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Evolving concepts of sameness, similarity and extended equivalence for topical semisolids

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Outline

Complexity of topical semisolids, brief description

Extended concepts of pharmaceutical equivalence

/ aggregate weight of evidence / totality of evidence

EMA Draft guideline on quality and equivalence of topical products (2018)

- Steps, methodologies and acceptance criteria
- Model dependent approaches
- Microstructure and (in vitro / ex vivo) performance
- (Briefly) Dermatopharmacokinetics

Conclusions

Topical semisolids

Complex drug products, prudent approaches (1)

- Local, regional and / or systemic effects
- Solid like or liquid like depending on context
- Microstructure depending on composition and manufacturing
- Continuously changing (history, aging, sharing forces)
- The transformation continues after application
- Difficult to simulate this complexity with a single, biopredictive test
- Biorelevancy (simulating skin conditions) could be feasible, but complicated
- Difficult to correlate the results from various tests
- *IVIVC, feasible, but not mandatory*
- Overall, a prudent approach to reduce the risks of bio-inequivalence

Topical semisolids

Complex drug products, prudent approaches (2)

- Wide variety of dosage forms, with distinct mechanisms of release
- Difficult to identify the (in vivo) rate limiting step
- *May be considered extended release preparation (USP)*
- Barrier properties are essential
- In some clinical instance, barrier changes are extreme
- Comparing products across manufacturers depends on the degree of similarity
- It is assumed that there are no inert excipients
- Excipients have dose and concentration dependent effects (contextual)

Sameness requirements

Qualitative composition

- **Impact on Quality**

State of aggregation, interactions, diffusion (release), stability

- **Impact on Safety**

Irritation, sensitization, skin conditions (major changes of the barrier)
Systemic availability when local action is targeted may become a safety issue

- **Impact on Efficacy**

Local , regional and systemic availability
Proportionality between local/regional and systemic levels
Effective concentration C* (how fast, what level, for how long?)
Directly involved in the therapeutic outcome

Sameness requirements

Quantitative composition

- **Same excipients, in the same amounts, lower risks on safety and efficacy**
- **Excipients have dose and concentration dependent effects**

- **In vivo context-variables: dose (amount), surface, thickness**
- **Composition, manufacturing, application (device) and dose, together with local (physiological and pathological) context give transformation**
- **Transformation (*metamorphosis*) is complex, difficult to simulate, assumed to be critical for outcome**
- Excipients may undergo evaporation loss and penetration / permeation, changes in the state of aggregation which may be concentration dependent.

Sameness requirements

Dispersion and interaction of the components

- Drug may be dissolved or dispersed (partially suspended)
- State of aggregation of drug, surface of contact between phases of complex systems and the affinity (distribution) of drug are important for release and absorption
- Dissolution and / or (diffusional) release may be the rate limiting steps
- It is important to assess not only the dispersion of material, but also the interaction of the dispersed matter
- Interactions depend on the whole history of the matrix (manufacturing, aging, storage conditions, methods and means of administration etc.)

*Same*ness requirements

*Similar*ity requirements

- Due to complexity of the topical dosage forms, 1:1 copies are preferred
- This means decomposing accurately a reference product, but not only
- Interactions of components are process-dependent and dynamically changing throughout shelf-life
- Interactions means (micro)structure at rest and response under stress
- Reference product may be a variable / moving target

  (difficult to attain)
- Composition may be the easiest to copy (when possible), but understanding microstructure, changes and in vivo behavior may be challenging

  (site of action, rate of delivery, level of local exposure)
- Transition from same (1:1) to not exactly the same (similarity) should keep minimum the risk of non-similar in vivo outcome

EMA draft guideline (history)

on quality and equivalence of topical products

Concept paper (**2014**)

Draft guideline (**2018**)

Some DRA apply

Some DRA ignore

Nothing new (**2022**)

Experience gained

Document history

Draft guideline on quality and equivalence of topical products (PDF/256.86 KB)

Draft: consultation closed

First published: 14/12/2018
Consultation dates: 14/12/2018 to 30/06/2019
CHMP/QWP/708282/2018

