9 September 2024
EMA/CHMP/QWP/451535/2024
Committee for Medicinal Products for Human Use (CHMP)

Overview of comments received on 'Draft guideline on quality and equivalence of topical products' (EMA/CHMP/QWP/708282/2018)*

***NOTE**: following the revision of the draft document after the public comments the title of the Guideline has changed to "Guideline on quality and equivalence of locally applied, locally acting cutaneous products" to more accurately reflect the products concerned by the guideline.

Interested parties (organisations or individuals) that commented on the draft document as released for consultation.

Stakeholder no.	Name of organisation or individual
1	AESGP (Association of the European Self-Care Industry), Brussels, Belgium
2	DermoCosmetics, Service of Dermocosmetic Assesment IQAC-CSIC, Barcelona – Spain
~~3~~*	~~Dr Kalliopi Dodou, University of Sunderland, United Kingdom~~*
4	EFPIA (European Federation of Pharmaceutical Industries and Associations), Brussels, Belgium
5	EUFEPS (European Federation for Pharmaceutical Sciences), Frankfut am Main, Germany
6	Prof. Yogeshvar KALIA, Dr. Maria LAPTEVA, Julie QUARTIER, Ninon CAPONY School of Pharmaceutical Sciences, University of Geneva
7	Strallhofer Pharma GmbH, Siegendorf, Austria
8	Zakłady Farmaceutyczne POLPHARMA S.A., Starogard Gdański, Poland

* Stakeholder/Commenter #3 provided comments on a different guidance document.

1. General comments – overview

Comment no.	Stakeholder no.	General comment (if any)	Outcome (if applicable)
1	1	**Post approval changes** For Post approval changes, an In Vitro Release Test (IVRT) could demonstrate equivalence of pre- and post- changes (test and reference) in topical products, but there may also be other suitable approaches based on risk assessment such as further physicochemical testing and enhanced Quality Control (QC) testing during validation. For post approval changes only, this IVRT requirement is in-line with existing US and Canadian Health Authority guidelines (eg SUPAC-SS). However, for routine QC batch release, the USP Pharmacopeia Forum 44(5) in General Chapter < 3 > states "For semisolid dosage forms, in vitro drug release testing is currently not required for batch release". For routine QC batch release and stability testing IVRT has certain operational constraints such as equipment, materials and set-up variability, which require side by side comparison of reference to test product. This means that IVRT would be impractical to adopt as a routine QC test on a batch-by-batch basis without requalifying a reference product every 2 or 3 years depending on product shelf-life. Since the test is imprecise, each requalification could drift further and further away from the clinical baseline over product lifetimes of 30 or more years. Also, there is a very high costs and timelines associated with this test -above $100,000 and 6 months from receipt of sample are typical for a contract laboratory to develop and validate an IVRT method and its associated assay method and then run a side-by-side comparison between test and reference product). Again, due to the imprecision of the IVRT test, if drug release rate results are compared between runs (eg from one day to another) the results may not agree, even for the same batch. This imprecision could lead to repeated non-compliance to specification decisions when	Refer to the revised document, and specifically to sections 3, 4.3, 4.3.1 and 6.

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		used during batch-by-batch QC testing or stability studies. It would therefore be extremely problematic if this has to be implemented for commercial batch release, causing an increase to the cost of goods, delays in batch release timelines and potentially disruption to supply. IVRT is a product performance test which evaluates the impact on the physicochemical properties of the formulation matrix from a significant change to production. In addition to traditional QC testing, the impact can also be examined using alternative techniques such as microscopy, DSC, rheology etc. These alternatives should be sufficient enough, without IVRT, depending on the outcome of the risk assessment for the proposed change to determine its impact on the quality, safety or efficacy of the product. **For Product development** In Vitro Skin Permeation studies (IVPT) is performed during product development rather than IVRT as the experiment will show the release of the drug substance from the pharmaceutical form, as well as showing its permeation through the superficial layer of the skin. During the product development stage, a full risk analysis is performed, including the risks to the product performance leading to the development of a product control strategy of manufacturing and QC controls. By implementing this product control strategy to the release of each commercial batches routinely, as well as during the annual stability studies at each timepoints, the manufacturer ensures adequate product performance throughout its lifecycle and during its shelf life. **Comparator medicinal products** Comparator medicinal product: We understand for a product change, the comparator medicinal product would be the product that is being changed; for a new registration, the guideline should clarify that the comparator medicinal product should be selected	

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		in accordance with the legal basis of the application. For example, this would clarify that you cannot claim equivalence to a generic product.	
2	1	The following statement should be added in the scope: "Homeopathic medicinal products for human and veterinary use are not concerned by the quality and equivalence guideline" as following: "Scope: Guidance is provided on the quality of topical products, containing chemical active substance(s), not covered by other general quality guidelines The quality guidance applies to new marketing authorisation applications and post approval changes. Homeopathic medicinal products for human and veterinary use are not concerned by this guideline" **Rationale:** **-For quality guidance** • For homeopathic attenuations In many cases the active substance can no longer be identified in the finished product. Indeed, homeopathic attenuations are manufactured in infinitesimal dose (10-4 attenuation at least) which render the elucidation of structure of active substance impossible by classical analytical methods. • For homeopathic mother tincture Mother tinctures are considered as the active substance. They contain quality markers. Their identification represents a manufacturing quality indicator according to European Pharmacopoeia 2371 "Methods of preparation of homeopathic stocks and potentisation, mother tinctures and liquid potentisations" edition in force and European Pharmacopoeia 2029 Mother tinctures for homoeopathic preparations edition in force.	This is a CHMP guidance document. Homeopathic medicinal products are not in the remit of CHMP. Revised scope reads: "The guideline applies to locally applied and locally acting medicinal products for cutaneous use. These principles may also be relevant for other topical medicines, e.g. preparations for auricular or ocular use, and locally acting products, to be applied to vaginal mucosa or nails."

