capsules 0.5 mg product-specific bioequivalence guidance	(English only)	adopted	03.01.2017	
Gaucher disease: a strategic collaborative approach from the European Medicines Agency and Food and Drug Administration	(English only)	adopted	30.06.2017	
Guideline on clinical development of fixed combination medicinal products - Revision 2	(English only)	adopted	31.03.2017	
NEW Guideline on core SmPC and Package Leaflet for (68Ge/68Ga) generator - First version	(English only)	adopted	08.09.2017	
Guideline on core SmPC and Package Leaflet for nanocolloidal technetium (99mTc) albumin - First version	(English only)	adopted	03.02.2017	
Guideline on immunogenicity assessment of therapeutic proteins	(English only)	adopted	01.06.2017	

New "Guidelines"

Cont.

- **44 new guidelines or guidance documents including product specific guidelines**
  - 29 w/o veterinary and pharmacovigilance topics
  - 15 new product specific guidelines

Guideline on Influenza vaccines – Quality module Revision 1	(English only)	adopted	28.07.2017
Guideline on influenza vaccines – submission and procedural requirements (Rev.1)	(English only)	adopted	14.03.2017
Guideline on manufacture of the finished dosage form - Revision 1	(English only)	adopted	14.08.2017
Guideline on strategies to identify and mitigate risks for first-in-human and early clinical trials with investigational medicinal products - Revision 1	(English only)	adopted	25.07.2017
Guideline on the principles of regulatory acceptance of 3Rs (replacement, reduction, refinement) testing approaches	(English only)	adopted	24.02.2017
Implementation strategy of ICH Q3D guideline	(English only)	adopted	08.03.2017
International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use guideline M7 (R1) on assessment and control of DNA reactive (mutagenic) impurities in pharmaceuticals to limit potential carcinogenic risk - Step 5	(English only)	adopted	27.07.2017
Levodopa/Carbidopa/Entacapone film-coated tablet 200 mg/50 mg/200 mg, 175 mg/43.75 mg/200 mg, 150 mg/37.5 mg/200 mg, 125 mg/31.25 mg/200 mg, 100 mg/25 mg/200 mg, 75 mg/18.75 mg/200 mg and 50 mg/12.5 mg/200 mg product-specific bioequivalence guidance	(English only)	adopted	03.01.2017
Paliperidone palmitate depot suspension for injection 25 mg, 50 mg, 75 mg, 100 mg and 150 mg product-specific bioequivalence guidance	(English only)	adopted	03.03.2017
Paliperidone prolonged-release tablet 1.5 mg, 3 mg, 6 mg, 9 mg and 12 mg product-specific bioequivalence guidance	(English only)	adopted	03.01.2017
Pazopanib film-coated tablet 200 mg and 400 mg product-specific bioequivalence guidance	(English only)	adopted	03.01.2017
Reflection paper on anthelmintic resistance	(English only)	adopted	24.04.2017
Vandetanib film-coated tablets 100 mg and 300 mg product-specific bioequivalence guidance	(English only)	adopted	03.03.2017
Vemurafenib film-coated tablets 240 mg product-specific bioequivalence guidance	(English only)	adopted	03.03.2017
Vortioxetine hydrobromide immediate release tablets 5 mg, 10 mg, 15 mg, and 20 mg; vortioxetine lactate oral drops solution 20 mg/ml product-specific bioequivalence guidance	(English only)	adopted	10.07.2017

Draft "Guidelines"

- 36 scientific guidelines or concept papers open for discussion
  - 27 w/o veterinary and pharmacovigilance topics
  - 8 new draft product specific guidelines

Document title	Language	Status	First published	Last update
Concept paper on a guideline on the evaluation of medicinal products indicated for treatment of influenza	(English only)	draft: consultation open	04.05.2017	
Concept paper on an addendum on terms and concepts of pharmacogenomic features related to metabolism to the Guideline on the use of pharmacogenetic methodologies in the pharmacokinetic evaluation of medicinal products (EMA/CHMP/37646/2009)	(English only)	draft: consultation open	07.07.2017	
Concept paper on predictive biomarker-based assay development in the context of drug development and lifecycle	(English only)	draft: consultation open	28.07.2017	
Concept paper on revision of the guideline on clinical development of vaccines	(English only)	draft: consultation open	23.06.2017	
Concept paper on the development of guidance on the non-clinical evaluation of radiopharmaceuticals - First version	(English only)	draft: consultation open	01.08.2017	
Concept paper on the need for the development of a reflection paper on regulatory requirements for the development of medicinal products for chronic non-infectious liver diseases (PBC, PSC, NASH)	(English only)	draft: consultation open	01.06.2017	
Concept paper on the revision of the guideline on quality, non-clinical and clinical aspects of medicinal products containing genetically modified cells - Superseeding document	(English only)	draft: consultation open	24.07.2017	
Concept paper on the revision of the guideline on the role of pharmacokinetics in the development of medicinal products in the paediatric population	(English only)	draft: consultation open	04.05.2017	
Draft dimethyl fumarate gastro-resistant capsules 120 mg and 240 mg product-specific bioequivalence guidance	(English only)	draft: consultation open	03.08.2017	
Draft dolutegravir film-coated tablets 10 mg, 25 mg and 50 mg product-specific bioequivalence guidance - First version	(English only)	draft: consultation open	28.07.2017	
Draft dronedarone film-coated tablets 400 mg product-specific bioequivalence guidance - First version	(English only)	draft: consultation open	28.07.2017	
Draft guideline for the notification of serious breaches of Regulation (EU) No 536/2014 or the clinical trial protocol	(English only)	draft: consultation open	23.05.2017	
NEW! Draft guideline on data requirements for multi-strain dossiers 4 for inactivated vaccines against avian influenza (AI), bluetongue (BT) and foot-and-mouth disease (FMD) - Rev.1	(English only)	draft: consultation open	18.09.2017	