Concept paper on the development of a guideline on quality and equivalence of topical products (PDF/93.46 KB)

Draft: consultation closed

First published: 22/04/2015
Last updated: 22/04/2015
Consultation dates: 22/04/2015 to 22/07/2015
EMA/CHMP/QWP/558185/2014

https://www.ema.europa.eu/en/quality-equivalence-topical-products#document-history-section

EMA draft guideline

on quality and equivalence of topical products

Word counting:

"justified" n=45

"relevant" n=20

also.., ..standards (guidance), may also be .., .. monographs, if .., all (other) .. data, cross-references to .. sections, .. CQA, where .., ..COMPARATOR, .. to efficacy, if possible and .., .. parameters, (or other..) criteria, STATISTICALLY RELEVANT, is also ..

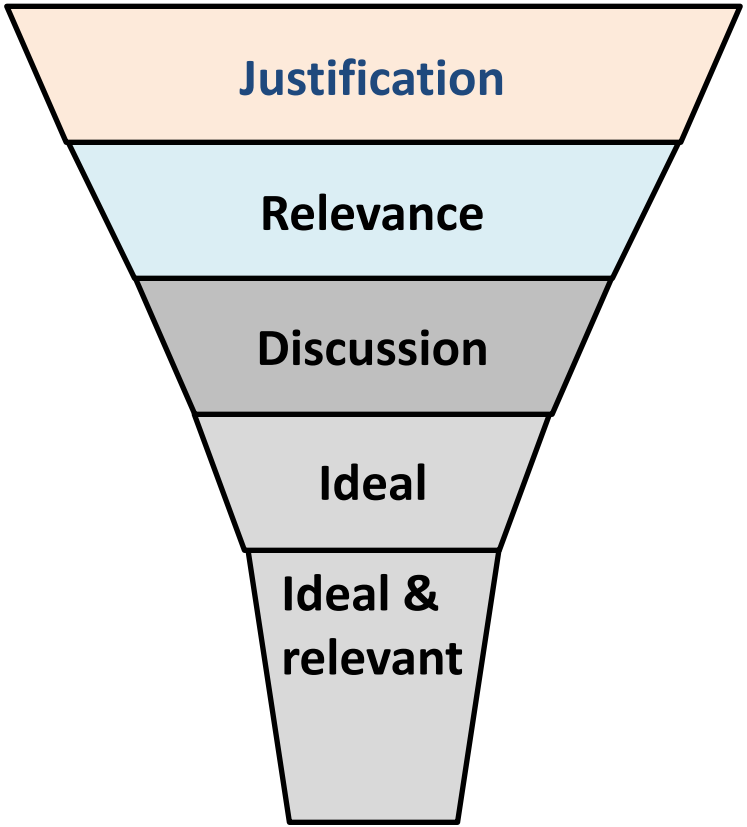
"discussed" n=16

"ideally" n=3

"explained and justified" or "discussed and justified" n=2

satisfactorily or fully "explained"

