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# EMA's proposed Guideline on Quality and Equivalence of Topical Products and Nanotechnology: Future Advances and Challenges

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## 1. Introduction

Showing bioequivalence of a generic topical product versus its reference product is not easy to achieve knowing that clinical sytemic pharmacokinetic does not always represent the site of action, which is mainly dermal. Bioequivalence clinical study are expensive and time consuming resulting in reducing companies endeavour to develop generic version of branded topical drugs. Consequently, many branded topical products are on the market well after the expiration of the originator, without the option to have cost effective generic alternatives which could benefit the patients.

Nanotechnology is an emerging technology which has not yet an harmonized status regarding safety toxicity and labeling because it is a technology. It is used in medical products or cosmetics to increase the bioavailability of the drug or affect the look and feel of the cosmetic product. Nanomaterial ranges from 1 nm to 100 nm and can exhibit different chemical, physical or biological effects compared to larger scale couterparts.

This abstract aims to make an overview about the updated regulations and the alternative methods for showing equivalence of topical products and safety of nanotechnology.

## 2. Overview

### *Regulatory update*

The draft EMA guideline CHMP/QWP/708282/2018 will soon replace the following guideline:

- annex 1 of the Guideline on Quality of Transdermal Patches (EMA/CHMP/QWP/608924/2014) - annex on In vitro permeation studies.
- questions and Answer on Guideline: Clinical Investigation of Corticosteroids Intended for Use on The Skin (CHMP/EWP/21441/2006).

Its novelty is the introduction of the extended pharmaceutical equivalence concept provided by in vitro drug release testings, rheological comparison and in vitro skin permeation and skin absorption using tape stripping.

The in vitro pharmacodynamic test for infective agents and the vasocontriction assays allow to reduce the number of patients in group.

### *Topical Classification System*

Vinod Shah et al.,[1] have developed the Topical Classification System (TCS), a framework analogous to the Biological Classification System (BCS) for solid dosage forms, which classifies them based on solubility, permeability, and dissolution. Just as the BCS allows developers a biowaiver in some cases so they can bypass clinical bioequivalence testing, so does the TCS [1].

### *In vitro drug release, in vitro skin permeation and distribution*

Performing IVRT and IVPT correctly require skilled technicians, and results can vary, due to differences in operator training, in instrumentation, and other factors.

IVRT does not enable to show the effect of ingredient onto skin such as permeation enhancer. In this case IVPT is complimentary.

A single air bubble can form under a skin sample, for example, affecting the data. To reduce variability of data skins issued from esthetical surgery can be prepared dermatomed and provided by Xenometrix (Switzerland) and good manufactured equipment with controlled stirring can be provided by the Dry Heat Diffusion Testing System from Teledyne HANSON Research (USA) Before applying products the skin quality can be evaluated with the Vapometer (from Delfin, Finland) which enables to measure transepidermal water loss without changing receptor fluid.

As drugs increase in size and lipophilicity the levels permeating through the skin can quickly approach

the analytical detection limits of even modern liquid chromatography–mass spectrometry equipment. To add to these challenges associated with minimizing data variation, the guidance documents also require that any analytical methods to be fully validated.

IVPT in static Franz cells does not take into account the effect of skin metabolism or blood flow. To overcome this latter, it is proposed to use the Dry Heat Diffusion Testing System RDS with automated collection from Teledyne Hanson (USA). This system enables to collect all samples at the same time and at short time sampling interval, increasing reproducibility, and thus reliability.

Group of Professor Kalia at the University of Geneva setup recently a new method which enabled to quantify the amount of an anti-fungal drug as a function of position thorough the cutaneous layers from the stratum corneum to the upper dermis[2].

*In vivo pharmacodynamic effect*

Bioequivalence clinical studies often involve a large patient population (n > 100) to provide sufficient data for statistical evaluation. Cost and time for conducting these studies can be significant. An alternative approach to clinical endpoint for topical corticosteroid products, is the application of the vasoconstrictor assay (VCA), otherwise known as the human skin blanching assay. This assay is effectively a bioequivalence study with a pharmacodynamic endpoint. To measure this effect, an alternative to the chromameter is the C-Cube dermatocope by Pixience (Pixience, France), an instrument that provides an optimized image and accurate colour quantification.

Measuring skin absorption of certain active drug in vivo has been shown using the gen 2-Skin Composition Analyzer (gen2-SCA) from RiverD (Netherlands).

*Nanotechnology in topical products*

Almost 15000 personal care products and more than 7000 constituents ingredients consists of nanotechnology although their exposures and potential risks are not well known [3]. Nanoparticle in cosmetics can exist as labile nanoparticle which disintegrate when applied to the skin or insoluble particle which remain insoluble such as $TiO_2$ found in sunscreen topical products. Due to smaller dimension and larger surface area and potential to have a facilitated penetration, as well as shape, charges aggregation and solubility are other properties of nanomaterial which can influence toxicity. Thus, each newly synthesized material must be assessed individually. The biggest safety risk is due to the inhalation of particles. Some relevant toxicological endpoints are induction of cellular stress, cell damages or cytotoxicity which can be evaluated using the skin explant Genoskin (Genoskin, France) which is viable for 7 days.

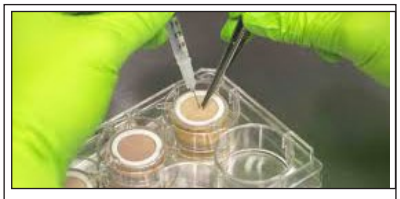

***Figure 1*** *ex vivo skin explant from Genoskin (France)*

Other factor that should be addressed include the potential to find different type of impurities occurring in the final products. A newly assay (Xenometrix, Switzerland) enables to evaluate the genotoxic potential of an impurity, at less than 1 mg, extracted directly from the product.

HoloM4 (PHI, Sweden) provide 3 D imaging enabling to quantify and visualize in vitro the effect of nanoparticles in human cell culture stain free and quantify it, thus under in situ conditions and in real time[4].

## 3. Conclusions

Cumulative regulatory initiatives from the EMA and FDA are facilitating the regulatory pathways to demonstrate quality and equivalence of topical products. Nanotechnology which has not yet an harmonized regulation enables to deliver the drug at the site of action and gives a better sensory feeling for topical products The drawbacks is to avoid systemic absorption. Consequently information on dermal toxicity, absorption through the skin and toxicity through other routes of administration should be aimed. The first step to harmonization of nanotechnology regulation will be the labelling of nanomaterial in consumer products.

New biological material and equipments were recently developed which will bring advances for all the new regulatory challenges.

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