Draft "Guidelines"

Cont.

- **36 scientific guidelines or concept papers open for discussion**
  - 27 w/o veterinary and pharmacovigilance topics
  - 8 new draft product specific guidelines

Draft 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	(English only)	draft: consultation open	04.04.2017	
Draft guideline on Guideline on core summary of product characteristics (SmPC) and package leaflet for iopamidol 300	(English only)	draft: consultation open	26.04.2017	
Draft guideline on Guideline on core summary of product characteristics (SmPC) and package leaflet for iopamidol 370	(English only)	draft: consultation open	26.04.2017	
NEW Draft guideline on non-clinical documentation in applications for marketing authorisation/registration of well-established and traditional herbal medicinal products - Revision 1	(English only)	draft: consultation open	22.08.2017	
Draft ibuprofen 200 - 800 mg oral use, immediate release formulations product-specific bioequivalence guidance	(English only)	draft: consultation open	03.08.2017	
NEW Draft ICH E9 (R1) addendum on estimands and sensitivity analysis in clinical trials to the guideline on statistical principles for clinical trials, step 2b - Revision 1	(English only)	draft: consultation open	31.08.2017	
NEW Draft ICH S5 (R3) guideline on reproductive toxicology: detection of toxicity to reproduction for human pharmaceuticals, step 2b - Revision 3	(English only)	draft: consultation open	31.08.2017	
Draft paracetamol oral use, immediate release formulations product-specific bioequivalence guidance - First version	(English only)	draft: consultation open	28.07.2017	
Draft prasugrel hydrochloride film-coated tablets 5 mg and 10 mg product-specific bioequivalence guidance - Revision 1	(English only)	draft: consultation open	03.08.2017	
Draft reflection paper on statistical methodology for the comparative assessment of quality attributes in drug development	(English only)	draft: consultation open	31.03.2017	
Draft rilpivirine film-coated tablets 25 mg product-specific 4 bioequivalence guidance	(English only)	draft: consultation open	28.07.2017	
Draft tadalafil film-coated tablets 2.5 mg, 5 mg, 10 mg and 20 mg product-specific bioequivalence guidance - Revision 1	(English only)	draft: consultation open	03.08.2017	
Guideline on core SmPC and Package Leaflet for sodium iodide (131I) therapy capsule	(English only)	draft: consultation open	26.04.2017	
Reflection paper on the pharmaceutical development of medicines for use in the older population - First version	(English only)	draft: consultation open	01.08.2017	

Selected Draft "Guidelines"

- **Modeling, statistical methodology used for drug development**
  - End of consultation March 31 2018
- **Draft Reflection paper on the dissolution specification for generic oral immediate release products**
  - End of consultation 13 August 2016
- **Reflection paper on the dissolution specification for generic solid oral immediate release products with systemic action**
  - Adopted by the CHMPJune 2017

Selected Draft "Guidelines"

- **Product specific guidelines – drafts for:**
  - dimethyl fumarate gastro resistant cps;
  - dolutegravir;
  - dronedarone;
  - ibuprofen;
  - paracetamol;
  - prasugrel hydrochloride;
  - rilpivirine;
  - tadalafil – revision 1

Product Specific Guidelines - Draft

- **Ibuprofen 200 - 800 mg oral use, immediate release formulations product-specific bioequivalence guidance**
  - end of consultation 31 October 2017

  What is suggested:

  - Single dose, cross over, fasting study in healthy volunteers using highest strength (linear PK 200 – 800 mg)
  - Analyte: Parent compound using enantioselective analytical method
  - Enantiomers have different PD and PK and the rate of absorption has been shown to affect the ratio of enantiomers
  - Pharmacokinetic variables: Cmax, AUC(0-t) and Tmax for S enantiomer

- Different formulations available (suspensions to rapidly dissolving tbl, cps)
- Majority of generic products registered using non- enantioselective analytical method
- ? Shall be removed from the market? What will happen during the MA renewals?

