



Topicals LALA, incl ophthalmics

Guideline on quality and equivalence of locally applied, locally acting cutaneous products (EMA/CHMP/QWP/708282/2018)
in force per April 2025

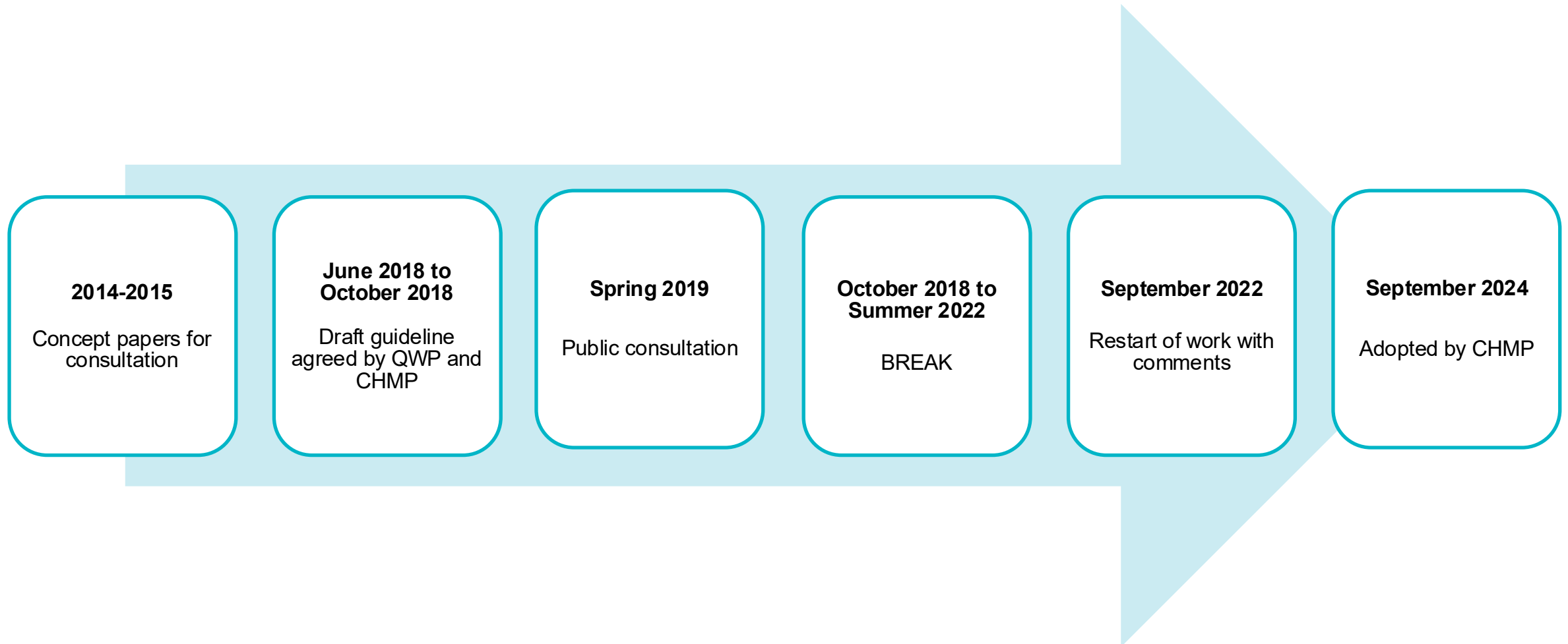
Peter Caspers

BioBridges 25 September 2026

Disclaimer

- *I attend this conference as an individual expert. The views expressed here are my personal views, and may not be understood or quoted as being made on behalf of the Medicines Evaluation Board or any of the working parties of the European Medicines Agency or reflecting the position of the Medicines Evaluation Board or EMA.*

Timeline



Scope of the Guideline

- Locally applied, locally acting products for cutaneous use
- May, where suitable, also be used for other LALA products
 - for auricular use
 - for ocular use
 - for vaginal use (locally acting)
 - nails
- Specific guidelines exist for other LALA products:
 - Inhalation products
 - Gastrointestinal tract
 - Nasal products (*draft*)
- EMA/QWP Q&A on the comparison of quality attributes to demonstrate therapeutic equivalence (*to be published*)

Q&A on the comparison of quality attributes to demonstrate therapeutic equivalence

- 1) Define and justify the Critical Quality Attributes (CQAs) that may have an impact on the efficacy and safety of the drug product and consequently need to be compared
- 2) Justify those attributes not considered critical and therefore do not need to be compared
- 3) Define and justify the similarity condition for each CQA
- 4) Define the marketed reference product, and characterise the reference product by testing all CQAs for a justified number of batches that together are representative of the variation observed in the reference product, also over storage
- 5) Consider the observed variability in the reference product for each CQA

Q&A on the comparison of quality attributes to demonstrate therapeutic equivalence

- 6) Define and justify the statistical method of comparison and associated acceptance criteria for each CQA based on the attribute, the similarity condition, and observed variability in the reference product.
- 7) Justify the selected number of test and reference batches to include in the comparison.
- 8) Incorporate points 6 and 7 in a protocol together with the sampling and testing plan and the validated analytical methods. The protocol should be approved prior to use.
- 9) Test the reference- and test batches for the CQAs. The studies should preferably be conducted by side-by-side testing of products in the same analytical campaign.
- 10) Evaluate the results, draw conclusions and summarise in a separate, approved report.

Guidance

- On the quality of cutaneous products, in addition to relevant Pharmacopoeial standards (Section 4)
 - All new marketing authorisation applications
 - Variations in composition and/or manufacturing process
- On equivalence testing in lieu of therapeutic equivalence studies with clinical endpoints (Section 5)
 - Abridged applications
 - Bridging in WEU applications
 - Bridging between investigational product and commercial product
 - Variations in composition and/or manufacturing process

Guidance

- Four specific annexes:
 - In-vitro release test (IVRT)
 - In-vitro skin permeation test (IVPT)
 - Stratum corneum sampling (tape stripping)
 - Vasoconstriction assay for corticosteroids

Quality of cutaneous product – Section 4

- 4.1 Description and composition of the drug product
- 4.2 Pharmaceutical development
 - 4.2.1 *Therapeutic objectives and product design*
 - 4.2.2 *Active substance*
 - 4.2.3 *Excipients*
 - 4.2.4 *Formulation development*
 - 4.2.5 *Product characterization***
 - 4.2.6 *Administration*
 - 4.2.7 *Manufacturing process development and manufacture (incl **in-process controls**)*
 - 4.2.8 *Container closure system*
 - 4.2.9 *Microbiological attributes*
- 4.3 Control strategy**
- 4.4 Stability program

