

Draft guideline on quality and equivalence of topical products (.. focusing on in vitro release and rheological assessments)

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Outline

- **Brief introduction to the complexity of topicals**
- **EMA CHMP/QWP/708282/2018. Draft guideline on quality and equivalence of topical products**
- **EMA CHMP/QWP/558185/2014. Concept paper on the development of a guideline on quality and equivalence of topical products**
- **A general approach on equivalence (Q1, Q2, Q3, Q4)**
- **Role of IVRT and rheological evaluation in similarity assessment**
- **EMA Draft guideline vs. US-FDA Product specific draft guidance**
- **Case-studies for development of IVRT and use in comparison of topicals**
- **Conclusions**



Brief introduction

Complexity of topical semisolid formulations

<u>Drug</u> (API)	Impact	
Drug - <u>Drug product</u> (API and excipients)	State of aggregation. Stability	Quality
Drug - Drug Product - <u>Microstructure</u> (API and excipients in specific arrangement)	Mechanism of release	Site of drug action
Drug - Drug Product - Microstructure - <u>Container</u> (API and excipients in specific arrangement and dose)	Dosing	Efficacy
Drug - Drug Product - Microstructure - Container - <u>Application</u> (API and excipients in specific arrangement and dose, as applied onto skin, result of complex transformation)	Dose applied and in vivo delivery	Safety

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Draft guideline on quality and equivalence of topical products



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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CHMP/QWP/708282/2018
Committee for Medicinal Products for Human Use (CHMP)

Draft guideline on quality and equivalence of topical products

Draft Agreed by QWP	7 June 2018
Adoption by CHMP for release for consultation	18 October 2018
Start of public consultation	14 December 2018
End of consultation (deadline for comments)	30 June 2019
Agreed by QWP	
Adopted by CHMP	
Date for coming into effect	

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The draft guideline served for revision (replacing) of two other documents:

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).

What's new?

- 1) Introduces the concept of **Extended Pharmaceutical Equivalence (EPE)**.
- 2) Includes comparative assessment of **rheological behavior**.
- 3) Officializes the use of in vitro release methodologies for topicals:
 - “required to support EPE”;
 - .. introduces the “routine release”.
- 4) Officializes the use of in vitro permeation methodologies for topicals.
- 5) Officializes the use of dermatopharmacokinetics (tape stripping):
 - sampling (.. removing) of the stratum corneum by adhesive tapes;
 - two sampling points, reflecting uptake (absorption) and clearance (elimination).

EMA/CHMP/QWP/558185/2014

Concept paper on the development of a guideline on quality and equivalence of topical products

Premises:

The guideline should consider the application of an extended pharmaceutical equivalence with alternative in vitro and in vivo models and methods to predict therapeutic equivalence with reference medicinal products, in lieu of therapeutic equivalence studies in patients.

But also (..):

*Clinical trials (CES) are in principle necessary to demonstrate therapeutic equivalence, but other models may be used, if adequately validated. **In many cases, these other models have exhibited poor accuracy, sensitivity, reproducibility, in vitro in vivo correlation and have been unable to provide convincing evidence to predict therapeutic equivalence.***

After 3-4 years (2018):

equivalence in (almost all) relevant attributes and performance data.

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Executive summary

LALA preparation for **cutaneous use** and other (auricular, **ophthalmic**).

Specific recommendation for *models and studies*:

- independent** proofs of quality, efficacy and safety;
- combined** (by applicant) in a product-specific protocol, support of claimed TE;
- same method of administration (as for comparator)*;
- evaluation of the patient inequivalence risk (needs to be minimal).

***Note:** methods of administration, administration device and dose delivered are key issues, including the transformation at the site of administration and requirement for residues equivalent in quality.

LALA-locally acting, locally applied; EPE-extended pharmaceutical equivalence;
TE-therapeutic equivalence.

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What is the target formulation?

Simple formulation:

Examples provided in EMA Draft guidance: single phase solution, gels, ointment.

.. or it falls under:

(i) more complex formulation category;

(ii) formulation containing excipients which may influence bioavailability / performance – additional permeation kinetic & pharmacodynamic (if possible).

(almost all excipients may influence BA, performance ..);

Where it's the site of action and what can be measured?

Permeation kinetics includes **IVPT**, TS/DPK, systemic PK/BE.