"ideally and when relevant" n=1



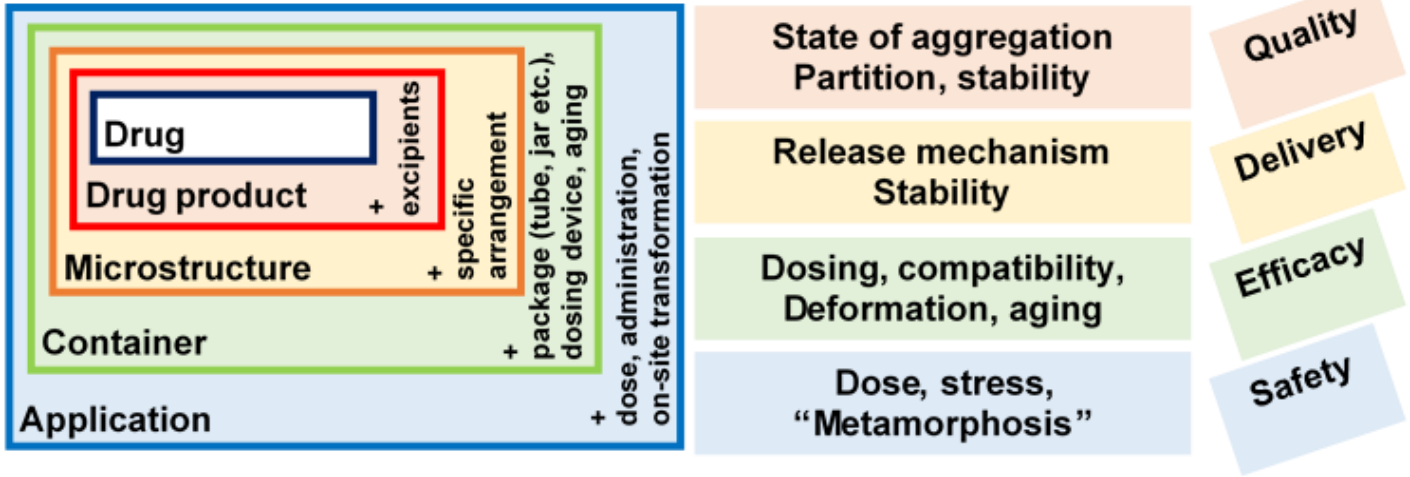
EMA draft guideline

Extended pharmaceutical equivalence

Extension of this waiver to other pharmaceutical forms may be possible, if based on an extended concept of pharmaceutical equivalence combined with additional measures of equivalence (2014)

Equivalence of quality = **Sameness based on narrow acceptance criteria**

FDA has been using "aggregate weight of evidence / totality of evidence"



EMA draft guideline

Extended pharmaceutical equivalence (Same, T vs. R)

- **Same drug**
- **Same salt**
- **Same excipients (“including grade, if necessary”)**
- **Same amounts of same excipients (some exceptions)**
- **Same pharmaceutical form**
- **(Essentially the same) Qualitative quality characteristics**
- **Same (narrow) acceptance criteria** to demonstrate ..
- **Same quantitative quality characteristics**
- **Similar method and means of administration**, which will achieve ..
- **Same dose on application**
- **Same transformation on application (residue)**

EMA draft guideline

Same qualitative composition

THINK OF PRODUCT PERFORMANCE AND ADMINISTRATION

Excipients to be the same (grade included)

Well-established, in usual amounts (discuss impact on solubility and BA)

Different excipients – no effect on local tolerance and safety

Excipient function relates to VEHICLE PROPERTIES OR EMOLIENCY

Excipient not related to PRODUCT PERFORMANCE or ADMINISTRATION

(antioxidants, antimicrobial preservative, colours) ..AND …

DO NOT HAVE ANY OTHER FUNCTIONS (BA, solubility, thermodynamic activity)

Paraffin homologues – strange example

It should be shown that the excipients DO NOT HAVE ANY OTHER FUNCTIONS OR EFFECT THAT INFLUENCE the active substance SOLUBILITY, THERMODYNAMIC ACTIVITY or BIOAVAILABILITY and PRODUCT PERFORMANCE

EMA draft guideline

Same quantitative composition

THINK OF PRODUCT PERFORMANCE AND ADMINISTRATION

+/-5% (example: 2% for an excipient, 1.9-2.1%)

+/-10% if:

Excipient function relates to VEHICLE PROPERTIES OR EMOLIENCY

Excipient not related to PRODUCT PERFORMANCE or ADMINISTRATION

(antioxidants, antimicrobial preservative, colors)

Again:

It should be shown that the excipients DO NOT HAVE ANY OTHER FUNCTIONS OR EFFECT THAT INFLUENCE the active substance SOLUBILITY, THERMODYNAMIC ACTIVITY or BIOAVAILABILITY and PRODUCT PERFORMANCE