Therapeutic equivalence – Section 5

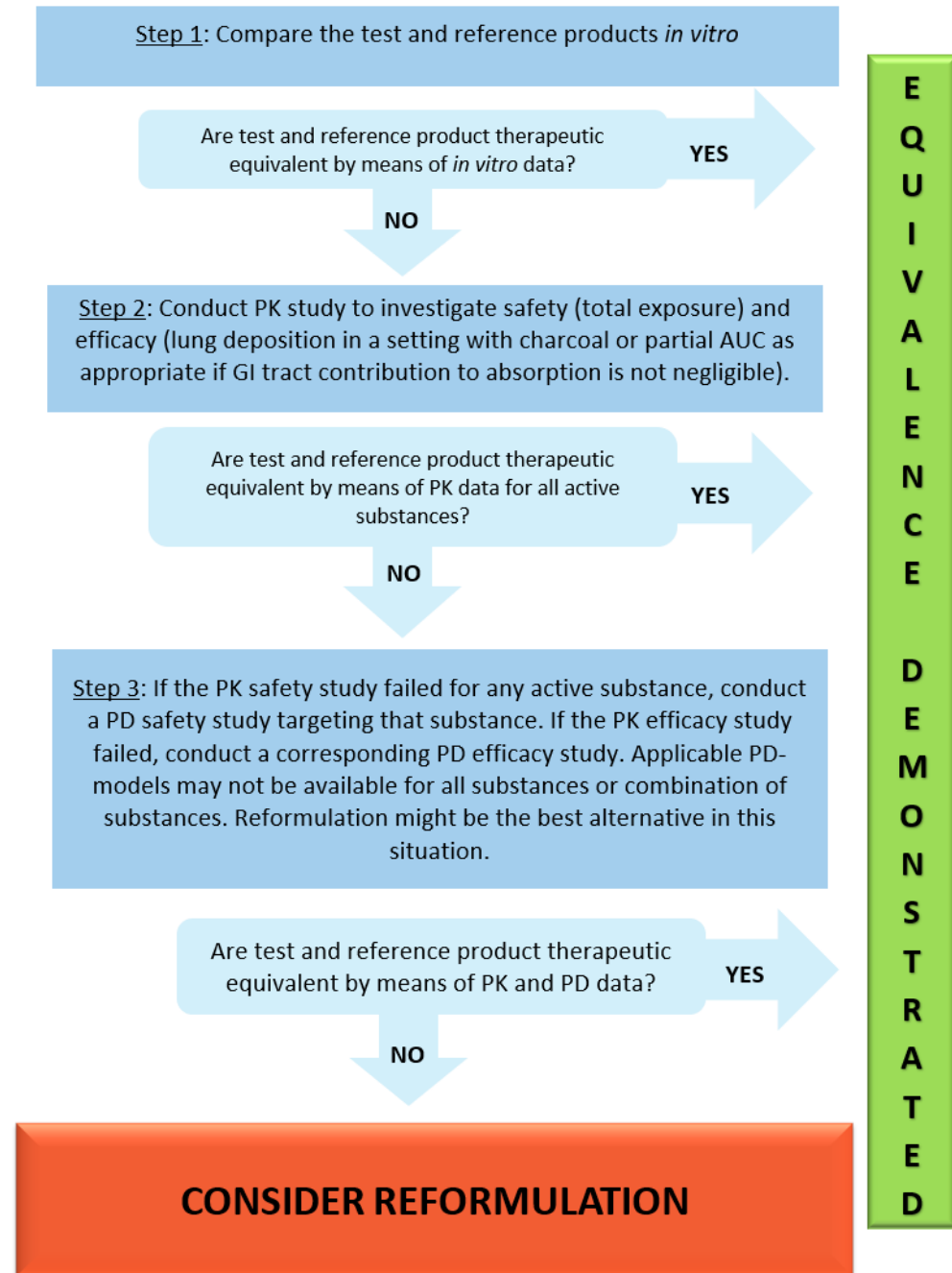
Therapeutic equivalence means that the efficacy and safety profile of the test and reference products is sufficiently comparable so that a clinically relevant difference between products can be reliably excluded.

Therapeutic equivalence

Stepwise approach

1. pharmaceutical equivalence only
2. permeation kinetic studies
3. studies with pharmacodynamic (PD) or clinical endpoints

Comparable with approach for Orally Inhaled Products



Principles

- It is generally very complicated to demonstrate equivalence with clinical outcome studies - to show therapeutic equivalence, a difference from placebo as such is not enough
- In general, in-vitro permeation test and pharmacokinetic studies are more sensitive to small changes in products than clinical outcome studies.
- The amount/concentration in plasma that is due to absorption from the skin, reflects both safety and efficacy because the amount available to go into the circulation (plasma) was also available to reach the site of action (skin) and equilibrium does not depend on the formulation once in the dermis, *or*
- If systemic exposure is similar, it is assumed that the exposure to and absorption through the skin is also similar

Therapeutical equivalence

The equivalence guidance (Section 5) does not apply:

- for products containing a narrow therapeutic index (NTI) drug
- to biological medicinal products, see guidelines on similar biological medicinal products.
- to herbal medicinal products.
- when equivalence with respect to efficacy is demonstrated by therapeutic equivalence clinical trials.
- when the pharmaceutical form of the test and reference products are not the same.
- when the method of administration is not the same.
- there are differences in the qualitative and/or quantitative composition of the excipients that may influence the condition of the skin to be treated

Definitions

Simple formulations are formulations with a single-phase base (matrix / vehicle) in which the active substance is in solution or suspension, e.g., solutions and suspensions in single phase liquids, -gels, or -ointments, and do not contain excipients that are intended to enhance drug permeation or are difficult to characterise (e.g. of biological origin).

Complex formulations are multiphase systems, which are difficult to characterise structurally (e.g., emulsions), or formulations with excipients that are difficult to characterise, and formulations containing excipients that are intended to enhance drug permeation.

Step 1 – pharmaceutical equivalence studies

- Same amount of the same active substance
- Same pharmaceutical form
- Pharmaceutical equivalence means that the products under comparison have the same qualitative (**Q1**) composition, similar quantitative (**Q2**) composition, and that physicochemical and structural characterisation (arrangement of the matter, **Q3**) is the same or at least sufficiently similar.

But also

- Same method of administration
- Same (performance) administration device
- when product-transformation occurs following administration, residue should be pharmaceutically equivalent (e.g., foam)

Step 1 – pharmaceutical equivalence studies

Q1 – same qualitative composition

Anti-oxidants, antimicrobial preservatives, colorants, and fragrances may be different, if Q3, incl IVRT, remains similar and no local safety issue

Paraffin homologues are acceptable if no impact on product performance (Q3, incl IVRT, and moisturising effect, remains similar and no local safety issue)

Step 1 – pharmaceutical equivalence studies

Q2 – similar quantitative composition

Excipients that may impact active substance solubility or thermodynamic activity:

- Qualitatively (grade) the same and difference in quantity < 5%

Other excipients:

- difference in quantity < 10%, if it is demonstrated that active substance solubility, thermodynamic activity or bioavailability and product performance (e.g. moisturising or occlusive effect) are not impacted