Pharmacodynamic includes blanching or in vitro anti-infective / decolonization (in conjunction with other studies).

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There are (at least) 10 important questions

(according to *5 Equivalence of Topical Products / 5.1 Scope*)

1) Narrow therapeutic index?

In most instances, no.

2) Dose related systemic toxicity?

All available data (e.g. PAR, SmPC etc. and literature reports) should be **collected and assessed**. If oral formulation available, PK to be considered.

3) Means by which the drug reaches the local site of action are understood?

(e.g. dissolution, release, diffusion and permeation kinetics).

Local site of action to be identified and analyzed in relation to the formulation factors, absorption promoters, their mechanism of action etc.

Hair follicles are a targeted site? Is particle size critical for targeting?

4) What is the intended method of administration (the same as for reference)?

To be addressed (fingertip application onto skin, spreading, occluded / un-occluded, device, dose clearly indicated in cm or g).

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There are (at least) 10 important questions

(according to *5 Equivalence of Topical Products / 5.1 Scope*)

5) Fully characterized in terms of quality attributes?

5.1) Complex formulation? **Most of the creams, emulgels etc.**

5.2) Difficult to characterize due to methodological limitations?

6) Is it possible to measure permeation kinetics / pharmacodynamics?

6.1) Is the diffusion limited? **The extent is to be assessed.**

6.2) Are the tests sensitive?

7) Are the permeation kinetics and pharmacodynamic studies, in vitro and in vivo, applicable (sufficiently predictive for the clinical response)?

Dose applied, application method, area, (systemic) exposure.

8) Is the product applied on open wounds / ulcers?

Barrier function of the skin is compromised.

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There are (at least) 10 important questions

(according to *5 Equivalence of Topical Products / 5.1 Scope*)

9) What and how to test (availability of relevant comparator)?

Comparative quality data (..) on at least three different batches of both test and comparator product;

12 replicates / batch / experiment;

10) Is comparison between products relevant?

Characteristics of product to remain **consistent and equivalent** throughout designated shelf-life.

Relevant comparator medicinal product.

Availability of the comparator product is a key issue.

At least three batches to be procured and analyzed.

Different markets, different manufacturing sites, distinct history (age)?

A general approach on equivalence

(qualitative and quantitative composition, microstructure, in vitro release and more ..)



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



In vitro release methodology (before the draft guidance) History and (bio?)relevance

From 1990's:

- development of methodology based on vertical diffusion cells;
- hydrocortisone 1% cream proposed for performance verification;
- comparative assessment of marketed products;
- reports on rank order relationship between the dermatopharmacokinetic, pharmacodynamic and IVR characteristics for marketed creams.

1997: Postapproval Changes: Chemistry, Manufacturing, and Controls; In Vitro Release Testing and In Vivo Bioequivalence Documentation (SUPAC-SS guidance)(US-FDA)

1998: Topical Dermatological Drug Product NDAs and ANDAs - In Vivo Bioavailability, Bioequivalence, In Vitro Release, and Associated Studies (draft guidance)(US-FDA)

2012: draft guidance on acyclovir 5% ointment (US-FDA).

2013: USP chapter <1724> Semisolid drug products-performance tests

2014: EMA/CHMP/QWP/558185/2014

2016: draft guidance on acyclovir 5% creams (US-FDA).

2018: qualification and validation of IVR, acyclovir 5% cream (Tiffner KI et al).

2018: EMA/CHMP/QWP/708282/2018



In vitro release tests (1)

- performance test reflecting release rate of drug through layers of semisolids;
- high (pseudo-infinite) dose applied;
- use of inert membranes and media providing sink conditions;
- no significant changes of the formulation expected during tests;
- steady state release rates are compared.

Advantages

- reliable and reproducible;
- simple, but potentially reflecting the combined influence of several factors controlling the release (vehicle, particle / droplet size, dissolution and / or partition within heterogenous system etc.)

Limitations

- inertness of support membrane not sensitive to active excipients;
- not informative of the interactions between formulation and skin;
- unrestricted diffusion has no in vivo correspondent.



In vitro release tests (2)

A. Current applications

1. Development of generics, in selection of the optimal formulation candidate;
2. Screening defined changes (composition / manufacturing) or scale-up;
3. Comparative assessment with RLD if in vitro option available (US-FDA);
4. Stability studies;
5. Selection of representative batch of RLD (JP).
6. Support of **Extended Pharmaceutical Equivalence** (EMA, 2018).