Product Specific Guidelines - Draft

- **Paracetamol oral use, immediate release formulations product-specific bioequivalence guidance**
  - end of consultation 31 October 2017

What is suggested:

- BCS Class I biowaiver possible, Paracetamol is high solubility compound with >85% absorption

or

- Single dose, cross over, fasting study in healthy volunteers (paracetamol is highly soluble and shows linear PK, in principle any strength may be used)
- Analyte: Parent compound
- Pharmacokinetic variables: Cmax, AUC(0-t) and Tmax

Product Specific Guidelines - Adopted

- **Paliperidone palmitate depot suspension for injection 25, 50, 75, 100 and 150 mg product-specific bioequivalence guidance**

  Regulatory requirements (EMA/CPMP/EWP/280/96 Corr1)

  - Abridged application general considerations
    - Healthy vs patients
    - Single dose and/or multiple dose studies
    - *(…in patients, preferably after both single and multiple dose administration in line with recommendations below. If it is not feasible to conduct single dose studies in patients, these can be replaced by multiple dose studies.)*
  - New chemical entity as Intramuscular/subcutaneous depot formulations SD, MD studies, dose proportionality, site of administration etc. (EMA/CPMP/EWP/280/96 Corr1)

Product Specific Guideline for Paliperidone

Healthy Volunteers vs Patients

- **Study population**
  - Release duration of paliperidone from 1st day until at least 4M (SPC Ch.5.2)
  - Aripiprazol: Life-threatening adverse events attributed to acute laryngeal dystonia have been reported following administration of a single dose of 30 mg aripiprazole to healthy volunteers
  - Healthy not feasible for any approached CRO
- **Product specific guideline**
  - Paliperidone palmitate, Extended-release suspension; intramuscular (FDA Recommended Aug 2011; Revised Dec 2013; Dec 2015)
  - **Additional comments:** FDA does **not recommend that studies be conducted using healthy subjects** or patients on a different antipsychotic treatment.

Patient population

Product Specific Guideline for Paliperidone

Study Design – Single Dose vs Multiple Dose

- Stable patients needed (1-3 month of stable patients conditions)
- Documented tolerability of investigated compound preferable
- Wash-out not feasible
- Co-administration under single dose conditions used for the explorative purposes only
- Significant consequences of co-administration for study participants documented
- Single dose study design not feasible for pivotal BE study design
- Regulatory requirements acknowledging abovementioned facts

Patient population under multiple dose conditions suggested

EMA/CHMP/474825/2016
Committee for Medicinal Products for Human Use (CHMP)

21 July 2016

Paliperidone palmitate depot suspension for injection 25, 50, 75, 100 and 150 mg product-specific bioequivalence guidance

Draft

Draft agreed by Pharmacokinetics Working Party	June 2016
Adopted by CHMP for release for consultation	21 July 2016
Start of public consultation	1 August 2016
End of consultation (deadline for comments)	31 October 2016

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

Keywords	***Bioequivalence, generics, paliperidone***

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EMA/CHMP/474825/2016
Committee for Medicinal Products for Human Use (CHMP)

23 February 2017

Paliperidone palmitate depot suspension for injection 25 mg, 50 mg, 75 mg, 100 mg and 150 mg product-specific bioequivalence guidance

Draft agreed by Pharmacokinetics Working Party	June 2016
Adopted by CHMP for release for consultation	21 July 2016
Start of public consultation	1 August 2016
End of consultation (deadline for comments)	31 October 2016
Agreed by Pharmacokinetics Working Party	December 2016
Adopted by CHMP	23 February 2017
Date of coming into effect	1 September 2017

Keywords	***Bioequivalence, generics, paliperidone***

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Product Specific Guideline for Paliperidone

Draft guidance

Bioequivalence study design**	**Multiple dose:** any dose/strength (if the test product has the same concentration of active substance as the reference for all the strengths), patients **Background:** single-dose studies in healthy volunteers are not considered feasible.
	cross-over or parallel

Adopted guidance

Bioequivalence study design** *in case a BCS biowaiver is not feasible or applied*	**Single dose:** any dose/strength (if the test product has the same concentration of active substance as the reference for all the strengths), in healthy volunteers (if feasible) or in patients stabilized on other antipsychotic medication. **Multiple dose:** any dose/strength (if the test product has the same concentration of active substance as the reference for all the strengths) in patients.
	cross-over or parallel

Selected Draft "Guidelines"

Draft guideline on locally applied and acting drugs in GIT

- End of consultation 30 September 2017

Drug interactions – concept paper

- End of consultation 30 June 2017 (potential impact on fixed dose combinations)

Medical devices – concept paper

- End of consultation 16 May 2017

Inhalation and nasal products quality – concept paper

- End of consultation 30 June 2017

Orally inhaled products therapeutic equivalence – concept paper

- End of consultation 31 May 2017

Draft "Guidelines" -
Locally Applied, Locally Acting Products in GIT

- 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
  - End of consultation 30 September 2017