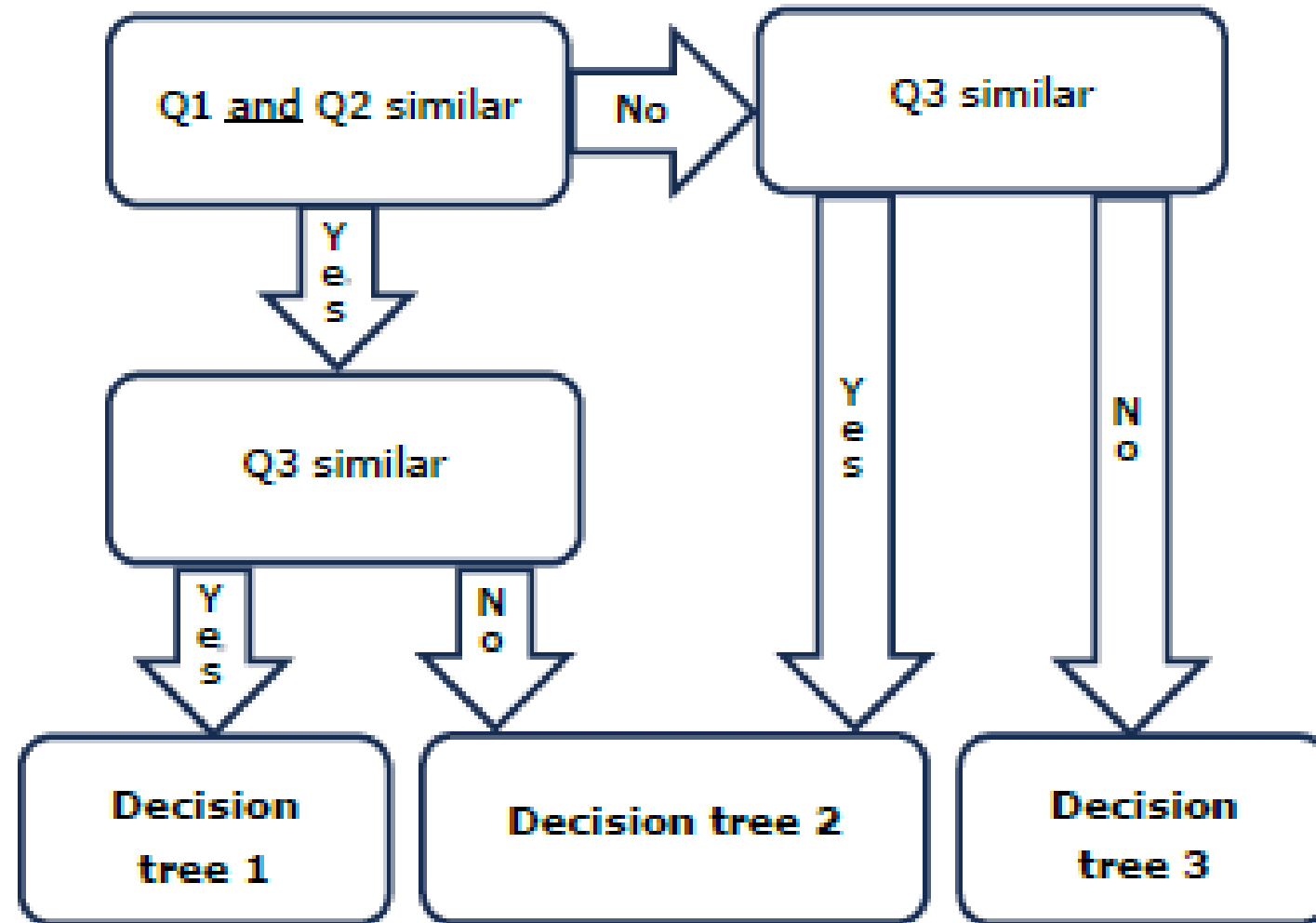
Step 1 – pharmaceutical equivalence studies

Q3 – physicochemical and structural characterisation

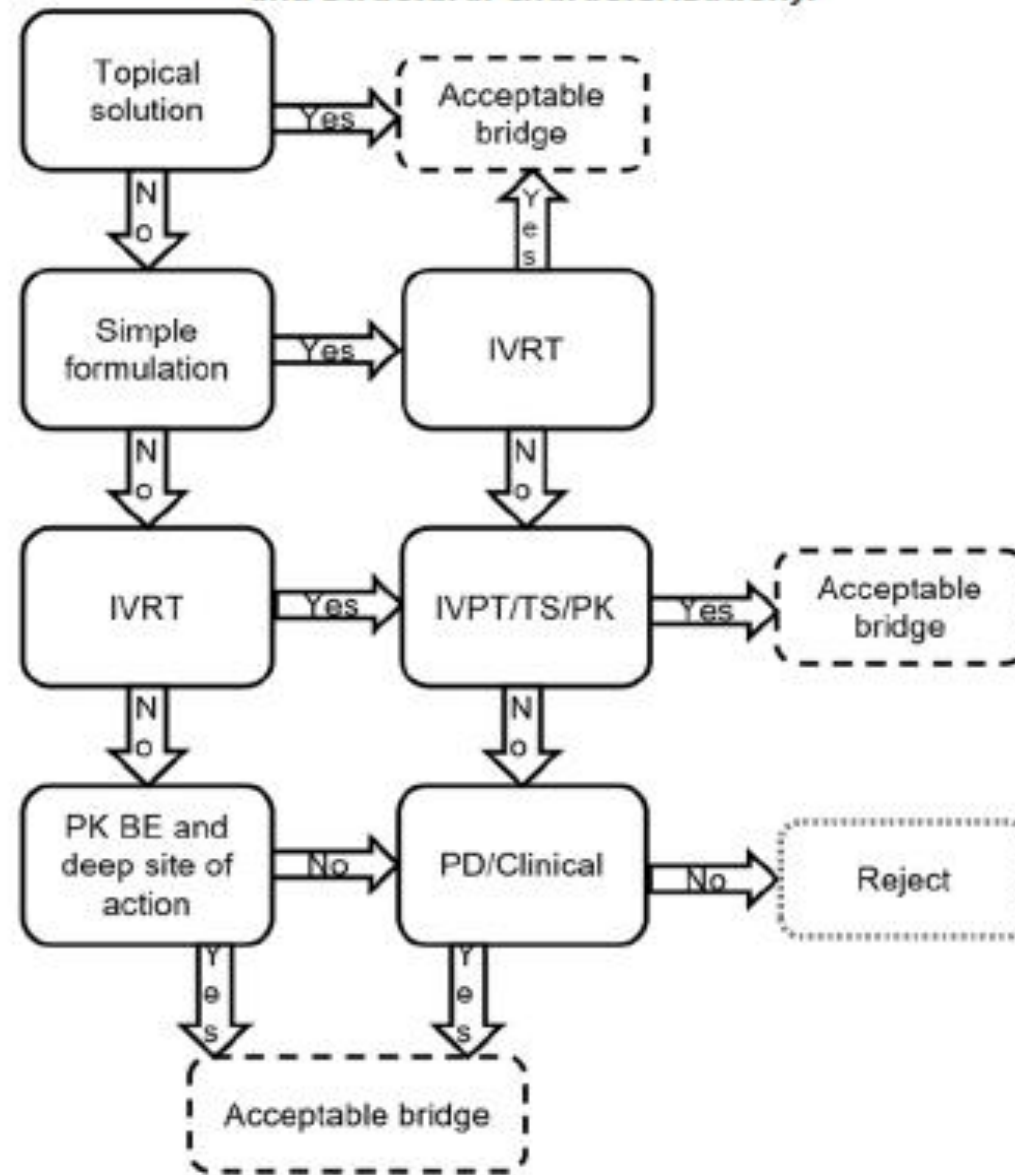
- Applicant should identify all critical quality attributes (CQAs)
- Compare 3 test vs 3 reference batches, 12 units per batch
- Protocol with predefined methods and acceptance criteria
- Quantitative quality attributes:
 - Average bioequivalence: ratio T/R 90% Confidence Interval within range $\pm 10\%$ to 20% depending on variability in reference product
 - Test within a range based on the underlying distribution of the reference product (scientific advice recommended)
- IVRT:
 - Average bioequivalence: ratio T/R 90% Confidence interval within range $\pm 10\%$ to 20% depending on variability in reference product
- Non-quantitative attributes: essentially the same