EMA draft guideline

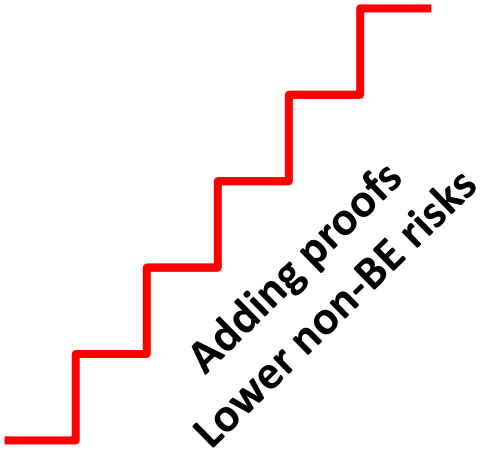
Same qualitative and quantitative composition

- Usually, higher number of excipients (e.g., compared to oral IR)
- Comparator in different countries may have different composition
- Identifying the composition of the comparator may be highly difficult
- Errors of some decomposition methods are greater than ± 5%
- Some excipients exhibit huge differences in characteristics between providers or even between batches
- Some excipients are mixtures of components
- Some components are common between different excipients
- Sameness cannot be achieve due to patent pending
- Excipients usually have multiple functions
- It is difficult to justify that an excipient will not impact S, BA, TA
- Excipients related to vehicle properties usually create problems

EMA draft guideline

Stepwise approach

- Sameness on composition is just the starting point
- The physicochemical comparative assessments to be added
- Choice of applicable, reliable, relevant tests
- Development of a product specific protocol



Added approaches

- Rheological assessments (complex, relevant for understanding interactions)
- In vitro release tests (required to support the Extended concept)
- In vitro permeation tests (already used, considered as relevant)
- Skin stripping (dermatopharmacokinetics)
- Vasoconstriction assay (already in place)

EMA draft guideline

Stepwise approach

Pros

- Collect more data
- Request in depth understanding of the comparator (reference)
- Considers the complexity of dosage forms and ways to fail in providing the outcome
- Adds in vitro performance data
- Brings IVRT (in vitro release) and IVPT (in vitro permeation) into arena
- Somehow, in line with other DRA

Cons

- Idealized
- Attempts to justify may be risky
- Many requirements are questionable
- Too many parameters to collect
- One-size fits all criteria (90-111%)
- Some approaches, still not standardized
- Mitigating variability may not be so easy
- Representative comparator – batches
- Interpretable

No significant difference (NSD)

could be a change in the approach

Q3 Similarity

Similar components and composition to RLD

and **Similar** Physical and Structural Properties

No Difference

in inactive ingredients or other aspects of the formulation relative to RLD

that may significantly affect local or systemic bioavailability

(Q1/Q2 sameness, but not necessary)(Ref: S Raney, 2019; NSD, Ref: S Raney, 2022)

Rheological behavior (properties); Q3 (2003)

(many topical products are not in thermodynamic equilibrium)

Advisory Committee for Pharmaceutical Science Meeting (October 21-22, 2003).

Dissolution tests described as a Q3 evaluation.

Different particle size (non-Q3) may still lead to BE. Q3 similarity not needed.

Q3 is particularly important for topical semisolids (consensus).

Methods to be selected based on **improved classification tree, defining different dosage forms: suspension, lotion, gel, cream, ointment.**

Q3 must be demonstrated to be related to THERAPEUTIC EQUIVALENCE OF GENERIC TOPICAL PRODUCTS.

Q3 differences may manifest themselves as differences in physical properties, e.g., rheology or in dissolution (in vitro release) rate.

Microstructural similarity

Viscosity is not enough. Wide intervals as per specification - not scientifically justified.

EMA: ***Appropriate characterization of rheological properties may enable the identification or design of a simpler test to be used in the FINISHED PRODUCT SPECIFICATION.***

- ***Primary assessment:***

  Particle and droplet size (extreme fractions are to be assessed for impact on stability and clinical relevance, e.g., particle size for ophthalmic suspension).

- ***Secondary assessment:*** **Same dispersion does not mean same interactions.**

  Non-newtonian – shear-dependent viscosity, yield stress (solid/liquid-like behavior depending on stress).