Draft "Guidelines" –
Locally Applied, Locally Acting Products in GIT

Key elements – executive summary

- Generic or hybrid applications
- Summary of requirements to waive the clinical trials or PD endpoint trials
- Strong emphasis on bioequivalence studies
- Defines use of *in vitro* equivalence tests

- **Why**
  - Alternative methods have higher sensitivity than traditional clinical or PD endpoint trials
  - Direct or indirect comparison of concentrations at the site of action as a surrogate of similar clinical response
- Waiver of CT for immediate or modified release products

Locally Applied, Locally Acting Products in GIT
- Assay Sensitivity

Dose of orlistat (mg)	FFE (% intake)
10 mg	5%
12 mg	8%
20 mg	17%
25 mg	14-18%
30 mg	21%
50 mg	20-24%
60 mg	**30%**
120 mg	**36%**
200 mg	32-35%
240 mg	31%
400 mg	27%

Hauptman et al, 1992

Locally Applied, Locally Acting Products in GIT - Assay Sensitivity

	Azithromycin (1,000 mg)	Azithromycin (500 mg)	Azithromycin (500 mg) plus loperamide
N	50	56	56
Average duration (h) of diarrhoea after beginning treatment			
All cases	34	34	11
All bacterial causes (n)	33.6 (21)	38.1 (31)	9.2 (36)
Percent well at hours of study			
0	8	18	50
6	18	34	66
12	38	46	79
18	40	50	79
24	54	59	84
48	78	73	93
72	80	79	96
Treatment failure: Total (%)	10 (20)	12 (21)	2 (4)