Decision trees have been included to clarify the stepwise approach

Scheme 1. Selection of decision tree in the stepwise approach

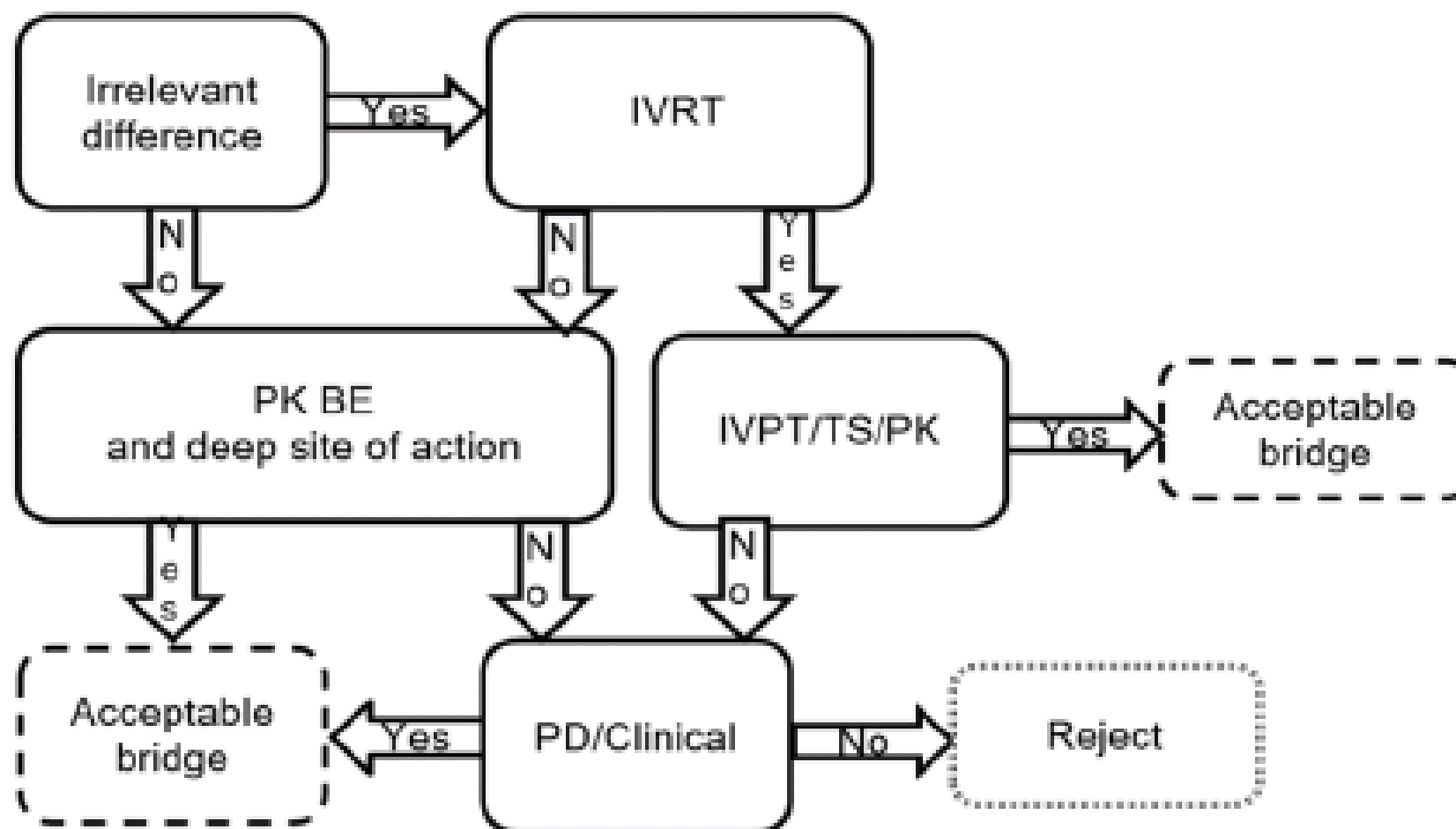


Decision tree 1 (same qualitative and quantitative composition and same physicochemical and structural characterisation).



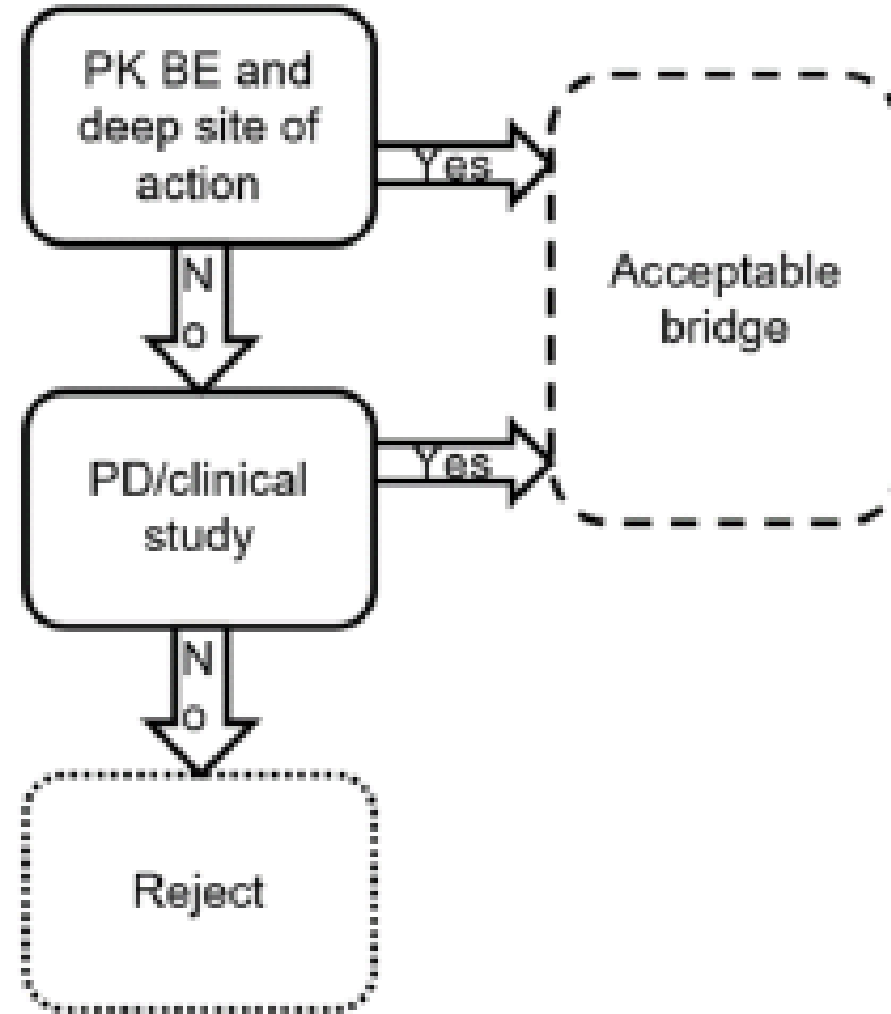
* *IVRT: in vitro release test, IVPT: in vitro permeation test, TS: tape stripping, PK: pharmacokinetics, PK BE: pharmacokinetic bioequivalence study, PD: pharmacodynamic.*

Decision tree 2 (In case of small differences in qualitative and quantitative composition and/or physicochemical and structural characterisation).