  Degree of non-Newtonian behavior, relaxation time of the material, distinction between dosage forms.

Rheology

Rotational approach

Creep and recovery

- Creep curve: deformation, load (stress) phase
- Creep and recovery: reformation / retardation (rest) phase
- Zero shear viscosity determined at the end of the creep (load) phase
- Expected to correlate with IVR rate

1-3 parameters

Shear stress ramp / steps

- Modeling approach

  (Oswald de Waele, power law mode, assumes no yield stress)
- Fluidity (flow-behavior) index
- Measurement of the pseudoplastic behavior (rate of structural changes vs. shear rate; time and share dep.)
- Areas under the curve (EMA, 2018: thixotropic relative area, S_R)
- Extracted values of viscosity at preset share rates

4+ parameters

Rheology

Oscillatory approach

Stress amplitude sweep (CS)

- G'-deformation energy that is stored (reversible deformation, elastic)
- G"-deformation energy that is lost (irreversible deformation, viscous)
- G'=G", crossover / flow point, sol/gel transition point (tanδ=1), tanδ (δ, phase angle)
- LVER characteristics, 3, 5 or 10% deviation from linearity
- Yield stress: spreadability, perception

5+ parameters

Frequency sweep tests (CD, CS)

- G'-deformation energy that is stored (reversible deformation, elastic)
- G"-deformation energy that is lost (irreversible deformation, viscous)
- Modeling approach
- When CD, crossover frequency gives an indication on elastic behavior
- Higher crossover frequency, decreased elastic behavior, less tendency to roll-up onto the skin.

3-5+ parameters

EMA draft guideline

Rheological step

Pros

- Microstructure is important (critical) to understand performance
- Flow behavior impacts product quality and performance throughout shelf-life (processability, pourability, spreadability, release etc.)
- Rheology is discriminative for aging
- Adaptive to wide variability of semisolid characteristics
- Particularly useful to understand quality target and stability profile

Cons

- Too many parameters to be compared
- Same parameter, different method, different values
- Difficult to discuss / justify their lack of relevance
- The results depend on history of the product / batch (not known for comparator), parameters (intervals, time of application, modeling, calculation)
- Temperature dependent outcome
- Variability may be (very) high

EMA draft guideline

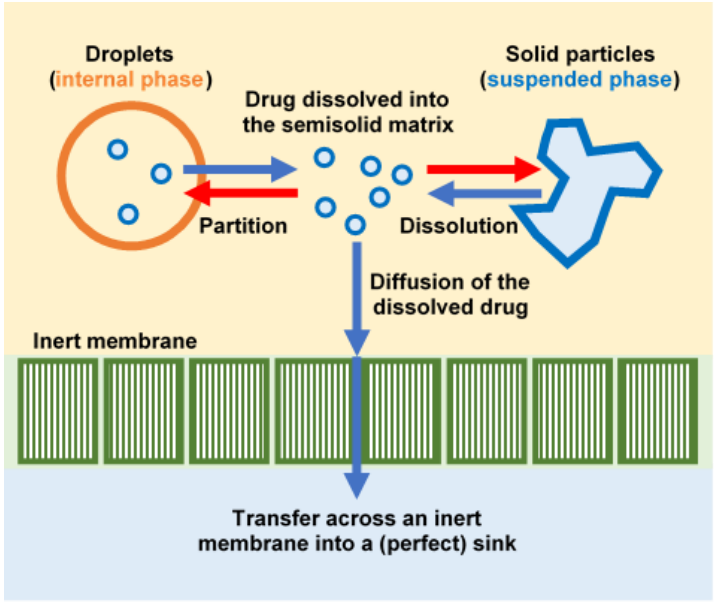
In vitro release tests (IVRT), the history behind a simple test