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		These markers may be analysed by analytical methods to prove the good manufacture of the stock and mother tincture preparation. Moreover the characterisation of quality markers is not easy because of: -Complex structure and diversity of raw materials -Natural variability in composition of constituents for example herbal substance according to seasonal conditions. **-For equivalence guidance** Not applicable for homeopathic medicinal products. Homeopathic medicinal products are not concerned by this guideline as it is mentioned for the herbal medicinal products. (line 187) **-Safety and efficacy assessment** **From an efficacy point of view:** The totality of a homeopathic drug product, rather than an isolated component, is considered responsible for its homeopathic therapeutic effect. Thus, the "active ingredient" of a homeopathic drug product is the homeopathic attenuation, not a singular chemical entity in the starting material. No clinical studies are required for homeopathic products according to directive 2001/83/EC. Nevertheless the active substance must be supported by relevant literature data justifying the traditional homeopathic use in claimed indications. Efficacy in terms of product strength and posology is not applicable for homeopathic medicinal product according to Directive 2001/83/EC The strength and posology are selected according to bibliographical data confirming the homeopathic use. **From a safety point of view:**	

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		For each constituent of the homeopathic medicinal product and in case of no bibliographical data a worst-case approach with a total (100%) skin penetration is considered for the FSD (First Safe Dilution) calculation.	
3	2	In **Annex II** In vitro skin permeation studies (IVPT), the recommended dosing amount is in the range of 2-15mg/cm2 **(page 29).** We normally use infinite dosing (i.e 300mg/cm2) for kinetic studies. The low amount recommended is normally used for penetration studies, not for permeation ones. For this bioequivalence test it could happened that we do not find enough permeated compound in the receptor fluid to study the kinetics. Please send me your comments.	"The recommended dosing amount should be ~~in the rage of 2-15 mg/cm2~~, based on SmPC posology, unless otherwise justified."
4	3	~~I would like to suggest the following publications to be added to **the References on p. 22:**~~ ~~o Wolff HM, Irsan, Dodou K. (2014) "Investigations on the viscoelastic performance of pressure sensitive adhesives in drug-in-adhesive type transdermal films" *Pharmaceutical Research* 31(8), 2186-2202.~~ ~~o Ho KY, Dodou K. (2007) Rheological studies on pressure sensitive silicone adhesives and drug-in-adhesive layers as a means to characterise adhesive performance. *International Journal of Pharmaceutics* 333(1-2), 24-33.~~ ~~These papers are useful reference materials explaining the adhesion/cohesion balance and cold flow, and refer to the following parts of the document:~~ ~~o 4.2.4., p.9: "In terms of quality with respect to the administration and use:…."~~ ~~o 4.2.6.3., p.12: "Adhesive properties"~~	Comment not considered as it refers to a different document.

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		~~o "Definitions", p.20: "Cold flow:…"~~ ~~**The References on p. 22** should be styled using either Vancouver or Harvard international referencing standards, and should be shown in the text. Otherwise, the listed items on p.22 should be labelled as **Bibliography** instead of **References.**~~	
5	4	EFPIA welcomes the possibility to comment on this important guidance document. We are broadly in agreement with the guidance. Additional comments (both general and detailed) can be found in the document below. In our opinion, the scope of the guidance is not entirely clear: is it for all topical drug products, or for generic drug products and post approval changes to these only? It is also unclear if the guideline will address development of new drug products as well as life cycle management. We would welcome a clarification, and requirements for each of the categories should be clearly specified in separate sections throughout the text. Furthermore, the draft guidance raises rather complex and detailed matters that are expected to be understood for this product type (e.g. permeation kinetics, product microstructure/physical properties and formation mechanisms during processing. Such detailed fundamental understanding may be difficult to achieve and can, potentially, be mitigated to some degree by the control strategy applied to the product. In addition, such detailed fundamental understanding should not be required for products approved prior to the generation of this guidance.	It is noted that the revised document reads: "The quality guidance applies to new marketing authorisation applications and post approval changes. The equivalence guidance is applicable to certain cases of demonstration of therapeutic equivalence of a new cutaneous medicinal product with an existing cutaneous medicinal product." Refer also to section 6 of the revised document. It is also confirmed that the guideline has no retrospective application but for future changes to existing products (post approval) the GL will apply.

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6	4	We noticed that some sections of the text include reference to the module 3 documents in the CTD-dossier and others do not (e.g. the sections 4.1, 4.2, 4.2.4 + 4.2.5). It should be clarified what the intention is with including or not including these references.	References are meant to aid the reader where it is more likely this information to be found.
7	4	In addition, EFPIA has noticed that this draft guideline is overlapping with other guidelines, in relation to quality and characterization of the topical products. It is important for industry to achieve a harmonized approach to the development program of new topical products for all markets. With overlapping scope there is a risk of conflicting frameworks of the different guidelines worldwide. It is also preferred to align the guideline with requirements in Ph.Eur. and USP, where possible. According to the USP general chapter *<1724> Semisolid drug products - performance tests* in vitro release testing is not required for batch release. Ph. Eur. has no description of equipment or test methods related to IVRT or requirements to performance of this test. Some examples of overlap/conflict are given below: • Line 470-475, The description and the definitions of bulk product and intermediate product conflict with "Manufacture of the finish dosage form EMA/CHMP/QWP/245070/2015. It is unclear what is intermediate product and what is bulk products. • In paragraph 4.2.4 (Formulation Development) and 4.2.6 (Administration), warnings regarding paraffin-based products are required. EFPIA believes such warnings are out-of-place in a Guideline on quality and equivalence of topical products and such warnings – where considered relevant - should find a place in the framework of the European Commission Guideline on 'Excipients in the Labelling and Package Leaflet of Medicinal Products for Human Use' (EMA/CHMP/302620/2017).	With regard to the inclusion of performance tests and limits in the product specification new text has been drafted. Refer to definition of the "Guideline on manufacture of the finished dosage form". Agreed. Text regarding products containing flammable material or accelerant has been minimised.