** IVRT: in vitro release test, IVPT: in vitro permeation test, TS: tape stripping, PK: pharmacokinetics, PK BE: pharmacokinetic bioequivalence study, PD: pharmacodynamic.*

Decision tree 3 (different qualitative and quantitative composition and different physicochemical and structural characterisation).



**** PK BE: pharmacokinetic bioequivalence study, PD: pharmacodynamic.***

Step 2 – Permeation kinetic studies

Permeation kinetic studies are always required if the formulation (test or reference) is a complex formulation:

- Is a multiphase system, which are difficult to characterise structurally
- Includes excipients whose function is to enhance drug permeation:
 - ethanol, isopropanol
 - propylene glycol, PEG
 - surfactants: sodium laurylsulfate, polysorbate
 - DMSO
 - urea
 - fatty acid esters
- Includes complex excipients where different suppliers or grades may affect the in vivo performance or stability of the active substance

Step 2 – Permeation kinetic studies

- In vitro skin permeation (IVPT: see Annex II for specific guidance)
- In vivo Stratum Corneum Sampling (Tape Stripping: see Annex III for specific guidance)
- Pharmacokinetic bioequivalence (see Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1 for specific guidance).

Pharmacokinetic bioequivalence studies are recommended when the active substance has quantifiable systemic bioavailability.

- If not, but drug diffuses through the skin to permit quantification in the receptor cell, IVPT studies are preferred.
- Tape stripping: if no skin permeation, yet quantifiable diffusion through stratum corneum
- If there is no quantifiable drug concentration in the stratum corneum, studies with PD or clinical endpoints are needed (Step 3)

Step 2 – Permeation kinetic studies

In those cases where the products are Q1, Q2, or Q3 not similar, but differences considered to be irrelevant, equivalence could still be concluded if it is demonstrated that the IVRT and the permeation kinetic are equivalent and it is justified that those differences have no different impact on the condition of the skin (hydration, softness).

Both products should produce a similar occlusion, hydration of the skin, transepidermal water loss, and have no different effect on skin microflora, skin pH, skin desquamation, lipid structure, etc.

This may require specific in vitro and/or in vivo studies on the condition of the skin.

Otherwise, studies with PD or clinical endpoints are needed (Step 3)

Step 2 – Permeation kinetic studies

In case of deep site of action, relevant differences in composition can be bridged by PK studies (so not by IVPT or TS) or clinical endpoint studies

Examples: diclofenac, ibuprofen

Step 2 – Permeation kinetic studies

Section 5.3.2 – *General Considerations on Study Design* contains detailed guidance on the permeation kinetic studies

- Managing variability
- Dose
- Sample sizes
- Acceptance criteria
- Batches to be tested
- Accreditation

It should be ensured that the performing laboratory is qualified to undertake the studies and that an effective quality system is in place.

Step 3 – Pharmacodynamic Studies

- Vasoconstriction test corticosteroids (Annex 4) in combination with Step 1: only minor differences in composition allowed; difference may not influence the condition of the skin to be treated
- Microbiological, in combination with Step 1
- Ocular pressure drop
- ...

For skin antiseptics for use prior to invasive procedures, a study in compliance with ASTM E1173 – 15 Standard Test Method for Evaluation of Pre-operative, Pre-catheterization, or Pre-injection Skin Preparations or an equivalent European methodology would be acceptable.

Safety

- For drugs with dose related, systemic toxicity, a bioequivalence study showing a similar systemic pharmacokinetic profile would be required to conclude that systemic exposure is not higher for the test product than for the reference product. Otherwise, clinical safety studies will be required.
- For cutaneous products, with a regional site of action, where the active substance has systemic bioavailability, bioequivalence studies provide evidence of both efficacy and safety.
- If the excipients are not qualitatively the same or not quantitatively similar, impact on the systemic and local safety profile should be addressed, including e.g., irritation, sensitisation, and phototoxicity.

Product Specific Equivalence Protocols

Equivalence may be concluded if results comply with the protocol criteria specified a priori.

Product-specific equivalence protocol should comprise:

- Justification that the drug product is within the scope of this guideline
- If applicable, justification for the absence of safety studies
- Pharmaceutical equivalence studies and equivalence in the method of administration
- If applicable, justification for the absence of a PK study
- Pharmacodynamic studies should be appropriately validated and related with the therapeutic situation

Post-authorisation changes

For any proposed change, a risk assessment should be performed to determine its impact on quality, safety, or efficacy of the product.

Some examples with potential significant impact

- change in the physicochemical state and / or thermodynamic activity of the active substance
- change that affects dissolution, in vitro release, and/or in vitro permeation kinetic characteristics of the drug product
- change that affects occlusivity, emolliency, and/or skin hydration
- change in the manufacturing process, e.g. a change in a critical process parameter

In all cases, the change should be supported by appropriate and representative batch data of the original and proposed change of all CQAs.

Example 1 – Mupirocine ointment 2%

- Reference product is Bactroban ointment
- Homogeneous single-phase matrix
- Macrogol 400 and Macrogol 3350 as only excipients
- Manufacturing process:
 - Mupirocine is dissolved in (liquid) Macrogol 400
 - Solution is added to molten Macrogol 3350 (mixing)
 - Homogeneous ointment-mixture is cooled on mixing.
- Approved (2005) based on non-inferiority study in children with impetigo
- According Guideline (2024) also approvable based on similar Q1, Q2, and Q3 (simple formulation)

Example 2 – Corticosteroid cream

Reference product	Test product
Hydrocortisonbutyrate 1 mg/g O/W emulgators Liquid parafin Preservatives pH corrigens Water	Hydrocortisonbutyrate 1 mg/g O/W emulgators Liquid parafin Vaseline Preservatives pH corrigens Water

- Results of the VasoConstriction Assay (VCA) have been provided and demonstrate similarity
- **Has therapeutical equivalence adequately been demonstrated?**

Example 2 – Corticosteroid cream

The vehicle itself may influence the disorder. Therefore, a pharmacodynamic model, e.g. the vasoconstriction assay (VCA), is sufficient only if the generic medicinal product possesses the same or a similar qualitative and quantitative composition to that of the reference product.

Example 3 – Fluoruracil cream

- Complex formulation: O/W multiphase system
- The active substance fluorouracil has a quantifiable systemic bioavailability.
- IVPT or PK as permeation kinetic study?