B. Other (current or potential) applications

1. Characterization of microstructural similarity (relationship IVR - Q3);
part of aggregate weight of evidence (US)
2. Batch-to-batch consistency / routine release (**EMA**, 2018).

Relevance of IVR comparison depends upon the similarity of composition.



Validation of in vitro release methodologies (1)

Development	Validation (qualifications and controls)
<p>Cell design Temperature and hydrodynamics Receptor media Membrane Pre-treatment of membrane Sampling Quantitation Data analysis</p>	<p>Qualification</p> <p>Solubility (sink), stability Inertness and compatibility</p> <p>Analytical method validation Linearity, range, precision. Reproducibility, recovery, mass balance, dose depletion, discrimination sensitivity, specificity and selectivity. Robustness.</p>

**US-FDA Acyclovir 5% cream draft guidance
(revised Dec 2016).**



Validation of in vitro release methodologies (2)

Design	Validation
<p>Choice of membrane</p> <p>Choice of receptor media</p> <ul style="list-style-type: none">• sink conditions (below 30% of maximum attainable concentrations)• back diffusion,• pH changes avoided. <p>Ideally at least 70% of the active substance applied is released, at least 6 points.</p> <p>Amount applied ($\pm 5\%$) and method.</p> <p>Analytical method validation.</p>	<p>Discrimination:</p> <ul style="list-style-type: none">• strength• changes in critical quality attributes, critical manufacturing variables or quantitative composition (excipients) <p>Intermediate precision.</p> <p>Robustness (stirring, temperature, media, amount applied).</p> <p>Comparison based on 90% CI for ratio means (release amount and rate, n=12), acceptance interval 90-111%.</p> <p>Similar lag time ($\pm 10\%$)</p>



Microstructural assessment of topical semisolids (1)

Rheological testing protocols including a variety of evaluations (rheometer!):

- Oscillatory tests (strain / stress, frequency);
- Rotational tests;
- Axial tests.

(Viscosity evaluation, part of routine QC, wide specifications).

Appropriate design of test **and evaluation** of the results, considering:

- temperature, relevant for storage conditions or site of application;
- thickness of the layer of semisolid formulation - in vivo conditions;
- changes in composition and microstructure during and after administration.

Reflective (directly or indirectly) of:

- type and intensity of internal interactions;
- response to shearing forces (before and during the application);
- stability (temperature sweep / swing test).



Microstructural assessment of topical semisolids (2)

Indications available:

- draft guidance documents (product specific or general);
- available reports (expert meetings);
- compendial chapters (USP, EP) or ISO documents.

Product variables:

- complexity composition, microstructure;
- packing (semisolids available as tubes of various sizes);
- application device (methods and means of administration);
- changes in time (within shelf life).

Adaption of testing parameters to product (non-Newtonian) characteristics.

No general approach for assessing similarity in comparative assessment (US-FDA Product-Specific Draft guidance).

Useful in understanding differences in performance (in vitro / in vivo).

Microstructural assessment of topical semisolids (3)

EMA, 2018 draft guidance:

-**complex excipients** (mixture) are to be identified (composition) and characterized (including rheologically; section 4.2.3. Excipients);

-part of the product (comparative) characterization:

Complete flow curve (linear segments of the up-curve or down-curve);

Fitting with Ostwald de Waele (power law) model or others (at least two parameters result and are to be compared);

Yield stress (not clear what method to be used, results depend on procedure);

Creep testing (elastic and viscous deformations) – recovery step not clearly indicated;

Rheological behavior to be stated: Newtonian, pseudoplastic, dilatant etc.

Metrics identified: viscosity at a specific shear rate, hysteresis areas, yield stress, modulus within LVR, loss tangent etc.

May be part of the evaluation for description of the “*transformation of the product on administration*”, considering the range of shearing rates and temperature.

Many parameters to compare => increased chances of non-similarity (+/- 10%).

Identification or design of a simpler test (Finished Product Specification).



Topical drug Classification System (TCS)

Shah VP. *et al*, Int J Pharm. 2015, 2016

**Q1, Q2 Same
Q3 Same**

TCS class 1

**Q1, Q2 Same
Q3 Different**

TCS class 2

**Q1, Q2 Different
Q3 Same**

TCS class 3

**Q1, Q2 Different
Q3 Different**

TCS class 4



Role of **in vitro** release and rheological tests in the evaluation of topical drug products

Comparative assessment based qualitative and quantitative composition and IVR.