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8	4	There may be instances where IVRT is not suitable to assess the equivalence of semi solid products, that is before and after a change. Other physical and chemical tests can be used as measures of equivalence. The guideline should be clear about the limitations of test as the in vitro/ in vivo correlation for semisolid products is not as well established as in vitro dissolution is as a surrogate for in vivo bioavailability of solid oral dosage forms.	IVRT is not the sole parameter to determine equivalence. It is seen together with the other physicochemical parameters. In any case it has to be justified by data why IVRT is not appropriate e.g., over discriminatory Refer to the stepwise approach in section 5.1
9	4	Finally, EFPIA is of the opinion that a glossary should be added to the guidance, defining e.g. "CQAs" (here used in another context than normally, e.g. l. 296: CQA is normally not used for excipients but only for drug product) "extended pharmaceutical equivalence" (l. 570 ff), "product quality equivalence" (l. 578), "drug product stability study quality specification" (l. 530), and other examples.	Comment noted but a glossary was not considered necessary.
10	5	It is recommended to clearly address that this guideline is to be applied to generic developments and hybrid applications as well.	According the QA – Generic Applications (Q11) all "generic" MAAs for LALA products fall automatically under the hybrid legal basis 10.3 https://www.hma.eu/fileadmin/dateien/Human_Medicines/CMD_h_/Questions_Answers/CMDh_272_2012_Rev06_2020_03_clean_-_Q_A_on_generics.pdf

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11	5	Furthermore, applicability and relevance for scale up and post approval changes should be specified.	It is noted that: "The quality guidance applies to new marketing authorisation applications and post approval changes. The equivalence guidance is applicable to certain cases of demonstration of therapeutic equivalence of a new cutaneous medicinal product with an existing cutaneous medicinal product." Refer also to section 6 of the revised document.
12	5	In general the guideline document should include a chapter referring to specifications for batch release. Basic principles should be defined. The option for a waiver of certain tests justified by the Critical Quality Attributes identified for the product in question should be possible.	Refer to the revised document.
13	5	Provided that certain aspects of the guideline document shall also be of relevance for newly developed drug products this should also be specified.	Refer to the scope in the revised document. Also note: "This guideline applies mainly to Marketing Authorisation Applications for human medicinal products submitted in accordance with Directive 2001/83/EC as amended, under Art. 8(3) (full applications) and Art. 10(3) (hybrid

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			applications). It may also be applicable to Marketing Authorisation Applications for human medicinal products submitted under Art.10b (fixed combination), Art.10a (well-established use applications) of the same Directive, and for extension and variation applications in accordance with Commission Regulations (EC) No 1084/2003 and 1085/2003."
14	5	Section 5: General comment: PK-based approaches are expected to exhibit superior discrimination power provided that the compartment of determination is considered predictive - directly or indirectly - for the site of action. In such cases adequately validated PK-based approaches should be favoured when compared to skin PD-based approaches. There is common understanding that clinical therapeutic studies have the least discriminative power in regards to product quality. It is considered meaningful to address this hierarchy of preference. Furthermore, validation criteria may be added. However, discriminative power of clinical trials is extremely poor. Thus, criteria for discriminative power should be evaluated with a sense of proportion and scientific evidence of the potential to detect product difference when applying PK or PD methods should suffice to accept such methods as this is still "better" than clinical endpoint studies.. This would allow to evaluate existing and newly developed skin PK-based methods for their use in drug development and acceptance by EMA and therefore would de-risk their use by drug developer and enhance drug quality by encouraging to employ skin PK-based methods.	Agree with comment in principle. Already stated in the guideline. Refer to the stepwise approach in section 5.1

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15	5	It is recommended to strengthen the use of PK data - systemic availability or dermal PK - to characterise product quality of locally acting and locally applied patches. As example lidocaine patch was mentioned. However, for capsaicin patch also used in neuropathic pain a different approach might be meaningful as the effect is not correlated with a continuous variable like exposure but instead a threshold in exposure needs to be exceeded. Thus, in this case IVRT and IVPT might suffice.	Refer to the stepwise approach in section 5.1
16	5	There was strong interest in allowing adequately validated PBPK modelling, eg Symcyp-based, as supportive tool to demonstrating equivalence provided that Critical Quality Attributes are adequately considered. However, as the data base is still sparse further effort is needed to fully validate the modelling systems. There was some agreement that mentioning this modelling approach in the guideline would strengthen the effort to obtain further data which allow a better data base.	Level of knowledge is considered premature at the moment to allow the use of PBPK modelling in this situations. However it maybe possible in the future or if the model shown to be predictive. In this regard seeking of Scientific Advice is strongly recommended to developers.
17	5	The auditorium also discussed the so-called "TCS" introduced by some scientists in US (including Vinod Shah, former FDA) but the majority was not in favour of this approach as too little is known about the in-vivo relevance of for example Q1 and Q2 differences even if similarity in Q3 has been demonstrated. In general proven similarity in Q1, Q2 and Q3 should qualify for a waiver of efficacy trials in humans depending on the product characteristics.	Refer to the stepwise approach in section 5.1
18	5	A general comment was to consider more the quality characteristics of the reference product in case of generic applications.	Agreed in that the reference product should be fully characterised. Characterisation on case by case depending on application.

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19	6	After careful review of the 'Draft guideline on quality and equivalence of topical of products', we consider that the EMA working group has prepared an excellent document that aims to address the unmet need of filling the regulatory gap concerning the assessment of quality and equivalence of topical products. However, in our opinion, the proposed tests to assess equivalence *in vitro* (i.e *in vitro* release testing (IVRT) and *in vitro* skin permeation testing (IVPT)) are limited by the fact that drug delivery is not quantified directly inside the skin; i.e. at its therapeutic action site, given that most topically acting drugs target the viable epidermis or dermis. We would like to propose an alternative technique able to assess equivalence of topical products *in vitro* and thus complete the *in vitro* skin permeation studies (IVPT). This technique, that we have termed "Cutaneous Biodistribution Method", was first reported by Lapteva *et al.* (Lapteva, Mondon et al. 2014) and used in several other studies into the cutaneous penetration of therapeutic agents with dermatological indications (Chen, Zahui et al. 2015, Kandekar, Singhal et al. 2019, Lapteva, Mignot et al. 2019). We have also used it to investigate intracorneal drug delivery (Santer, Del Rio Sancho et al. 2017). The method consists in performing a skin permeation study (IVPT) using an *in vitro* skin model as described in the draft guideline. At the end of the experiment, a small skin area is punched out. The skin discs obtained are snap-frozen in isopentane cooled by liquid nitrogen and then cryotomed to obtain a series of lamellae each with a pre-defined thickness ranging from 20 to 100 µm. Drug extraction and quantification in each lamella enables the determination of drug location as a function of depth down to a depth of ~800 µm with "user-defined" variable	The Guideline includes the most established methodology. If Q1,2,3 are similar then it is anticipated that the amount crossing the skin layers should be also similar. New methods could be acceptable if justified and validated by applicants.