Ericsson et al, 2007

Locally Applied, Locally Acting Products in GIT
- Assay Sensitivity

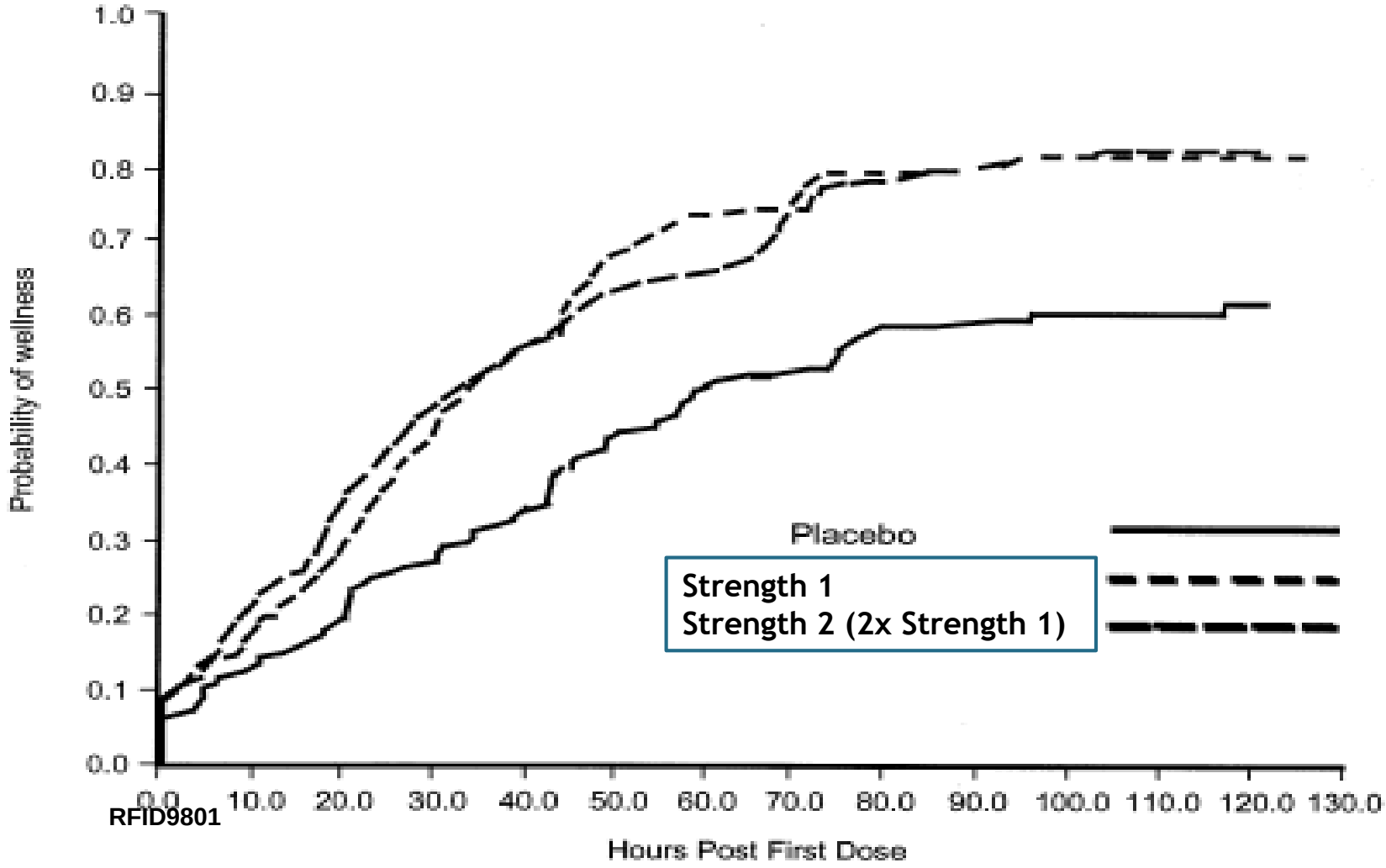


Figure 1. Probability of TLUS for the intent-to-treat population.

Draft "Guidelines" –
Locally Applied, Locally Acting Products in GIT

Types of locally applied and acting GIT products

- Site of action (mouth, stomach, intestine)
- Mechanism of action (antacids, osmotic agents…)
- Biopharmaceutical and PK properties (absorbable, non-absorbable)
- Pharmaceutical form (solutions, solid dosage forms, modified release…)
- The state of the drug in the dosage form (solute or solid in solution or solid)

Draft "Guidelines" –
Locally Applied, Locally Acting Products in GIT

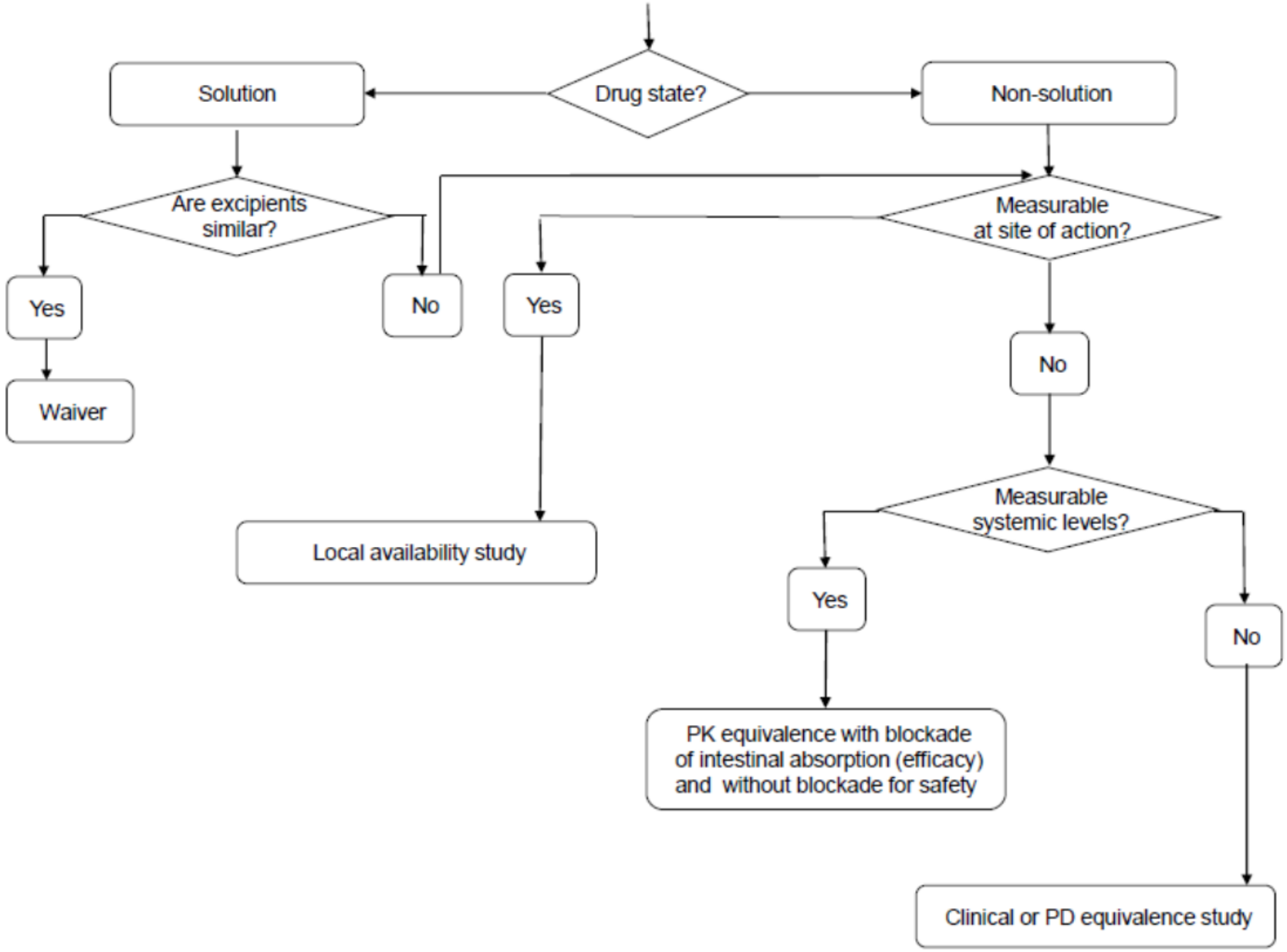
Body of evidence

- 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

- In case PK data are used for safety demonstration, only the 90% confidence interval range for the ratio test/reference should not exceed the upper limit of the acceptance range
  - Otherwise within 80 – 125%