Example 3 – Fluoruracil cream

- According the GL a PK study should be submitted, as fluorouracil has a quantifiable systemic bioavailability.
- However, fluorouracil is genotoxic. PK study in healthy volunteers is therefore not preferable.
- Alternative options should be considered:
 - PK study in patients
 - IVPT

Ophthalmics

- Locally applied, locally acting?
 - Cutaneous?
 - Stepwise approach?
 - Step 1: In-vitro comparison
 - Step 3: Clinical outcome studies e.g. ocular pressure
- Also regional acting?
No
Yes, but no step 2 known



Step 1 – In-vitro comparison

- Aqueous solutions and simple suspensions
 - Same amount of the same active substance
 - Same excipients in similar amounts
 - Results of critical quality attributes are the same or similar

pH	Buffer capacity (if not near physiological pH)
Surface tension	Droplet volume
Density	Opalescence
Viscosity	Particle size (suspensions)
Osmolality	Suitability of the dropper

→ EMA/QWP Q&A on the comparison of quality attributes to demonstrate therapeutic equivalence (*to be published*)

Suitability of the eye-dropper

- Devices need not to be similar, but are assessed on their own merit (EU)

Please note

- Many complaints from HCPs and patients about eye-droppers
- Many different devices and different handlings
- Too fast, too slow
- Sharp edges
- EMA Q&A: What information on the functional qualities of plastic containers for eye drops should be included in the MAA dossier?
- EMA Q & A: Quality data requirements to demonstrate suitability of multidose containers for preservative free eye drops
- MEB always asks for samples for testing

Differences in excipients composition

- Step 1 complicated: how to show no impact on absorption
- No or little success with in-vitro models
- Models need to be clinically validated

Complex formulations (e.g. cream)

- Step 1 complicated: IVPT and PK not suitable for eye products?
- No or little success with in-vitro models
- Models need to be clinically validated

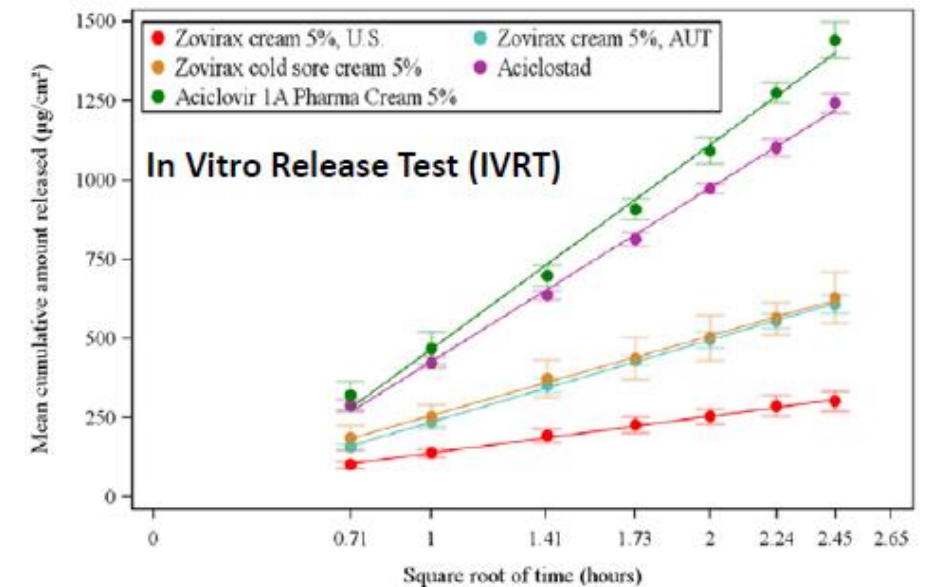
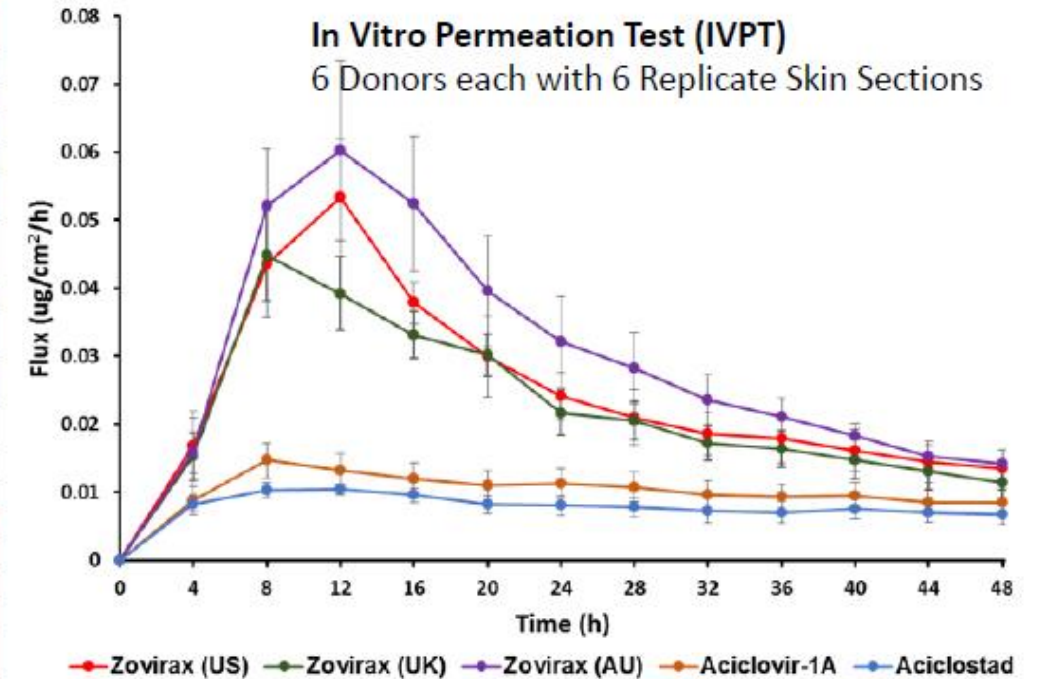
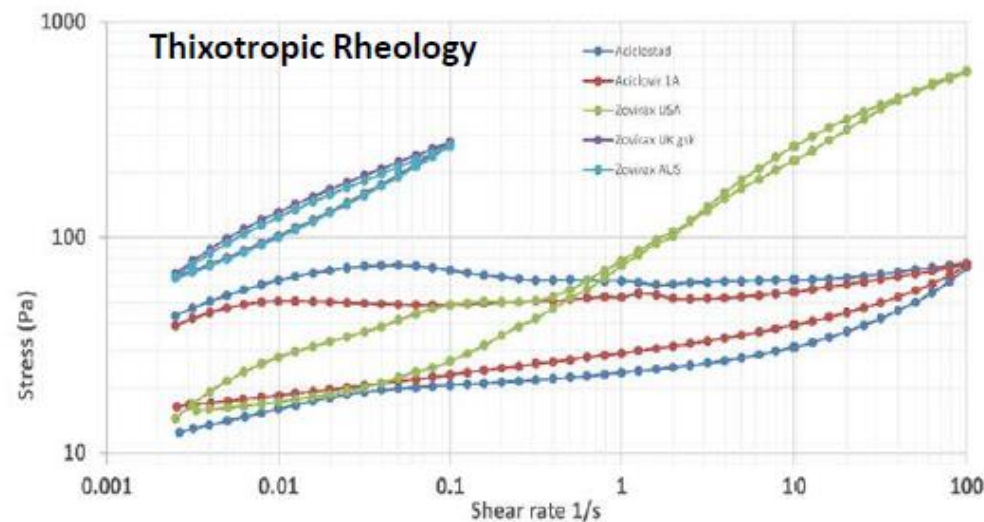
Take home messages

- Copy the formulation and device of the reference product
- Apply the 10 steps for in-vitro comparison of critical quality attributes (Q&A)
- If step 1 and step 2 not succeed, adjust the product (cutaneous)
- Copy the administration instruction of the reference product