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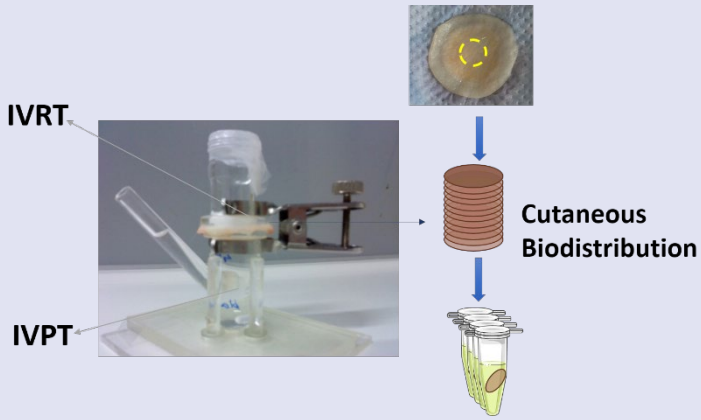
		resolution, encompassing the stratum corneum, viable epidermis and dermis, respectively (**Figure 1**).  **Figure 1: Complementarity of IVRT, IVPT and biodistribution assays in assessing bioequivalence of topical products in vitro** To validate the method and study its applicability for the determination of bioequivalence *in vitro* we have compared reference cream, generic and non-generic formulations of econazole nitrate. The draft manuscript has been submitted for publication and we are happy to append a copy to this comment. Other formulations are being currently tested. We sincerely hope that the working group considers the above-described technique as being of interest and that it might be recommended in the draft guideline.	

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		REFERENCES Chen, Y., T. Zahui, I. Alberti and Y. N. Kalia (2016). "Cutaneous biodistribution of ionizable, biolabile aciclovir prodrugs after short duration topical iontophoresis: Targeted intraepidermal drug delivery." Eur J Pharm Biopharm **99**: 94-102. https://www.ncbi.nlm.nih.gov/pubmed/26592154 Kandekar, S. G., M. Singhal, K. B. Sonaje and Y. N. Kalia (2019). "Polymeric micelle nanocarriers for targeted epidermal delivery of the hedgehog pathway inhibitor vismodegib: formulation development and cutaneous biodistribution in human skin." Expert Opin Drug Deliv **16**(6): 667-674. https://www.ncbi.nlm.nih.gov/pubmed/30995141 Lapteva, M., M. Mignot, K. Mondon, M. Moller, R. Gurny and Y. N. Kalia (2019). "Self-assembled mPEG-hexPLA polymeric nanocarriers for the targeted cutaneous delivery of imiquimod." Eur J Pharm Biopharm. DOI: 10.1016/j.ejpb.2019.01.008. https://www.ncbi.nlm.nih.gov/pubmed/30641138 Lapteva, M., K. Mondon, M. Moller, R. Gurny and Y. N. Kalia (2014). "Polymeric micelle nanocarriers for the cutaneous delivery of tacrolimus: a targeted approach for the treatment of psoriasis." Mol Pharm **11**(9): 2989-3001. https://www.ncbi.nlm.nih.gov/pubmed/25057896 Santer, V., S. Del Rio Sancho, M. Lapteva and Y. N. Kalia (2017). "Targeted intracorneal delivery-Biodistribution of triamcinolone acetonide following topical iontophoresis of cationic amino acid ester prodrugs." Int J Pharm **525**(1): 43-53. https://www.ncbi.nlm.nih.gov/pubmed/28414134	

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20	7	Well established use (Art. 10a) is not mentioned.	Included in the revised document.
21	8	The draft guideline describes quality and equivalence requirements of topical products. Among topical products which can be applied to the skin the **ocular products** are also specified. Based on the Ph. Eur. definition for **Eye preparations, Ophtalmica**: "eye preparations are sterile liquid, semi-solid or solid preparations intended for administration upon the eyeball and/or to the conjunctiva, or for insertion in the conjunctival sac." Please note that phrase "ocular" is not used in the Ph. Eur. definition. On the other hand, looking at the Standard Terms (EDQM) the phrase "ocular" is defined: "Administration of a medicinal product upon the eyeball and/or conjunctiva" Please include the precise definition of the **ocular** products (dosage forms) which will be covered by the guideline. In our opinion the draft guideline in not enough precise in relation to the solutions as a dosage form. Through the document there are no references to the dosage form such as eye drops, solution, which are by far more simple products in comparison to the ointment, cream, emulsion etc. Examples which are presented in the draft document strictly refer to the penetration through the skin, *e.g. factors such as "indication and disease state of skin; age, appropriateness, patient acceptability, administration and usability, administration site; efficacy in terms of product strength and posology, solute status of the active substance, and bioavailability and/or penetration enhancement; emolliency; safety in terms of*	The scope in the revised document reads: "The guideline applies to locally applied and locally acting medicinal products for cutaneous use. These principles may also be relevant for other topical medicines, e.g. preparations for auricular or ocular use, and locally acting products, to be applied to vaginal mucosa or nails."

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		ingredient toxicity, impurities, microbial quality; and quality in terms of physical and chemical stability, critical quality attributes and compliance with pharmacopoeial and regulatory requirements. The local site of action should be identified: skin surface; skin interior (stratum corneum, epidermis or dermis); or subcutaneous, adjacent tissues below the skin (regional)" are thoroughly described. Please specify which dosage forms, among ocular/ophthalmic products, are covered by the guideline? Should we use it in order to prove quality for dosage form such as: eye drops, solution? If not, please exclude this dosage form in the general description of the guideline.	
22	8	**4.2.5 Product characterisation** The draft guideline describes requirements to statistical data evaluation in product comparison: *"Characterisation data should be derived from a representative number of batches taking account of the **likely variation seen with disperse systems compared with simple solutions**, and should not be less than three batches. To enable statistical evaluation, the number of samples should be representative, with at least 12 units per batch for each experiment. Between batch variability e.g. due to batch size, date of manufacture and period of storage, should also be taken into account."* Please make a comment, if solutions are considered simple (e.g. eye drops, solutions) should they be fully taken in the comparison evaluation as described in the point 4.2.5 Product characterisation.	Number of batches depends o inter-batch variability. Number of units per batch depends on intra-batch variability. This GL also includes solutions. The requirement for 3 different batches and 12 units per batch is meant when variability is low. Text in GL will not change.