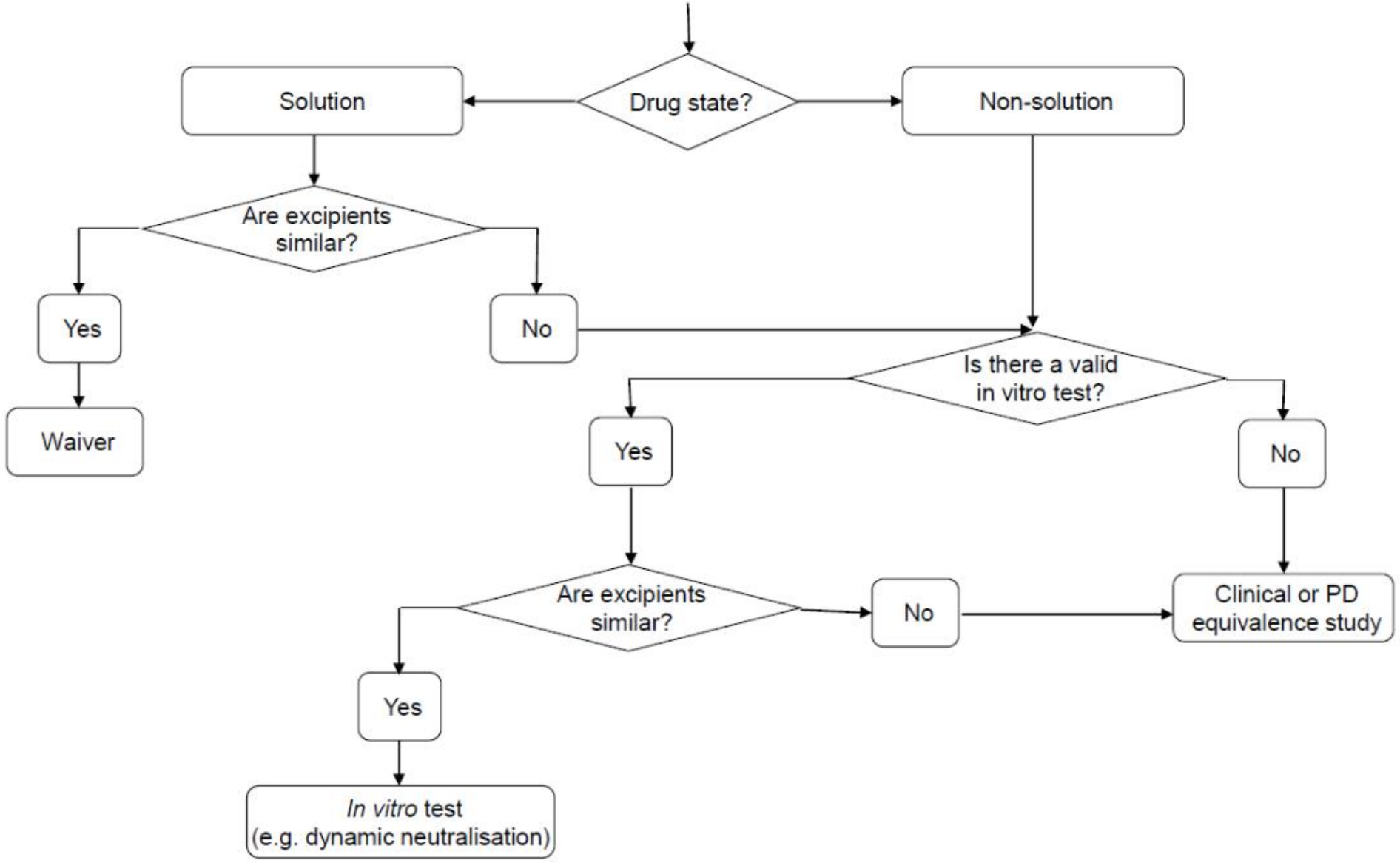
Locally Acting in the Mouth and/or Throat

- **Solution**
  - *In vitro* data (viscosity…)
- **Non-solution**
  - Saliva concentrations Cmax, AUC
  - Amounts remaining in dosage form at different time points
  - Charcoal study to evaluate absorption from mouth