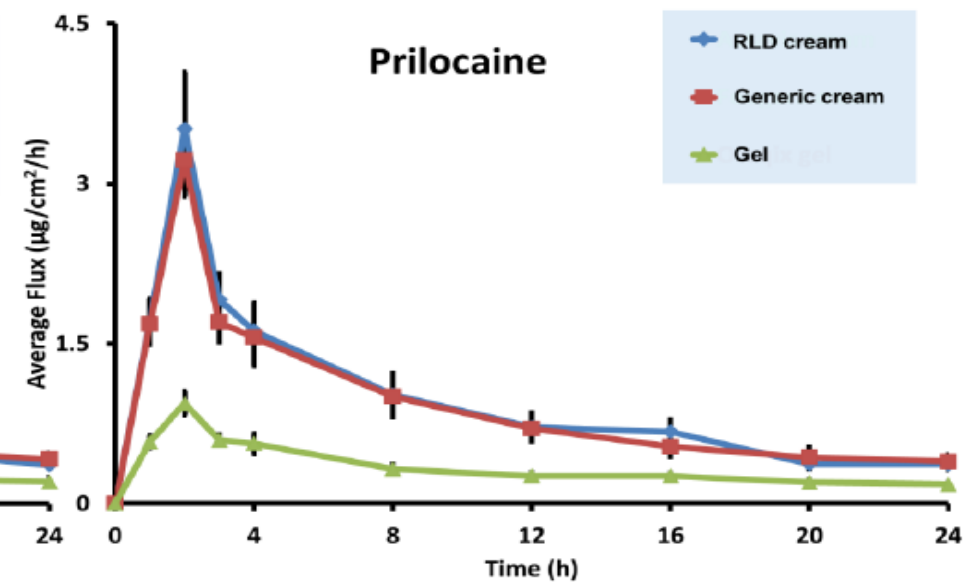
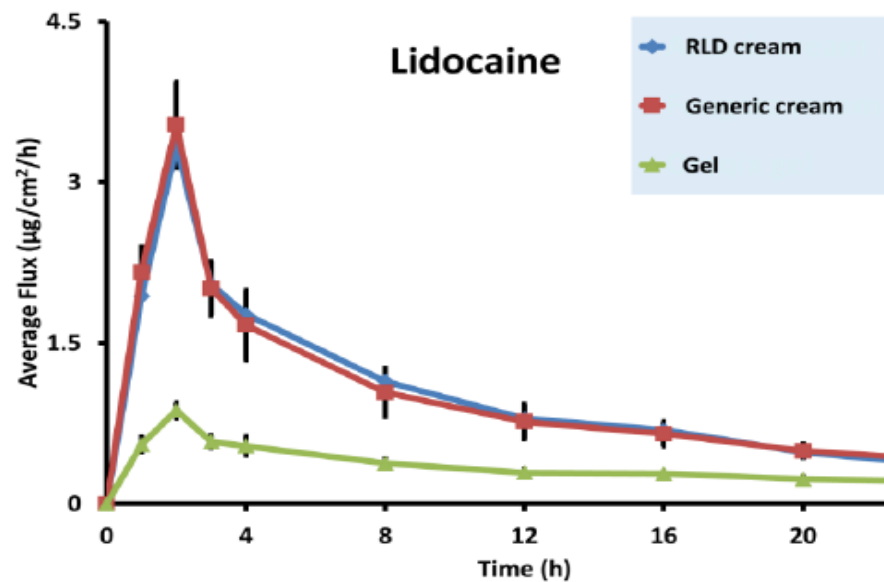
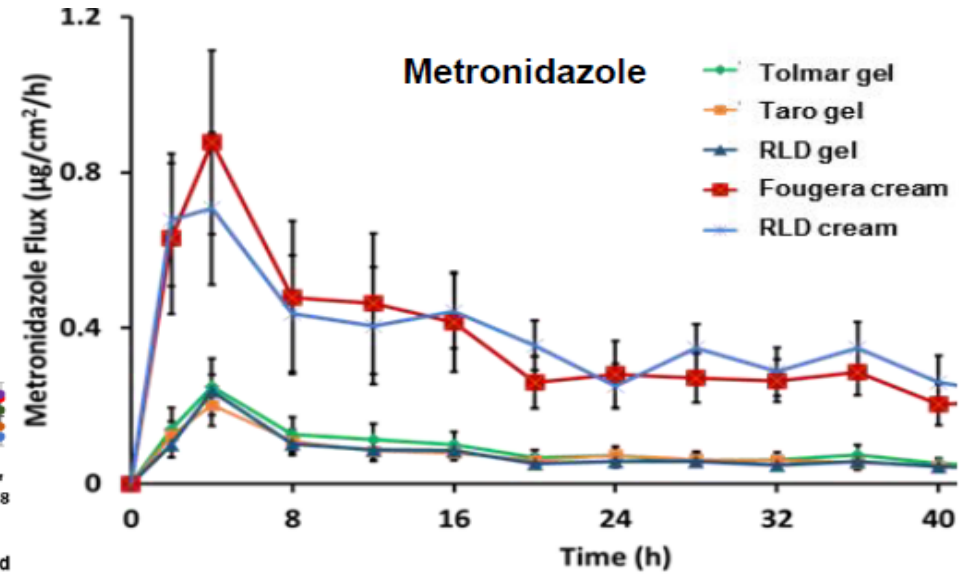
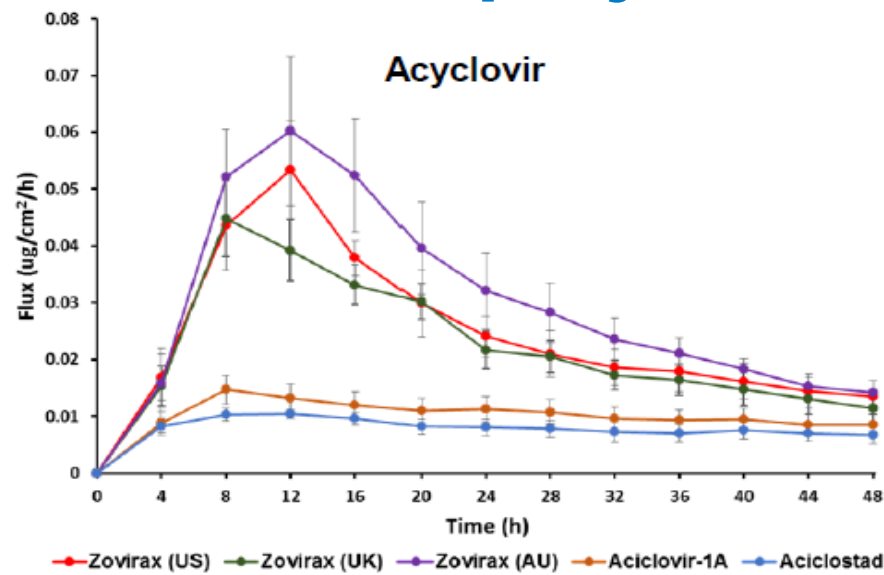
Back up slides