2. Specific comments on text

Comment no.	Line no.	Stakeholder no.	Comment and rationale; proposed changes	Level	Outcome
1	78 – 79 and 176 - 177	1	**Comment:** Products in the scope should be clarified. As the guideline is related to topical forms, other topical routes of administration should be specified as e.g. buccal, nasal, vaginal and rectal. **Proposed change:** The guideline applies to locally applied and locally acting medicinal products for cutaneous use and is also relevant for other medicines e.g. topical preparations for auricular ocular, buccal, nasal, vaginal and rectal use as well as for regionally acting products. "Homeopathic medicinal products for human and veterinary use are not concerned by this guideline"	1/3	Revised scope reads: "The guideline applies to locally applied and locally acting medicinal products for cutaneous use. These principles may also be relevant for other topical medicines, e.g. preparations for auricular or ocular use, and locally acting products, to be applied to vaginal mucosa or nails." We agree with comment but there is no need to list every possible form. Homeopathic medicinal products are not in the remit of CHMP refer to response to general comment 2.
2	89 - 90	1	**Comment:** The guideline states: *"[…] when the method of administration is the same […]".* Method of administration comprises several aspects, such as dose applied, frequency of dosing and surface of application. Determining equivalence when all these aspects are identical limits options. Thus, equivalence should be considered when only route of administration is the same. **Proposed change:** "…when the ~~method~~ route of administration is the same and risks of inequivalence to the patient are minimal."	4	Not agreed. It has to be the same method of administration. The specific part of the draft Guideline text has been revised significantly.

Comment no.	Line no.	Stakeholder no.	Comment and rationale; proposed changes	Level	Outcome
3	114 - 121	1	**Comment:** The guideline states: *"The indication, target population and site of action […] may influence the condition to be treated."*. This section does not pertain to quality and should therefore not be discussed in this guideline. **Proposed change:** Delete lines 114-121. ~~"The indication, target population and site of action need to be understood to enable informed choices 115 with respect to pharmaceutical form, composition, and method of administration.~~ ~~The principal function(s) of the drug product need to be understood. This may simply be administration of the active substance to the surface of the skin. In many cases, bioavailability is increased by including in the product formulation excipients that change the thermodynamic activity of the active substance, e.g. by solubilisation and supersaturation, that modify active substance diffusion, or disrupt the physiological barrier - penetration enhancers. Occlusion and the vehicle itself, e.g. moisturisers and emollients, may influence the condition to be treated."~~	1	This text describes aspects that should be considered during pharmaceutical development and is thus retained.
4	132-133	4	**Comment:** in vitro performance, if appropriate? **Proposed change:** It needs to be clarified when in vitro performance testing is required or examples should be given.	4	If appropriate allows for justification to waive in vitro release test if another parameter is shown during pharmaceutical development to be a surrogate for in vitro release test.
5	137-174	4	**Comment:** General comment to whole section: include references to the relevant sections in this Guideline	3	Accepted. Added.
6	153-155	1	**Comment:** The guideline states "*In the case of solutions, e.g. cutaneous solutions, a waiver of therapeutic equivalence data may be accepted based on quality equivalence alone, when the*	3	Not agreed. The release from the dosage form needs to be compared

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			method of administration is the same". This approach should be acceptable for other dosage forms, such as creams, where it can be shown that the active substance is solubilized. **Proposed change:** "In the case of ~~solutions, e.g. cutaneous solutions,~~ dosage forms such as solutions and creams where it can be shown that the active substance is solubilized, a waiver of therapeutic equivalence data may be accepted based on quality equivalence alone, when the method of administration is the same."		with regard to the reference product as per section 5 of the guideline.
7	170-171	4	**Comment:** Define simple formulations or give examples e.g. solutions, liquids etc. **Proposed change:** Definition (in Glossary) and/or examples should be included.	1,3	Refer to the revised document: "For the purpose of this guideline, simple formulations are formulations with a single-phase base (matrix or vehicle) in which the active substance is in solution or suspension, e.g., solutions and suspensions in single phase liquids, -gels, or -ointments, and, do not contain excipients that are intended to enhance drug permeation or are difficult to characterise (e.g. of biological origin)." "For the purpose of this guideline, complex formulations are multiphase systems, which are difficult to characterise structurally (e.g. emulsions), or formulations with excipients that are difficult to

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					characterise, and formulations containing excipients that are intended to enhance drug permeation."
8	190	4	**Comment:** It is unclear how this guidance can be useful if it does not apply "when the pharmaceutical form or qualitative and quantitative composition of the test and comparator products are not the same or equivalent." This exclusion is NOT understood. Is this meant to only exclude different pharmaceutical forms? **Proposed change:** Please clarify this exclusion.	1,3	A step wise approach has been elaborated. Differences in qualitative and quantitative composition between test and reference product are addressed in the GL. The equivalence guidance (section 5) does not apply when the pharmaceutical form of the test and reference products are not the same Refer to the revised document section 5.1.
9	192 – 212 Section 3 Legal Basis	1	**Comment:** Types of applications to which this guideline would apply should be listed such as in section 3 of the Guideline on equivalence studies for the demonstration of therapeutic equivalence for locally applied, locally acting products in the gastrointestinal tract (CHMP/QWP/708282/2018). **Proposed change:** add "<u>This guideline applies mainly to Marketing Authorisation Applications for human medicinal products submitted in accordance with Directive 2001/83/EC as amended, under Art. 10(3) (hybrid applications). It may also be applicable to Marketing Authorisation Applications for human medicinal products submitted under Art. 8(3) (full applications), Art.10b (fixed combination), Art.10a (well-established use applications) of the same Directive, and for</u>	1,3	Accepted.

