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The Relations Between Q3 Measurements, *In vitro* Release and TCS

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The Topical drug Classification System (TCS) is a framework specifically design for the comparative assessment of semisolid dosage forms. Compared to the Biopharmaceutics Classification System, TCS relies on the assessment of the qualitative and quantitative compositions as well as on the sensitivity of the *in vitro* release tests (IVRT) to signal potential differences in the microstructure. The arrangement of the components of the semi-solid matrix is the complex results of the nature and intensity of interactions between the excipients, the impact of the manufacturing process and the changes which occurring during the shelf life of the product. When applied *in vivo*, a topical dosage form is subjected to shearing forces for spreading at the site of administration. The complexity of structural changes is difficult to simulate *in vitro* and a wide variety of methods have been proposed to evaluate the internal interactions for a cream, gel or ointment.

For the comparative assessment of topical semisolids, the available guidance documents have strict requirements in terms of similarity of the qualitative and quantitative composition (Q1 and Q2). Differences in the amounts of the same excipients are usually limited to +/-5%, considering their potential role in the permeation and penetration across the skin barrier. Larger limits, i.e. +/-10% are mentioned ingredients with specific functionality by the current version of the European Medicine Agency draft guidance on quality and equivalence of topical products. For mitigation of the risks associated with the manufacturing process, several rheological parameters are to be evaluated, i.e. yield stress, storage and loss modulus, zero-shear viscosities or areas and model parameters associated with the thixotropy loops. Considering the product-specific draft guidance issued by US-Food and Drug Administration (US-FDA), the assessment of Q3 (microstructural) similarity depends upon the complexity of the dosage forms

and may include, in addition to rheology, specific parameters, such as particle or droplet size determination, crystal behavior, polymorphism, fraction of drug dissolved etc.

IVRT was initially mentioned in the SUPAC-SS guidance of US-FDA (1997) for the evaluation of well defined, level 2 changes of composition or manufacturing process, based on the ability to reflect in aggregate the influence of several critical variables. Gradually, its role and applicability have been extended to comparison of topical semisolid across manufacturers.

In the 1998 draft guidance Topical dermatological drug product NDA's and ANDA's - *In vivo* bioavailability, bioequivalence, *in vitro* release, and associated studies, IVRT was proposed for the evaluation of the lower strength, once the bioequivalence for the higher strength of a generic product has been demonstrated in relation with the reference. Moreover, as part of "sponsor-specific comparability protocol", IVRT was to be used for approval of more extensive variations, beyond SUPAC-SS level 2. Even though this part was never contested, it was withdrawn together with the dermato-pharmacokinetics methodology in 2002. Currently, the EMA draft guidance (2018) assigns a central role to IVRT, as it is "required to support" the new concept of extended pharmaceutical equivalence. An additional level of similarity has been mentioned, considering the impact of methods and means of administration (Q4). The device may alter the microstructure of the semi-solid before the application, therefore test conditions mimicking the *in vivo* use are essential for adequate comparison.

The term history of formulation includes transformation occurring beyond the manufacturing process. The creams, gels and ointments are subject to time, shear and temperature dependent modification of the arrangement of the matter, which may alter their quality and performance.

Table 1 Definitions of Q1, Q2, Q3 and Q4 similarity

Q1	Qualitative sameness	Same components	In some instances. subject to patent pending. Q1 & Q2 = / ≠ Q3
Q2	Quantitative sameness (±5%; US-FDA)	Same components Same quantities	
Q3 / Q4	(Micro) Structure sameness Methods and means of application	Same arrangement Similar (device)	IVRT Rheological behavior Globule / particle size Crystal habit Polymorph Density Flow / deformation (rheology)
(E) PE	Pharmaceutical equivalence EMA (2018): <i>Equivalence with respect to quality:</i> Extended PE concept Relevant data, Relevant comparator (reference product)	-Drug -Strength / Concentration -Dosage form (Complexity) -Route (methods and means?) Comparable (<i>adequate</i>) labeling Meet compendial & other applicable requirements.	Same:
TE	Therapeutic equivalence		TE = PE + BE

IVRT has been in use for the assessment of stability, base on its assumed ability to reflect the overall changes.

TCS relies on the sensitivity of IVRT for signaling significant differences in the in vivo performance. When Q1, Q2 and Q3 is concluded for the compared products, this corresponds to TCS class 1 and the approach is similar to the current regulatory framework (either product specific draft guidance of US-FDA including an *in vitro* option or EMA draft guidance). A biowaiver may be granted when *in vitro* release similarity is concluded after a critical analysis of Q1 and Q2 difference. This case illustrates TCS class 3 and represents the potential extension of the use of IVRT beyond the strict requirements of sameness (e.g. +/-5% or +/-10% limits in the percentage of the same excipients).

It is assumed that an adequately developed and validated *in vitro* methodology will signal potential inadequate performance of the topical semisolid. For excipients, an inert / non-inert dichotomy has been proposed, considering their functional role, i.e. the impact on the permeability of biological barrier. Even though an artificial membrane is not a reactive barrier like the skin, it will be discriminative if nor overly discriminative for the changes induced in the microstructure by an absorption promoter.

The presentation will include examples illustrating the relations between the composition, the manufacturing process, the resulting microstructure and IVRT. As a first step for validation of TCS principles, evaluations of marketed, multisource topical products were conducted. The results confirmed the sensitivity of IVRT for microstructural

differences, as the complex result of interactions within the semisolid matrix. Prototype formulations with controlled changes in the preparation or composition were design and subjected to the same methodologies. The available data supports the initial assumptions of TCS.

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