IVPT – FDA project with universities

	Zovirax (USA)	Zovirax (UK)	Zovirax (Austria)	Aciclovir (Austria)	Aciclovir-1A (Austria)
Water	Water	Water	Purified water	Water	Water
Propylene glycol	Propylene glycol	Propylene glycol	Propylene glycol	Propylene glycol	Propylene glycol
Mineral oil	Liquid Paraffin	Liquid Paraffin	Liquid Paraffin	Liquid Paraffin	Viscous Paraffin
White petrolatum	White soft paraffin	White soft paraffin	White Vaseline	White Vaseline	White Vaseline
Cetostearyl alcohol	Cetostearyl alcohol	Cetostearyl alcohol	Cetostearyl alcohol	Cetyl alcohol	Cetyl alcohol
SLS	SLS	SLS	SLS		
Poloxamer 407	Poloxamer 407	Poloxamer 407	Poloxamer 407		
		Dimethicone 20	Dimethicone 20	Dimethicone	Dimethicone
		Arlacel 165	Glyceryl Mono Stearate	Glyceryl Mono Stearate	Glyceryl Mono Stearate
		Arlacel 165	Polyoxyethylene stearate	Macrogol stearate	Polyoxyethylene stearate
Density (g/cc)	1.02	1.02	1.02	1.02	1.01
Content Uniformity (%)	97.9 ± 0.7	99.6 ± 1.4	100 ± 2.2	99.7 ± 1.7	98.3 ± 2.6
Polymorphic Form	2,3 hydrate	2,3 hydrate	2,3 hydrate	2,3 hydrate	2,3 hydrate
Crystalline Habit	Rectangular	Rectangular	Rectangular	Ovoid	Ovoid
Particle size (d50) (µm)	3.8	2.5	3.4	6.8	6
pH	7.74	7.96	7.54	4.58	6.05
Work of Adhesion	59	81	60	17	18
Drug in Aq (mg/g)	0.49	0.64	0.49	0.37	0.26
Drying Rate (T-30%)	>12h	~8h	~7h	<1h	<1h
Water Activity	0.75	0.73	0.74	0.95	0.95



IVPT – FDA project with universities



IVPT – FDA project with universities

1. In vitro cutaneous PK study using IVPT

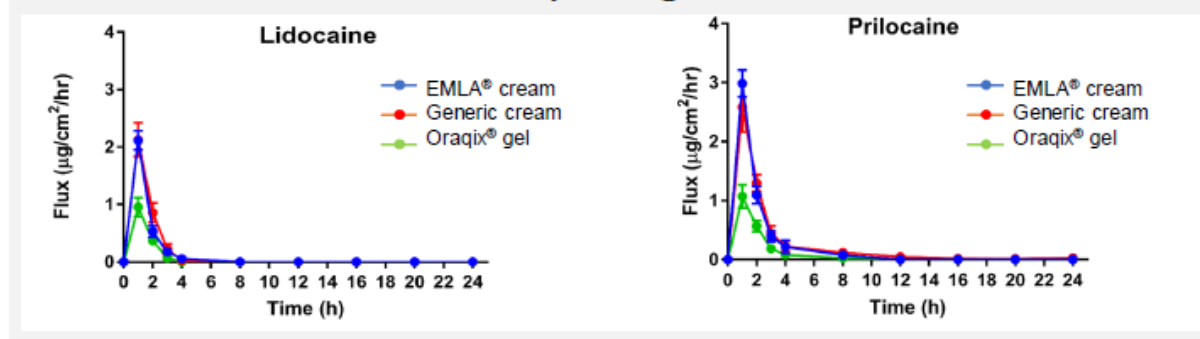


Figure 5. Cutaneous PK (flux profile) of lidocaine and prilocaïne in vitro from topical applications of the same dose of EMLA® cream, the generic cream, and Oraqix® gel. Data are shown as Mean $\pm$ SEM from 6 donors and 6 replicates.

2. In vivo cutaneous PK study using dOFM

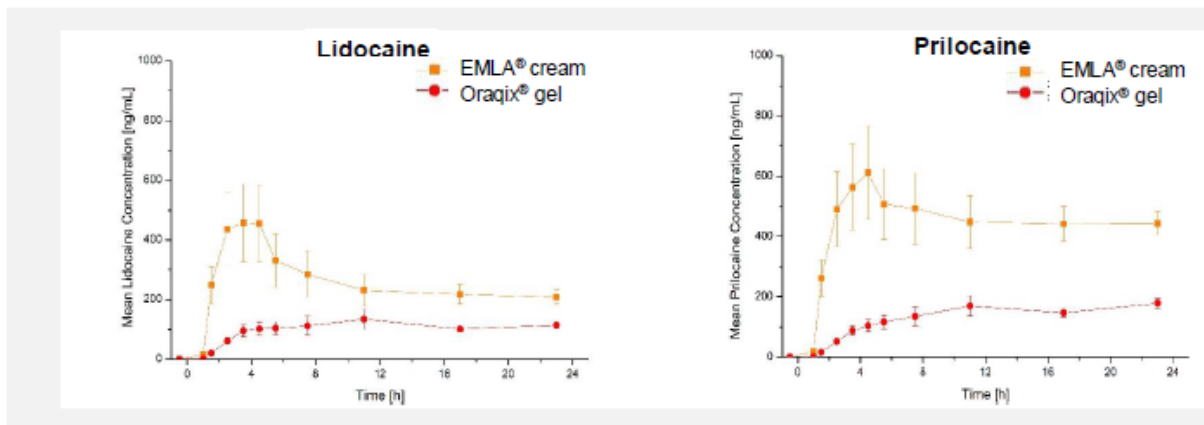
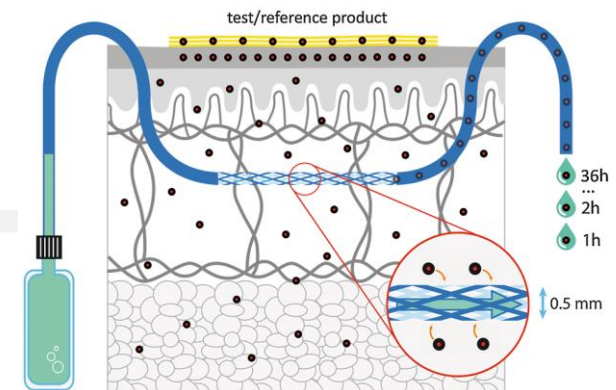


Figure 6. Mean lidocaine and prilocaïne concentration-time profiles ($\pm$ SE) for EMLA® cream and for Oraqix® gel following application of 10 mg/cm² of products. Data are shown as Mean $\pm$ SEM from six subjects.

Lidocaïne/prilocaïne
cream, cream, gel

- in-vitro characterisation
- IVRT
- IVPT
- dermal open flow
microperfusion (dOFM)



IVPT – FDA project with universities

Literature:

Cutaneous Pharmacokinetics of Acyclovir Cream 5% Products: Evaluating Bioequivalence with an In Vitro Permeation Test and an Adaptation of Scaled Average Bioequivalence. Pharm Res (2020) 37: 210 (University of Maryland)

Open Flow Microperfusion as a Dermal Pharmacokinetic Approach to Evaluate Topical Bioequivalence. Clin Pharmacokinet DOI 10.1007/s40262-016-0442-z. (2016) (University of Graz)

Cutaneous Pharmacokinetics-Based Bioequivalence: A Clinical Dermal Open Flow Microperfusion Verification Study Using Lidocaine and Prilocaine Combination Topical Products. European Journal of Pharmaceutical Sciences Volume 200, 1 September 2024, 106827.

GDUFA - [Generic Drug User Fee Amendments \(GDUFA\)](#)
[Browse Outcomes - The Center for Research on Complex Generics \(CRCG\)](#)