Comment no.	Line no.	Stakeholder no.	Comment and rationale; proposed changes	Level	Outcome
			extension and variation applications in accordance with Commission Regulations (EC) No 1084/2003 and 1085/2003."		
10	195	4	**Comment:** Draft guideline ICH Q12 to be added to the list	2	Accepted and added.
11	237-540	4	**Comment:** It is not clear whether this section both include general considerations about development of a topical drug product and/or only information to be included in the 3.2. P.2 in the dossier. **Proposed change:** include an introduction to section 4 that states all general information related to drug product development. The following sub-sections will then only include information related to the registration dossier.	1,3	The information in section 4 concerns the information required in the dossier in relation to pharmaceutical development.
12	244 - 245	1	**Comment:** The guideline states: "*The name should include the grade or brand (commercial) name, if required for consistent manufacturability and product quality.*" The requirement to state the brand name of an excipient appears to be too restrictive and does not allow a change between suppliers in the case that quality is identical. **Proposed change:** "The name should include the grade ~~or brand (commercial) name~~, if required for consistent manufacturability and product quality."	3	Brand (commercial) name, is not mandatory. Reworded text: *"The excipient name should include the grade, and if informative also brand (commercial) name, if required for consistent manufacturability and product quality."*
13	246 - 248	1	**Comment:** The guideline states: "*It should be explicitly stated when an excipient contributes in a multifunctional way to the design and purpose of the drug product, e.g. propylene glycol acting as a humectant, penetration enhancer and solubiliser*." The term "contributes" does not reflect the fact that it can only be prospective.	1	Pharmaceutical development should investigate the function and impact of excipients. The function and impact of excipients should be known and is a

Comment no.	Line no.	Stakeholder no.	Comment and rationale; proposed changes	Level	Outcome
			Proposed change: "It should be explicitly stated when an excipient is expected to contribute in a multifunctional way to the design and purpose of the drug product, e.g. propylene glycol acting as a humectant, penetration enhancer and solubiliser."		prerequisite for proper characterisation of the formulation. Change not accepted.
14	246 - 248	4	**Comment:** The effect of every excipient may be difficult to ascertain throughout the development program, as some excipients may induce multiple unintended effects. It is recommended to modify this section to make it clear that it is the intent of the excipient's function that is meant. **Proposed change:** "It should be explicitly stated when an excipient **is intended to** contribute in a multifunctional way to the design and purpose of the drug product…"	1,3	Pharmaceutical development should investigate the function, the impact and criticality of excipients. The function and impact of excipients should be known and is a prerequisite for proper characterisation of the formulation. Change not accepted.
15	268-270	4	**Comment:** This is scientifically difficult to prove. **Proposed change:** Suggest removing this requirement, or adding "**If possible** the means and permeation kinetics by…"	4	It is expected that Pharmaceutical Development will at least try to investigate these aspects. Good product understanding and characterisation are key especially if the Therapeutic Equivalence options are to be applied.
16	276	4	**Comment:** Clarification is requested to indicate that this is applicable to the proposed marketed strengths, not other strengths that may have been used during development. **Proposed change:** "If applicable, the proportionality of different strengths **to be marketed** should be discussed."	2	It is confirmed the proportionality between strengths concerned by/mentioned in the application should be discussed. This includes the strengths to be marketed but also other strengths that are referred to in the application, for example strengths

Comment no.	Line no.	Stakeholder no.	Comment and rationale; proposed changes	Level	Outcome
					used during development and in stability studies.
17	291-296	4	**Comment:** This content is understood but may be more relevant to 'critical excipients' in the formula rather than being equally applicable to each and every excipient. **Proposed change:** Recommend these lines of the text are more focussed on understanding which (critical) excipients need this level of evaluation to be established.	3	The revised text elaborates more for excipients that have an influence on the active substance permeation and bioavailability and for Novel excipients. It is up to the Applicant to provide the relevant information and justify it.
18	297-300	4	**Comment:** The requirement to provide information about the excipients is too broad; it is recommended to specify that relevant information need to be provided. **Proposed change:** "**Relevant** information on those excipients which might have an influence on the active substance permeation and bioavailability…"	3	It is up to the Applicant to provide the relevant information and justify it.
19	301-303	4	**Comment:** it should be clarified that mixtures of components that are naturally occurring (e.g., oleyl alcohol) or compendial components are not the subject of this requirement. **Proposed change:** "In the case of **non-compendial** excipients presented as **an admixture** of compounds, details of the composition should be…"	3	Reference to Ph. Eur. may replace the information required. However there are cases of excipients that even when described in the Ph. Eur. they are known to have a large variability in characteristics. Characterisation of such excipients is very important.
20	333-334 and 353	4	**Comment:** Suggest to move these lines to section 4.2.5 as this is more related to the characterisation of the dosage foam. **Proposed change:** move lines 333-334 and 353 to section 4.2.5 as this is more related to the characterisation of the dosage foam.	2,3	The type of the pharmaceutical form is/should be part of the objective of the formulation development.

Comment no.	Line no.	Stakeholder no.	Comment and rationale; proposed changes	Level	Outcome
21	346-347	4	**Comment:** To be moved to section 4.2.7 (P2.3) **Proposed change:** move lines 347-347 to section 4.2.7.	2,3	It is agreed that the critical process parameters should be identified during manufacturing process development and appropriate control should then be derived. Often formulation development and manufacturing process development take place in parallel or in close sequence. This particular text should be seen as a prompt to address these aspects in the next steps. It is acceptable to cross refer to related CTD sections.
22	354-355	4	**Comment:** This information should be move to the section about control strategy (4.3) **Proposed change:** move lines 354-355 to section 4.3 (Control strategy).	2,3	It is acceptable to cross refer to related CTD sections.
23	359-362	4	**Comment:** A general warning on paraffins is not relevant. Warnings in product information should be based on product composition, product knowledge, experience from the clinical trials and feedback form the market etc. **Proposed change:** Delete lines 359-362.		It is clarified that a general warning is not required. It is also noted that the wording has changed in the revised document "Where the drug product vehicle contains a flammable material or accelerant (e.g. isopropyl alcohol, paraffin) appropriate warnings should be included in the product information (see also section **Error! Reference source not found.**)."

