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DELIM

REGULATORY-COMPLIANT Q1/Q2/Q3 DEVELOPMENT OF A GENERIC SEMISOLID TOPICAL PRODUCT IN ACCORDANCE WITH EMA GUIDELINE (EMA/CHMP/QWP/708282/2018 REV.1) ON QUALITY AND EQUIVALENCE OF LOCALLY APPLIED, LOCALLY ACTING CUTANEOUS PRODUCTS

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01 INTRODUCTION

The development of generic semisolid topical products has become a key regulatory focus, highlighted by the publication of the EMA guideline EMA/CHMP/QWP/708282/2018 Rev.1 in September 2024. This guideline establishes a structured framework for demonstrating therapeutic equivalence, with particular emphasis on achieving qualitative (Q1), quantitative (Q2), and physicochemical/structural (Q3) similarity to the Reference Listed Drug (RLD), which serves as the benchmark. Within this regulatory context, the present study aimed to develop a Q1/Q2/Q3 equivalent emulgel containing a non-steroidal anti-inflammatory drug (NSAID), designed to match the composition and performance of the benchmark RLD.

02 BACKGROUND & SCOPE

The diversity of cutaneous products is very wide given the complex nature of skin, the range of conditions to be treated and the variety of patients and their needs. Changes in formulation, dosage form, method of administration, or manufacturing process may significantly affect the efficacy and safety of topical products. Although therapeutic equivalence is generally demonstrated through clinical endpoint studies, the guideline endorses a stepwise approach that allows the use of *in vitro* and *in vivo* models to substitute for clinical data in certain cases. Section 5 of the guideline specifically addresses the demonstration of therapeutic equivalence between a new medicinal product and an existing reference product.

03 THERAPEUTIC EQUIVALENCE

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. Demonstration of therapeutic equivalence between cutaneous products is based on a stepwise approach.

04 PHARMACEUTICAL EQUIVALENCE

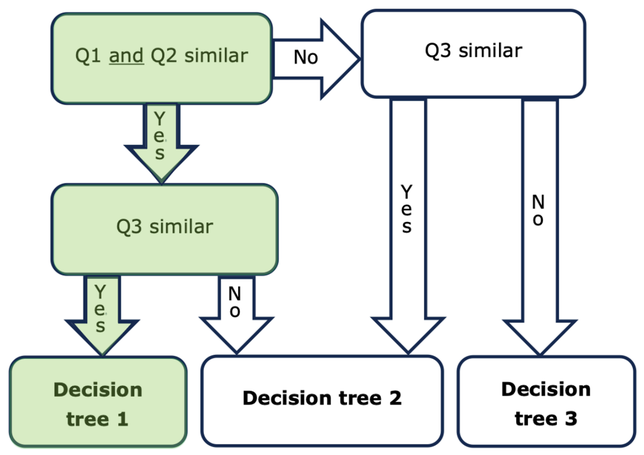
Pharmaceutical equivalence of developed emulgel has been demonstrated by matching:

- Q1: same qualitative composition
- Q2: similar quantitative composition
- Q3: comparable physicochemical and structural characteristics

The Q1/Q2 formulation of the RLD was obtained from reverse engineering and publicly available official sources. To establish Q3 similarity, a Quality by Design (QbD) strategy was implemented, including risk assessment and a Design of Experiments (DoE) approach to identify and optimize critical material attributes (CMAs) and critical process parameters (CPPs). This enabled the definition of a robust formulation and manufacturing process.

05 STEPWISE APPROACH

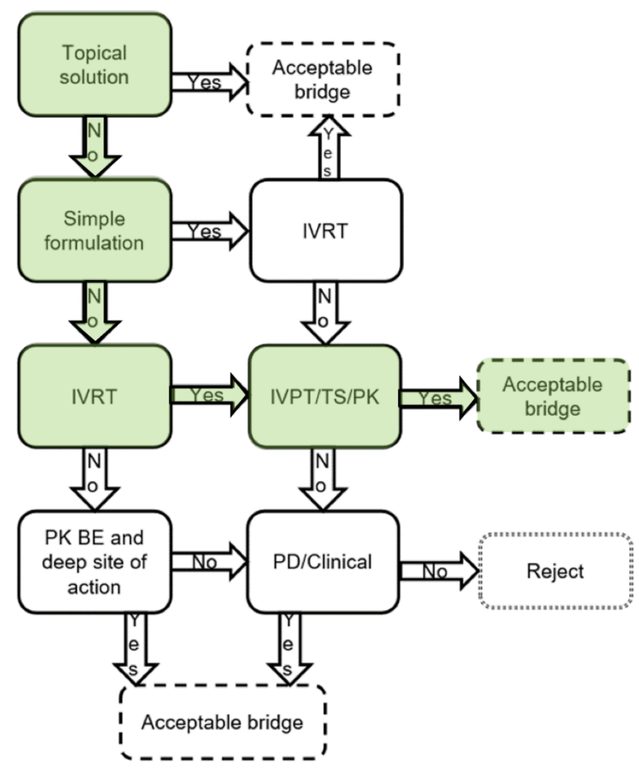
Q3 comparability was assessed based on critical quality attributes (CQAs) such as viscosity, globule size distribution, pH, density, spreadability and rheological behavior. In line with the EMA guideline, quantitative Q3 parameters were statistically compared between the test and reference products: the 90% confidence interval of the geometric mean ratio fell within a predefined acceptance range of ±10% (i.e., 90.00–111.11%), assuming log-normal data distribution. This statistical analysis was also applied for inter-batch comparability to confirm consistency across production lots.



Scheme 1. Selection of decision tree in the stepwise approach

For Q1, Q2, Q3 similar products, EMA guideline addresses a stepwise approach for testing, based on *decisional tree 1* and distinguishing among simple and complex cutaneous products. For the purpose of this guideline, developed product is considered to be a complex formulation as a multiphase system (emulsion) and consequently, *decision tree 1* reported in guideline schemes, led to a specific approach for *in vitro* & *in vivo* testing.

06 DECISION TREE 1



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

Following this pathway, an *in vitro* release test (IVRT) method was developed using Franz diffusion cells with synthetic membranes, in line with EMA recommendations (ANNEX 1). The method has been designed in terms of choice of membrane, receptor medium, sampling time, apparatus conditions, pH study, discriminative power and sensitivity to formulation changes. IVRT results has been used to support Q3 characterization and comparability with RLD. In complex formulations that are Q1, Q2, Q3 compliant and exhibit a similar IVRT, therapeutic equivalence may be concluded if its permeation kinetic is shown to be equivalent. Selected drug has no quantifiable systemic exposure but diffuses through the skin to permit quantification in receptor cell. Based on this considerations, the conclusive step was an *in vitro* permeation test (IVPT), in accordance with the *decision tree 1* outlined in the EMA guideline, to further support demonstration of Q3 similarity.This structured, regulatory-driven development strategy establishes a scientifically robust foundation for dossier submission and approval of topical generic product in the European market.

07 REFERENCES

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08 CONTACTS

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