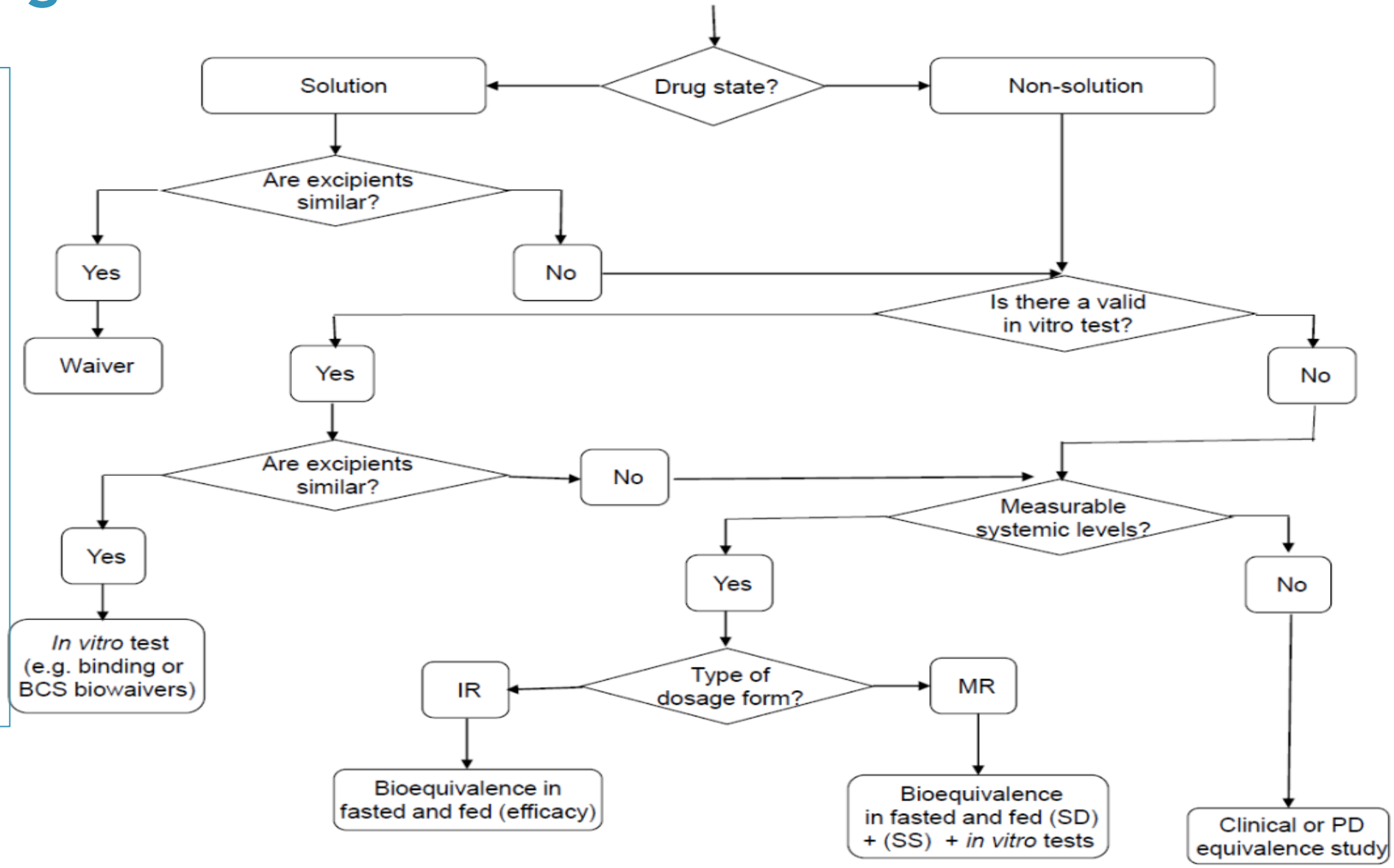
Locally Acting in the Stomach

- **Solution**
  - *In vitro* data (pH stability…)
- **Non-solution**
  - Dynamic and static neutralizing test
  - Hypothetically also BES in case of some absorption