Comment no.	Line no.	Stakeholder no.	Comment and rationale; proposed changes	Level	Outcome
24	363	4	**Comment:** Clarification is requested that this section is applicable to the registration batches, not during the development program.	1,3	Product characterisation is/should be part of the pharmaceutical development.
25	363-420	4	**Comment:** It is unclear how product characterisation should be performed in practise. Is the intention to perform it on validation batches? Is it a set of data performed once? **Proposed change:** Clarify above mentioned issue.	1,3	Product characterisation is/should be part of the pharmaceutical development.
26	369-371	1	**Comment:** The guideline states "*To enable statistical evaluation, the number of samples should be representative, with at least 12 units per batch for each experiment*." Testing 12 units per batch is excessive for a characterisation test, on a process that will normally already have been shown to give a homogeneous product. **Proposed change:** "To enable statistical evaluation, the number of samples should be representative, with at least 12 units per batch for each experiment. Fewer than 12 units per batch may be tested on a process that has been established to give a consistent product throughout the batch Between batch variability e.g. due to batch size, date of manufacture and period of storage, should also be taken into account."	4	The text has been modified to clarify the requirements for product characterisation from a quality point of view.
27	369-371	4	**Comment:** The selection of 12 units is not justified in all cases. **Proposed change:** "To enable statistical evaluation, the number of samples should be representative, ~~with at least 12 units per batch~~ for each experiment..."	4	The text has been modified to clarify the requirements for product characterisation from a quality point of view.

Comment no.	Line no.	Stakeholder no.	Comment and rationale; proposed changes	Level	Outcome
28	398-400	1	**Comment:** Rheological approach and texture analysis are usually used for the characterization of microstructure. For viscous dispersed systems (dispersions, emulsions) microscopy should be considered to understand microstructure. Moreover, as suspensions can be liquid or semi-solid, and the first example is for fluid preparations, the state of the suspensions concerned by this example should be specified. Finally, texture analysis such as consistency measurement could be an alternative method to rheology for specific products which have "wall-slip" behaviour under shear (e.g., most ointments and some creams). **Proposed change:** e.g for solutions and **liquid** suspensions – pH, buffering capacity, viscosity, density, surface tension, osmolality e.g for semi-solid formulations – pH, density, rheological behaviour**, texture analysis, microscopy, as required.**	4	The revised text reads: "-**e.g.,** for semisolid formulations – pH, density, rheological behaviour, water activity, impact on hydration of the skin (super)saturation, solubilisation." "**e.g.**" allows alternatives. See also response to comment 32.
29	401-416	4	**Comment:** It may be difficult to establish acceptable limit for parameters such as yield stress and the linear viscoelastic response, while a flow curve is a more well-established parameter. Even for this parameter some formulations like ointments can be very difficult to characterise by standardised rheological equipment due to slippage. **Proposed change:** Change the text in l. 403-409 to e.g.: "Rheological parameters relevant for the dosage form selected should be evaluated e.g. flow curve, power law, yield stress, creep testing, viscoelastic response."	4	Viscoelastic properties in the linear area describes the product characteristics at rest (or at least not heavy stirring). It will thus tell more about the microstructure than flow curves that in many cases are done at too heavy shear rates that the microstructure has been destroyed. Text has been modified to include "if feasible".

Comment no.	Line no.	Stakeholder no.	Comment and rationale; proposed changes	Level	Outcome
30	403-405	1	**Comment:** The meaning of "complete flow curve" should be clarified. **Proposed change:** "A ~~complete~~ flow curve of shear stress (or viscosity) versus shear rate, comprising multiple data points across the range of increasing and decreasing shear rates so that any linear portions of the up-curves or down-curves are clearly identified."	4	The proposed change does not actually change any meaning. Proposed change is accepted.
31	410	1	**Comment:** It should be clarified which dosage forms this would and would not apply to (i.e., creams vs solutions). **Proposed change:** "For semi-solid formulations: Rheograms should be provided and the product's behaviour classified according to shear and time effects e.g. pseudoplastic, dilatant, thixotropic, and characterised using appropriate metrics. For example: viscosities at specified shear rates across the rheograms (e.g. η100); plastic flow yield stress values; thixotropic relative area (SR); viscoelastic storage and loss moduli (G' and G"), apparent viscosity, loss tangent (tan δ)."	4	This is not agreed with. The differences between different formulations (lotions and creams or viscosity increased solutions and gels) are border-line. For example easy-flowing emulsions or viscosity-increased solutions would in the proposed case be exempted from this characterisation which is not the intention. Pseudoplastic behaviour is a typical behaviour for these products. Text has been modified.
32	415-416	1	**Comment:** Texture analysis such as consistency measurement could be an alternative method to rheology for specific products which have "wall-slip" behaviour under shear (e.g., most ointments and some creams). **Proposed change:** Appropriate characterization of rheological properties, **texture properties** (as required) may enable the identification or design of a simpler test to be used in the Finished Product Specification.	3	The proposed change is agreed and added.

Comment no.	Line no.	Stakeholder no.	Comment and rationale; proposed changes	Level	Outcome
33	418 - 419	1	**Comment:** For creams and gels that have the active substance(s) dissolved in the solvent system, the drug release is evaluated during the product development stage. A correlation between the drug release rate and the apparent viscosity/rheologic behaviour will be established during the product development and clinical study. With the product quality limits established for the tests such as appearance, pH, and rheology data, the drug release rate for the product should be well under control and the IVRT test may be waived for the product specification with justification. Please see page 1 general comments. **Proposed change:** "Appropriate tests to characterise product performance such as dissolution of suspensions and in vitro drug release (Annex I) should be developed and shown to be stable during storage <u>during the product development of new products.</u>"	4	No change is needed to the guideline since the text is already under the Pharmaceutical development heading. See also comments above.
34	418-419	4	**Comment:** It should be acceptable not to include a test for in vitro release on the drug product release and shelf life specification, if it is shown to be not the most discriminative test parameter. If e.g. viscosity is a more discriminative parameter, a test for viscosity should be included instead. Also, other tests such as viscosity or consistency may be relevant **Proposed change:** Include more examples of tests that could be used.	4	The comment is not relevant for the development studies. See specifications.
35	420	1	**Comment:** The guideline states "*In vitro skin permeation (Annex II) testing may also be of value*." It should be clarified that this tool is useful only during product development, as explained in the general comments (page 2).	4	The comment is agreed with. However, no change is needed to the guideline since the text is already under the Pharmaceutical development heading.