IVR similarity: identification of Q1 and Q2 differences and associated risks, considering:

limitations of IVR (dose, membrane, sink);

complexity of the microstructure (additional test);

impact on the skin permeability.

Evaluation of non-similarities:

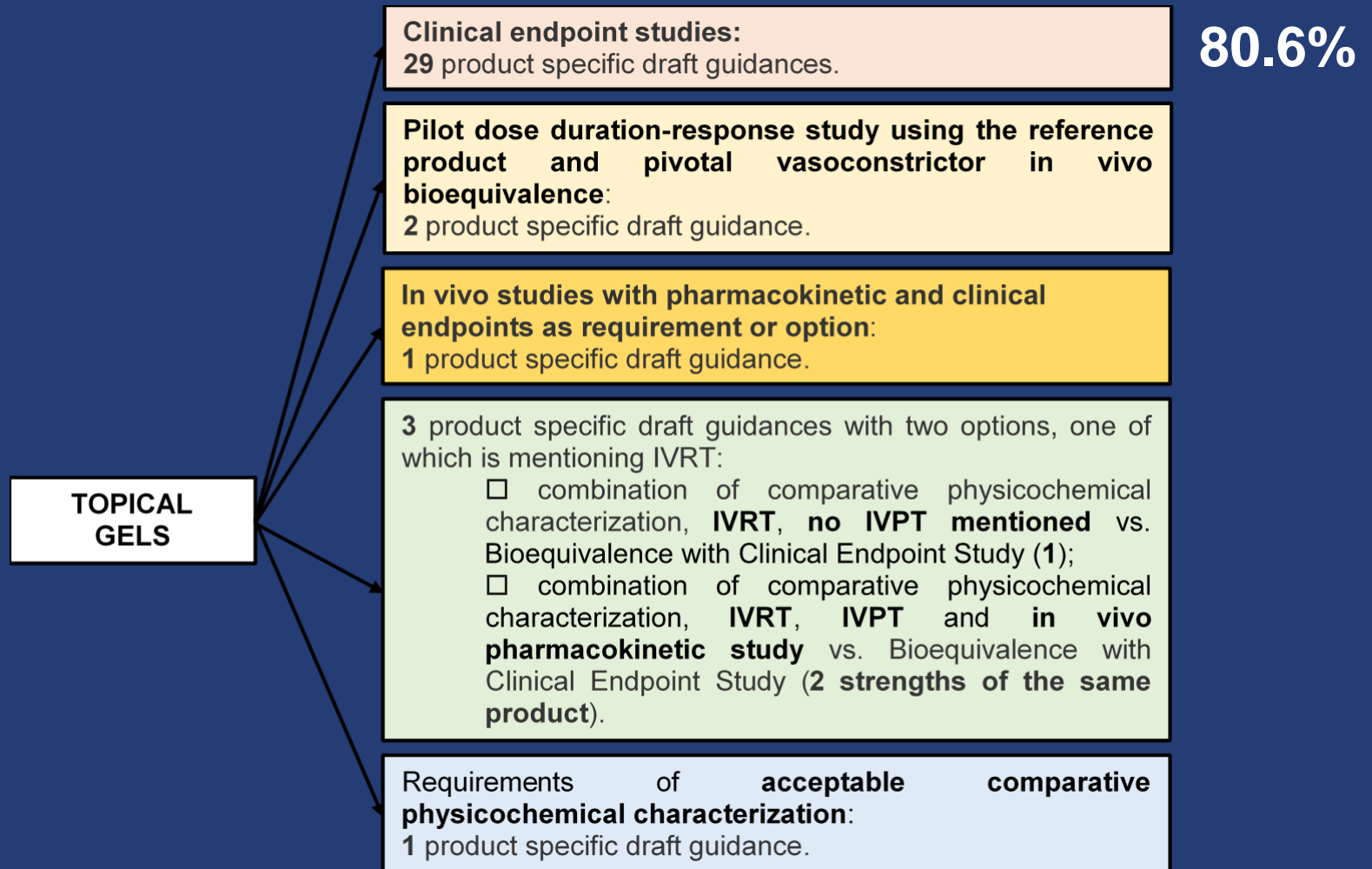
functionality of excipients,

percentage and amount applied,

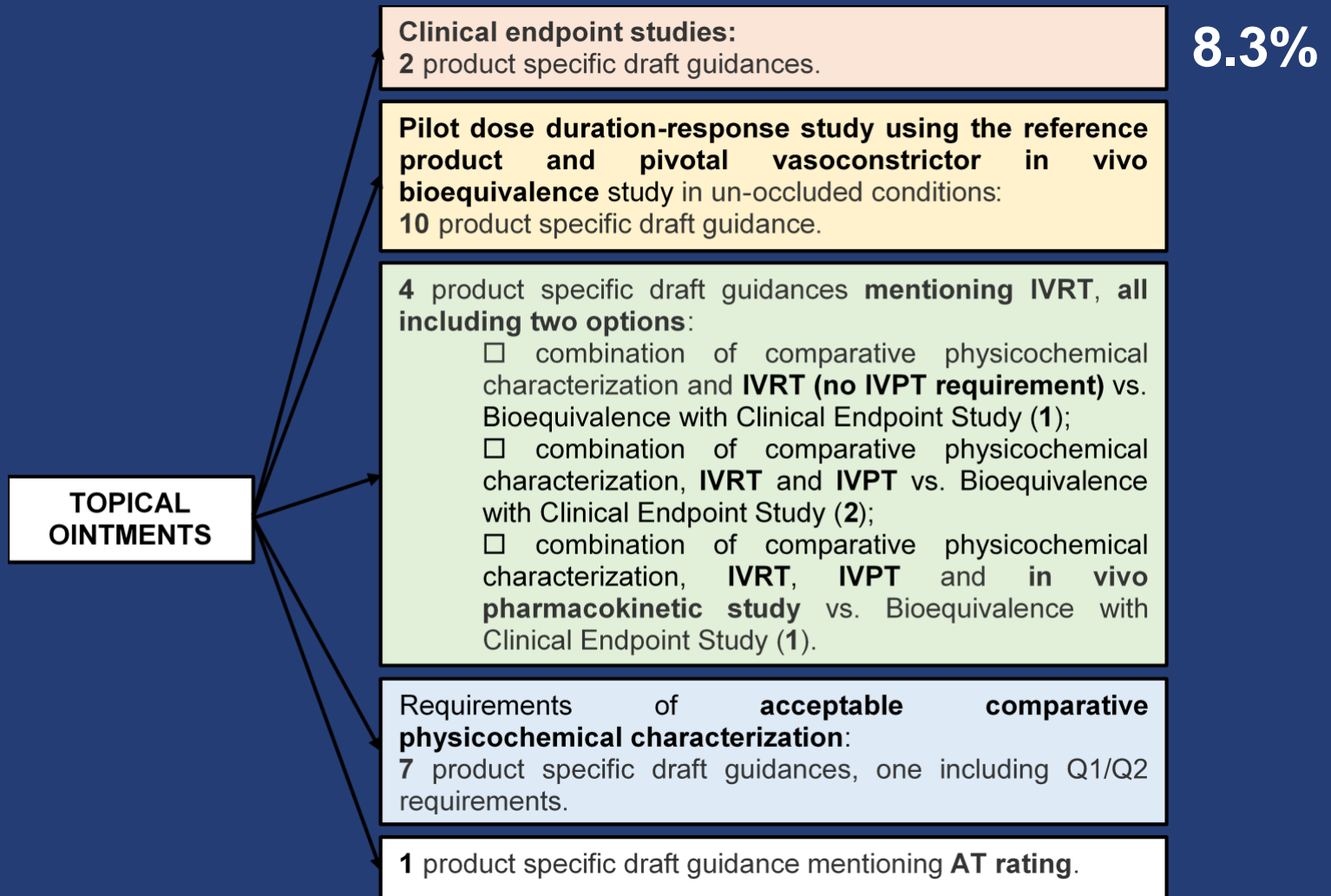
contribution to depth, rate and extent of penetration.

IVR differences: in vivo BE studies, independent of Q1 and Q2 similarity.

US-FDA, Product-specific draft guidance (topical gels) Last updated: April 2019



US-FDA, Product-specific draft guidance (topical ointments) Last updated: April 2019



US-FDA, Product-specific draft guidance

(topical creams) Last updated: April 2019

54.4%

TOPICAL CREAMS

Clinical endpoint studies:
31 product specific draft guidances.

