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The New EMA Guideline for Cutaneous Products
Changes from the 2018 Draft Guideline

keywords: cutaneous products, EMA, equivalence, IVPT, IVRT, quality

What is the guideline?

The European Medicines Agency (EMA) recently revised their guidance for demonstrating the quality and equivalence of cutaneous products. Initially drafted in June 2018, the revised version finally became effective in April of 2025. It is the "Guideline on quality and equivalence of locally applied, locally acting Cutaneous products," referred to below as simply the "Guideline."

What is the guideline for?

Any changes in a drug product's composition in the dosage form, in the manufacturing process, and so forth may have an impact on the efficacy or safety of it. If you manage such a product, it is up to you to prove that this is not the case. Therapeutic equivalence studies with clinical endpoints can do that. But these are typically time consuming and expensive.

Fortunately, the *Guideline* offers you support and guidance on how to use alternative methods like IVRT (in vitro release testing) and IVPT (in vitro permeation testing) to substitute for clinical data to demonstrate therapeutical equivalence.

What's new?

The new *Guideline* has:

A new title. The final document's title refers to "locally applied, locally acting cutaneous products," where the draft's title merely names "topical products." This reflects the final document's scope and focus.

An enlarged scope. The draft guideline is related to "locally applied and locally acting medicinal products for cutaneous use" and specifically mentioned "preparations for auricular or ocular use." But the new *Guideline* now also mentions products applied to the nail or to the mucosa.

Detailed guidance on quality. The final version provides more comprehensive guidance on the quality aspects of cutaneous products, including detailed sections on pharmaceutical development, product characterization, and stability programs.

A "stepwise" approach to equivalence testing. This includes steps to demonstrate pharmaceutical equivalence and to perform permeation kinetic and pharmacodynamic studies.

Updated annexes that provide detailed protocols for tests. IVRT, IVPT, stratum corneum sampling (tape stripping), and vasoconstriction assays for corticosteroids are discussed in detail. The IVRT and IVPT annexes are significantly expanded from those in draft version.

Quality and equivalence are the main subjects of the *Guideline*.

Quality

The quality guidelines are relevant for all new and generic drug products and for post-approval changes to them. The final quality guidelines differ little from those in the 2018 draft.

To guarantee a high-quality drug product, it is very important that you identify and know its critical quality attributes (CQAs). Drug release is one important CQA that must be specified and controlled for. In practice, doing so means performing IVRT on your clinical batch so that drug release specification limits can be referenced to that test data. IVRT is also part of the stability program and, if the drug goes into production, of commercial scale-up.

Equivalence

The equivalence guidelines are relevant whenever you must compare two products to each other—that is, for the development of a generic product, after a post approval change, and for scale-up.

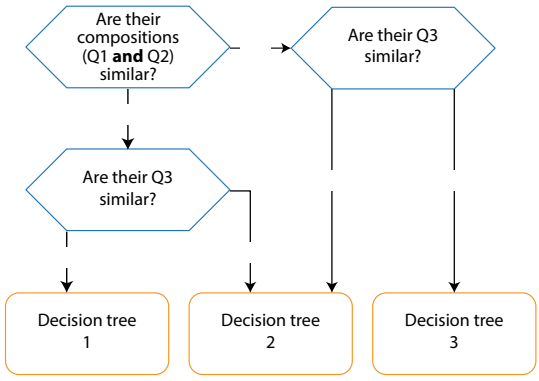
The *Guideline* takes a new "stepwise" approach to establish therapeutic equivalence. It includes steps with decision trees to demonstrate pharmaceutical equivalence and, if necessary, to perform permeation kinetic and pharmacodynamic studies.

Three attributes are considered:

Q1 - qualitative composition

Q2 - quantitative composition

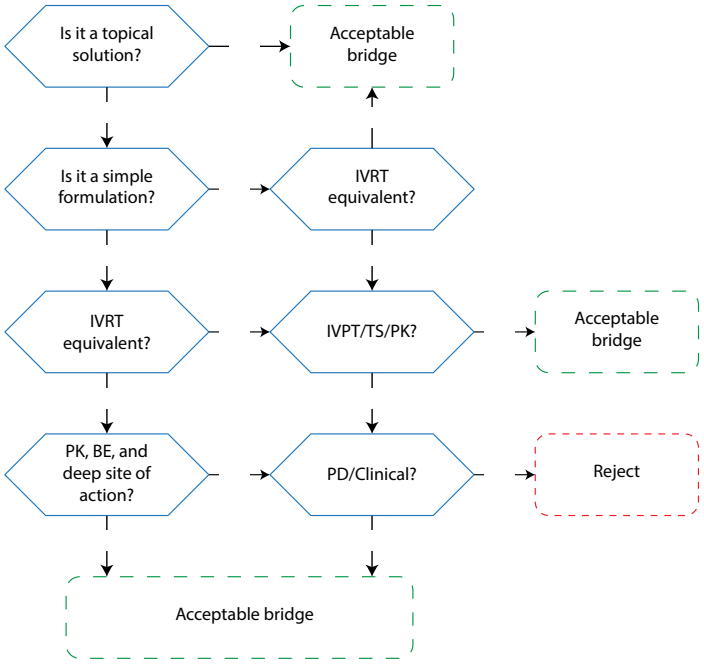
Q3 - physicochemical properties



The stepwise process

Step 1 – pharmaceutical equivalence studies

For solutions with the same Q1 and a similar Q2, you can conclude that they are equivalent if Q3 can also be shown and if pharmaceutical equivalence studies demonstrate equivalence (decision tree 1).