- It started as simple, in vitro screening tool for impact of changes (1997)
- It was developed in analogy with the in vitro dissolution test (back in 1970's)
- Reasonable extensions were proposed (1998)
- A version of PVT was proposed for diffusion cells (2009)
- Comparison of formulations across manufacturers for simple composition (2012)
- The apparati were described in compendial chapters, USP (2013)
- Mentioned in EMA concept paper (2014)
- Extension of the in vitro tests with IVPT for more complex topicals (2016)
- IVRT required to support EMA extended concept (2018)
- One-size fits all acceptance criteria proposed for product-adapted comparison;
- PSDG incl. physicochemical characterization, IVRT, IVPT (2016-2022)
- Revision to USP chapter 1724 is announced (2022)

EMA draft guideline

In vitro release tests (IVRT), how to use it

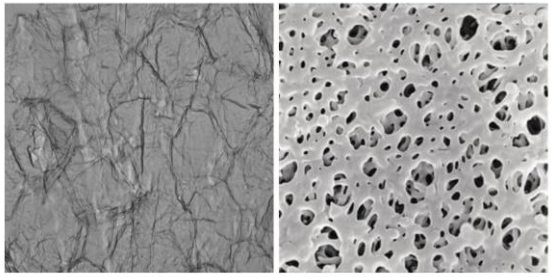
Higuchi model, applied based on a set of conditions.
At equilibrium (after short lag):



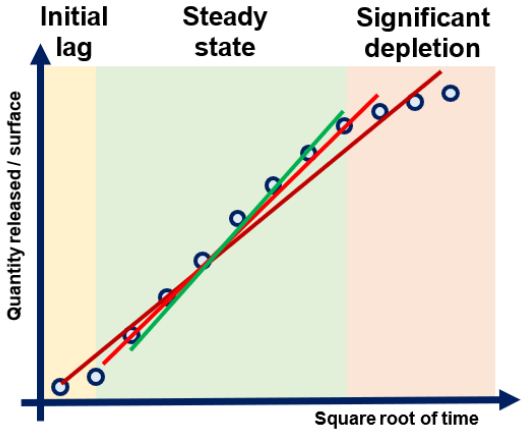
$R^2 > 0.90$

$R^2 > 0.95$

$R^2 > 0.97$



Skin on adhesive strips (400x) Polysulfone membrane



Setup (method) dependent | Formulation (property) dependent | Dose (and kinetics) dependent

$$Q_t = (2 \cdot C_0 \cdot \sqrt{D/\pi})\sqrt{t} \qquad Q_t = (\sqrt{2 \cdot D_m \cdot C_S \cdot C_t})\sqrt{t}$$

EMA draft guideline

In vitro release tests (IVRT)

Design	Validation
Choice of membrane Choice of receptor media • sink conditions (below 30% of maximum attainable concentrations) • back diffusion, • pH changes avoided. Ideally at least 70% of the active substance applied is released, at least 6 points. Amount applied (±5%) and method. Analytical method validation.	Discrimination: • strength • changes in critical quality attributes, critical manufacturing variables or quantitative composition (excipients) Intermediate precision. Robustness (stirring, temperature, media, amount applied). Comparison based on 90% CI for ratio means (release amount and rate, n=12), acceptance interval 90-111%. Similar lag time (±10%)

Development	Validation (qualifications and controls)
Cell design Temperature and hydrodynamics Receptor media Membrane Pre-treatment of membrane Sampling Quantitation Data analysis Higuchi model Mann Whitney U test 75-133.33%	Qualification Solubility (sink), stability Inertness and compatibility Analytical method validation Linearity, range, precision. Reproducibility, recovery, mass balance, dose depletion, discrimination sensitivity, specificity and selectivity. (supplemental selectivity) Robustness.

US-FDA Acyclovir 5% cream PSG(2016).