Pilot dose duration-response study using the reference product and pivotal vasoconstrictor in vivo bioequivalence in either occluded or un-occluded conditions:
12 product specific draft guidance.

7 product specific draft guidances **mentioning IVRT, all including two options:**

-two options:

- combination of comparative physicochemical characterization, **IVRT and IVPT vs. Bioequivalence with Clinical Endpoint Study (1);**
- combination of comparative physicochemical characterization, **IVRT (no IVPT requirement) vs. Bioequivalence with Clinical Endpoint Study (1);**
- combination of comparative physicochemical characterization, **IVRT, IVPT and in vivo pharmacokinetic study vs. Bioequivalence with Clinical Endpoint Study (1).**

-single option:

- combination of comparative physicochemical characterization, **IVRT, IVPT and in vivo pharmacokinetic study (1);**
- combination of comparative physicochemical characterization, **IVRT and IVPT (3).**

Requirements of **acceptable comparative physicochemical characterization:**

7 product specific draft guidances, one including an in vivo study option (Bioequivalence with Clinical Endpoint Study).

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Similarity requirements:

Q1

Same qualitative composition in terms of excipients

Q2

Same grade

Same quantities (more or less ..)

Special attention should be paid to excipients which alter the triad ***solubility, thermodynamic activity or bioavailability and product performance***.

Limits on the assessment of quantitative similarity +/- 5%, although exceptions (+/- 10%) are mentioned:

1) excipients not impacting administration or performance (antioxidants, preservative, colors);

2) excipients with role limited to vehicle or emolliency, without influence on triad - identified: paraffin homologues.

Most excipients are multifunctional (contextual role).

Personal note: (+/-5%) limits correspond to level 1, minor SUPAC-SS (except diluents), whereas (>+/-5% to +/-10%) limits correspond to level 2, moderate SUPAC-SS (except diluents).

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Acceptance criteria (definition of similarity):

For qualitative quality parameters

- Essentially the same.

Q3

For quantitative quality parameters

- 90% confidence interval for the difference of means test vs. comparator;
- assuming normal distribution;
- acceptance criteria: **+/- 10%** of the comparator mean.

For in vitro release / permeation testing (IVRT/IVPT)

- 90% confidence interval for the ratio of means test vs. comparator;
- acceptance criteria: **90-111% (IVRT)**
80.00-125.00% (IVPT) (exceptionally 69.84-143.19%).

For in vivo parameters

- 90% confidence interval for the ratio of means test vs. comparator;
- Acceptance criteria: **80.00-125.00%** (exceptionally 69.84-143.19%).
- Clinical justification for the enlarged acceptance interval may be problematic.

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What will be the best approach?

Step 1. Make sure EPE is applicable as concept to the product.

Step 2. Target Q1, Q2, Q3, Q4-same method (means) of administration etc.

Step 3. Confirm Q1, Q2, Q3 and in vitro release similarity.

Keep in mind that these are comparative assessments, therefore the outcome depends on the variability of the test and comparator.

Evaluate potential differences which may invalidate the overall approach.

Step 4. Select appropriate permeation kinetic / pharmacodynamic studies

Depth of penetration and site of action, together with available data on systemic exposure in maximized conditions should be used in support of studies included in protocol (extended PE, in vitro release test, efficacy equivalence using in vitro permeation study).

Justification for the absence of studies needs strong arguments.

Low and variable systemic concentrations support the absence of systemic BE approach, but may suggest CES.

Conclusions

In current form, the draft guidance is used for:

- enunciation of one (new) concept, Extended Pharmaceutical Equivalence,
- adding tape stripping as an approach for (non-corticoid) locally distributed drugs,
- adding IVRT and IVPT which will be required (routine QC / change control).

It is a generalized alternative to the Product-Specific, Aggregate Weight of Evidence.

Several requirements are similar to Product-Specific US-FDA draft guidances.

It relies on proven similarity in almost all attributes of the product.

For similarity, instead of adequate acceptance criteria (Concept paper), these criteria are clearly specified.

Several parameters are to be compared (e.g. a set rheological data),

The key element is the site of action and systemic exposure of the drug.

In several cases, in vivo proofs of equivalence will be required.

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