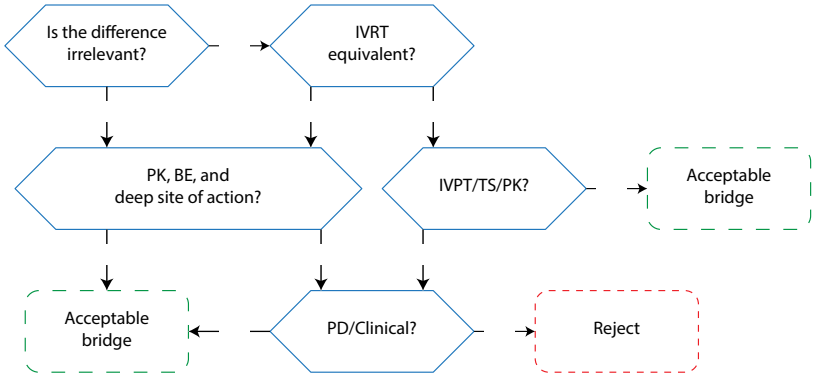


Decision tree 1

Demonstration of pharmaceutical equivalence requires comparative quality data with the relevant reference medicinal product.

Step 2 – permeation kinetic studies

If it cannot be established that Q3 are similar, equivalence might be demonstrated by performing IVRT (if the Q3 differences are irrelevant) and permeation kinetic studies. This is also true if Q1 and Q2 are not similar but Q3 are.

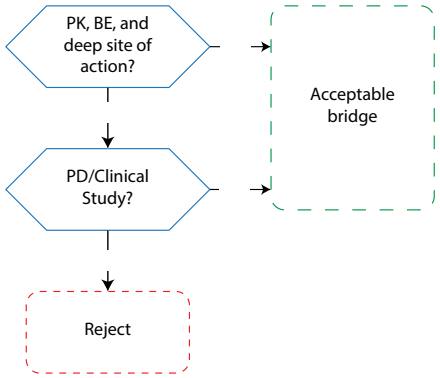


Decision tree 2

Permeation kinetic studies are always required if either the test or the reference solution has penetration enhancers or complex excipients.

Step 3 – pharmacodynamic studies

When Q1, Q2, and Q3 are not similar, you must perform a pharmacokinetic bioequivalence study, and possibly a pharmacodynamic study.



Decision tree 3

About the annexes

Annexes I (IVRT) and II (IVPT) have been significantly expanded from their draft versions.

Annex I: In vitro release test (IVRT)

- An IVRT using diffusion cells is called for, but other equipment (e.g., immersion cells) may be used.
- Regarding pharmaceutical equivalence testing, this is unchanged from the draft:

  > *The 90% confidence interval for the ratio of means of the test and reference products for the parameters (R) and (A) should be contained within the acceptance interval of 90.00 – 111.11%.*

  But this has been added:

  > In *case of higher variability of more than 10% in reference product is observed than the acceptance criteria might be widened up to 80-125% depending on the reference product variability* [...]

- The requirement that 70% of the active substance applied be released has been removed from the final guidance. Additionally, the consistency between samples of applied amount has been revised from 5% to 10%.

Annex II: In vitro skin permeation studies (IVPT)

- The use of ex vivo animal skin (as opposed to adult human skin) is explicitly deprecated, as it "is not currently sufficiently established to provide pivotal evidence."
- The determining mass balance is not always mandatory:

  The mass balance should be determined ***when possible*** [emp. added]. *Depending on the type of products and its composition, a justification for not determining mass balance could be accepted.*

  In the final *Guideline*, the phrase "when possible" is added, meaning that you, the applicant, can easily justify not determining mass balance when it is not possible for your product.

Why the Phoenix Systems?

The importance of In Vitro Release Testing (IVRT) and In Vitro Permeation Testing (IVPT) has significantly increased in the past few years. These methods are now central to demonstrating therapeutic equivalence and product quality for topical formulations, offering a structured, cost-effective alternative to clinical trials.

In this context, Teledyne LABS' Phoenix Robotic Diffusion Station (RDS) and Phoenix DB-6 Manual Diffusion System stand out as advanced, reliable platforms that enhance the accuracy, reproducibility, and convenience of IVRT and IVPT studies. The RDS automates sampling, collection, and media replacement of up to 24 cells. The DB-6 offers outstanding control of stirring speed and temperature using dry heat and is the only manual diffusion system built in with a computer control to assist with 21 CFR Part 11 compliance.

References

European Medicines Agency. Committee for Medicinal Products for Human Use (CHMP). Draft guideline on quality and equivalence of topical products (CHMP/QWP/708282/2018). London, 18 October 2018. Available online: https://www.ema.europa.eu/en/documents/scientific-guideline/draft-guideline-quality-equivalence-topical-products_en.pdf (accessed 20 October 2025).

European Medicines Agency. Committee for Medicinal Products for Human Use (CHMP). Guideline on quality and equivalence of locally applied, locally acting cutaneous product (CHMP/QWP/708282/2018 Corr.1). London, 9 September 2024. Available online: https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-quality-equivalence-locally-applied-locally-acting-cutaneous-products_en.pdf (accessed 20 October 2025).

See also

Teledyne LABS. Understanding EMA's Guideline on Quality and Equivalence of Cutaneous Products for IVRT. YouTube. 17 September, 2025. https://www.youtube.com/watch?v=wuKvz7CPQ8Y&t=1s (accessed 20 October 2025).