EMA draft guideline

IVRT step (required to support extended concept)

Pros

- Assumes that IVRT is the next step, reflecting the combined result of various physico-chemical and microstructural characteristics
- Not applicable to certain types of dosage forms (solutions, powders, foams)
- Aligns the BE approach for topicals to the current guidelines (PSG)
- Does not recommend a certain type of equipment (cell), but principles

Cons

- Theoretically, back diffusion and co-diffusion are always occurring
- +/-5% dose is useless (not included in calculations)
- Two additional parameters are subject to comparison (A, lag time) – (highly) variable, not relevant
- Ideal of 70% release may be challenging (linked with R^2>0.9)
- Not always Higuchian release
- Sample size and acceptance range

EMA draft guideline

IVRT step (discrimination of strength and CQA)

Challenges

- Strength discrimination is more permissive compared to US-FDA
- Keeping the state of aggregation for the additional strengths
- For solution-type system, relationship to be established
- For suspensions, relationship may not be discriminative
- +/-25% or +/-50%

Not justified

- Approaching as for a dissolution test
- 70% release, even if ideal, is in contradiction with model requirement
- Lag-time is a mainly a method dependent parameter (steady state)
- Establishing limits for routine QC (n=6)
- Even though “not model(ing) in vivo performance”, limits are to be justified “by reference to .. clinical batches”

EMA draft guideline

IVRT step (opposing a transition to routine QC)

- **The following statements are available in the Annex 1:**

Although the test does not model in vivo performance, the release rate (R) is a CQA to be specified in the finished product release and shelf life specification, unless otherwise justified. (..) tighter limits at release are set, to ensure that the product will remain within the shelf life specification. (..) For routine release, a minimum of 6 samples would be accepted.

- **Conclusion: IVRT to become a routine QC**
- **Based on history, IVRT HAS ALWAYS BEEN APPLIED AS A COMPARATIVE TEST.**
- **The use as QC test is still controversial due to i) lack of experience; ii) variability of the results due to continuous evolution of the semisolid matrix; iii) large limits which may result, difficult to justify in terms of in vivo relevance.**
- **For QC, would it be a stage comparison?**

EMA draft guideline

IVPT step (IVRT similarity concluded; add on, next)

- Not only skin samples replacing artificial membranes
- “.. of value in change control during life-cycle management ..”
- “ .. acceptable permeation kinetic test ..” (more biorelevant, biopredictive)
- Pilot and pivotal studies needed
- Variability is normally observed and considered as physiological
- Part of variability addressed by Blinding and randomization
- Blinding may be challenging
- Use of a negative control which is frequently referred to as 50% strength, even though permeation is not always strength dependent (analytically challenging)
- Flux and cumulative amount oriented

EMA draft guideline

IVPT step

Pros

- Ex vivo skin, complex barrier
- Comparison of products in context closer to clinical use (dose included)
- Finite (and relevant) dose, ±5%
- Allows transformation of semisolid product (controlled environment)
- Disposition below primary barrier can be analyzed
- Test duration may be relevant
- Blank controlled (parallel dosing)

Cons / challenges

- Not real skin
- Regional variations may be important (abdominal skin vs. other sites)
- Feasibility of 2-15mg/cm^2 (uniformity)
- Relevance of 24 hours leave on and of longer test duration
- Homogenous spreading of low dose
- Number of donors, replicates
- Cases with no relevant permeation
- Mass balance 90-110%

EMA draft guideline

IVPT step (start and finishing)

Application (t=0)

- Several techniques available:
  - Positive displacement pipette
  - Inverted HPLC vial
  - Spatula
  - Glove / Finger tip
- Differences in duration, variability of amount (+/-5%), evaporation loss, simulation of rubbing effect, metamorphosis
- Detailed description needed (forces, directions)

Acceptance criteria (J_{max}, A_{total})

- 90% CI T/R, mean ratio

  80.00-125.00%

  (69.84 – 143.19% if justified):

  High variability

  Low strength

  Limited diffusion

  No clinical relevance
- 90% CI NC/R and NC/T, mean ratio

  ENTIRELY OUTSIDE 80.00-125.00%
- Assumes some proportionality!