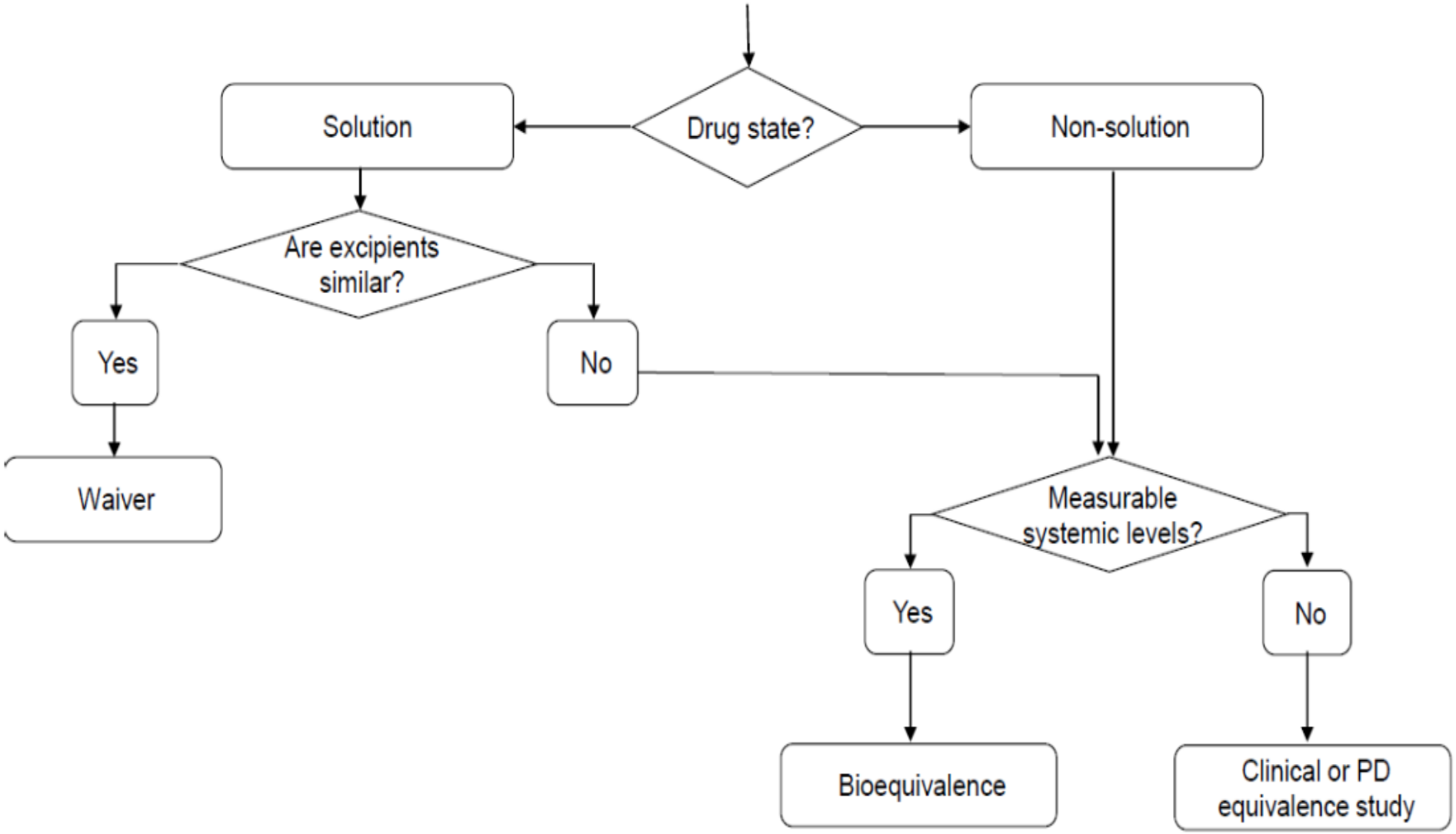
Locally Acting in the Intestine

- **Solution**
  - *In vitro* data (sorbitol, mannitol…)
  - BES in case of any absorption
- **Non-solution**
  - *In vitro* study – binding assays
  - BES in case of any absorption (fasting and fed)
  - Modified release product – partial AUC



Locally Acting in the Rectum

- **Solution**
  - *In vitro* data (local residence, tolerance…)
  - BES in case of any absorption
- **Non-solution**
  - BES in case of any absorption



Draft "Guidelines" – Orally Inhaled Products

- Concept paper on revision of the guideline on the 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) in adults and for the treatment of asthma in children and adolescents.
  - End of consultation 30 June 2017

Draft "Guidelines" –
Orally Inhaled Products – Original Concept

- ***In vitro* characterization**
  - Pharmaceutical equivalence/evaluation
- ***In vivo* characterization**
  - Pulmonary deposition - surrogate for efficacy
    - Describing extent (AUC) and rate (Cmax) of absorption delivered via lungs
    - Achieved by charcoal block
  - Systemic exposure - surrogate for safety
    - Describing extent (AUC) and rate (Cmax) of absorption delivered via lungs and gastrointestinal tract
  - Therapeutic equivalence/evaluation (PD endpoints acceptable)

Draft "Guidelines" -
Orally Inhaled Products - Reflections

Reflections to locally applied, locally acting products in GIT

- Demonstration of equivalence based on the *in vitro* data only difficult
  - Batch to batch variability of reference product
  - Within batch variability or reference product
    - IVIVC, testing of the side batches etc.
- PK studies more discriminative
  - The only evidence?
- Issues: selection of batches, strength and study population

Reflection from regulatory experience for OIP

- PD/clinical study difficult because of assay sensitivity
  - Requirements should be specified
  - FDC LABA/LAMA
  - Handling studies
- Issues: selection of batches, strength and study population
  - Better drug delivery from devices
  - Children – challenging requirements

Thank You For Your Attention!

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