EMA draft guideline

DPK step (tape stripping for dermatopharmacokinetics)

History

- 1998-2002 Draft guidance (FDA)
- 3 tretinoin gel products
- Contradictory results
- Reproducibility issues
- Train&error in sampling time
- Variability in SC thickness
- Inconsistency of adhesion
- Discard some samples (unabsorbed)
- Dermatopharmacokinetic profiles and parameters (AUC, A_{max})

Suggested approach

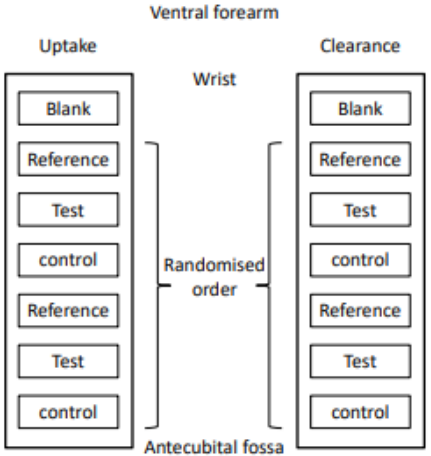
- Optimized based on reanalysis and testing of additional drugs / products
- Cleaning excess
- Minimizing edge effects
- Accurate sampling times
- Restriction of profiles to two points (uptake and clearance), n=2
- Negative control (discrimination)
- For drugs acting on/in skin BUT "suitable surrogate" for action below

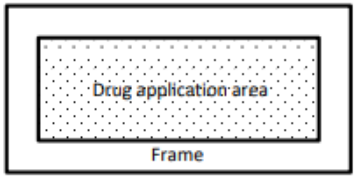
EMA draft guideline

DPK step (tape stripping for dermatopharmacokinetics)

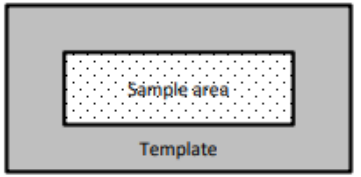
Not to be used / not suitable

- drug not penetrating into skin
- *drug products to be applied on significantly damaged skin (e.g. open wounds, burns) or skin of premature new-born*
- *any products that contain volatile drugs or target primarily the cutaneous appendages (e.g. hair follicles, sebaceous glands)*

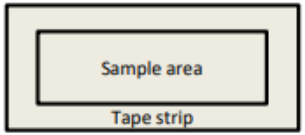




1) Drug is applied to the demarcated area and removed after the specified uptake time.



2) At the end of the uptake phase or after the specified clearance time, a template delineating the sample area is centered on the site.



3) Stripping begins using tapes that are larger than the sample area.

EMA draft guideline

DPK step (tape stripping for dermatopharmacokinetics)

Pros

- It is (use to be) a minimally invasive procedure
- It reflects the concentration at the site or action (BA) OR, combined with other methods, MAY reflect it
- Compares two products on the same subject at the same time
- 2 replicates / product / subject
- Staggered start, normalized for SC
- Reflects both uptake and clearance on perfused, real in vivo skin

Cons

- Experienced investigators
- Complex protocols and SOP's
- Application requirements as for IVPT
- Healthy subjects, volar forearms
- Negative controlled
- Intensive work, several studies needed for adequate design of pivotal studies
- Many parameters to be adapted to drug or product characteristics
- 2 point assessment

EMA draft guideline

Additional steps

- **Drug product must be within the scope of draft guidance**

- **Justification on absence of studies (therapeutic equivalence, safety)**
- **Relevance for efficacy of permeation kinetic studies**
- **Relevance (feasibility) of pharmacodynamic studies**
- **Novel studies are encouraged (development, validation, conduct)**

- **Cutaneous use, auricular and ocular use in addition**

Conclusions

Summary of pros and cons

- The draft guidance may be finalized soon.
- It is an important step forward, but not necessarely toward waivers.
- It is based on indepth understanding of comparator and on assuming the variability of the comparator.
- Rheology, IVRT and IVPT will be part of the comparative assessments, but restrictive requirements should be either relaxed or justified.
- One-size fits all may not be appropriate for product-specific protocols.
- Before transition to QC, feasibility should be assessed.
- Evaluating topicals based on experience gained on conventional dosage forms is not always sappropriate.
- Targetting sameness in all aspects may not generate a good product.