Comment no.	Line no.	Stakeholder no.	Comment and rationale; proposed changes	Level	Outcome
			Proposed change: "In vitro skin permeation (Annex II) testing may also be of value as a product development tool."		
36	420	4	**Comment:** It is not clear when an in vitro skin permeation test would be requested as part of the product characterisation. **Proposed change:** Please clarify.	4	In vitro skin permeation test is considered informative in most cases for product characterisation.
37	421-455	4	**Comment:** This section (4.2.6) is not applicable in a quality guideline and should be moved to another guideline, e.g. a relevant labelling guideline.	4,5	This is agreed, the text is modified accordingly.
38	458-467	1	**Comment:** The definition of *"[…] changes in formulation or manufacturing process […]"* should be clarified. The guideline should state that a Technical Transfer or scale up to a larger equipment size is not a manufacturing process change if the given and receiving equipment is of the same technology and has a reasonably similar design. The Critical Process Parameter may have to be adapted with a science-based rationale and verified through a process validation and need to demonstrate that the new set of equipment is capable to manufacture the product reproducibly with Critical Quality Attributes within specifications with an appropriate Ppk. **Proposed change:** "A change in manufacturing process is a significant change excluding for example a technical transfer to an equipment train of a similar technology but from a different brand or size done in the frame of a formal technology transfer. For dispersed drug products, e.g. two-phase emulsions, changes in formulation or manufacturing process may	1,4	Comment not accepted. Reference is made to section *6. Post Authorisation changes.* A risk assessment needs to be performed for the proposed changes to determine the impact of the changes in quality, safety and efficacy.

Comment no.	Line no.	Stakeholder no.	Comment and rationale; proposed changes	Level	Outcome
			influence the efficacy and/or safety of the product and are therefore important to evaluate and control. The order of addition of different components to the formulation can be of importance as well as process parameters such as temperature and homogenisation conditions e.g. speed and duration. In a typical manufacturing process, the critical points are generally the formation of a two- or multi-phase system from one-phase systems and the point at which the active substance is added. As the drug release rate, microstructure/physical properties and rheological profiles of the drug product may be susceptible to scale-up effects, it is particularly important that these properties are verified at the commercial scale."		
39	470-473	4	**Comment:** The definition of an "intermediate product" and "a bulk product" are unclear and in conflict with "Manufacture of the finish dosage form EMA/CHMP/QWP/245070/2015. Establishment of holding times are described in Manufacture of the finish dosage forms, EMA/CHMP/QWP/245074/2015. **Proposed change:** Delete line 470-473 to align and avoid conflicting guidelines.	1	Refer to definition of the Guideline on manufacture of the finished dosage form. (An intermediate product is defined as partly processed material that must undergo further processing steps before it becomes bulk product e.g. solution prior to filling, granulates, uncoated tablets etc. A bulk product is defined as any product which has completed all processing steps, up to but not including, final packaging.) Text revised to: "Many intermediate cutaneous products exhibit shear thickening in the days following manufacture. The time between

Comment no.	Line no.	Stakeholder no.	Comment and rationale; proposed changes	Level	Outcome
					intermediate product manufacture and filling may need to be optimised."
40	474	4	**Comment:** Terminology should be aligned: "Container" is traditionally used in conjugation with intermediate/bulk container, and "packaging" in relation to primary packaging materials. **Proposed change:** Change "packaging" to "container".	2	The proposed change is accepted.
41	480	4	**Comment:** Sterile topical ocular products, which meet antimicrobial preservative efficacy requirements are packaged in multi-use container. Sterile topical ocular products which are unpreserved are generally packaged in single use container. However, lately some unpreserved products are being packaged in multi-dose preservative free container (MDPF) that maintain product sterility during multiple use. The same could be applicable to other topical products, if justified. It should therefore be possible to justify a multi-use container for a sterile product. **Proposed change:** Drug products having sterile requirements should be packaged in single-use containers, **if not otherwise justified**.	3	Comment accepted.
42	498-503	1	**Comment:** IVRT is not necessary for routine batch control. Please see page 1 general comments. **Proposed change:** "General regulatory guidance on the establishment and justification of a control strategy for the drug product is given in other relevant guidelines, including	4	The relevant guidance in this respect has been revised. "General regulatory guidance on the establishment and justification of a control strategy for the drug product

Comment no.	Line no.	Stakeholder no.	Comment and rationale; proposed changes	Level	Outcome
			ICH Q8, Q9, and Q10~~. Attention should however be paid to the control of CQAs required for the control of drug release, i.e. the *in vitro* drug release / dissolution and, if appropriate *in vitro* skin permeation~~**.** If possible, pharmaceutical development should establish the link between product performance quality attributes and clinical efficacy.""		is given in other relevant guidelines, including ICH Q8, Q9, and Q10. Attention should however be paid to the control of CQAs required for the control of drug release, e.g., the *in vitro* drug release / dissolution (and, if appropriate, *in vitro* skin permeation) or other parameter(s) (e.g. microscopy, DSC, rheology) *if they are proven to be more discriminative with regard to controlling drug release.*" "Limits for performance tests, i.e. dissolution, in vitro release test (IVRT), *if included in the specification*,…"
43	508	5	**Comment:** It was recommended not to ask for IVRT as routine test. This is in accordance with the USP Pharmacopeia (Forum 44(5) General Chapter < 3 > "For semisolid dosage forms, in vitro drug release testing is currently not required for batch release".) For routine QC batch release and stability testing IVRT has certain operational constraints, e.g. need for repeated requalification. Requalification could result in a drift over product lifetime. **Proposed change:** Instead alternative techniques such as microscopy, DSC, rheology etc. should be favoured.	4	See response to comment 42.
44	512 - 516	1	**Comment:** Some context here around ICH M7 should be given so that it is clear if the approach would be different for genotoxic/mutagenic impurities.	3	Agreed; reference to M7 is added.

Comment no.	Line no.	Stakeholder no.	Comment and rationale; proposed changes	Level	Outcome
			Proposed change: "For topical products, the calculation of maximum daily dose for limits for degradation products is not as straightforward as for solid oral preparations or injections. The duration of treatment and amount required is usually more varied. The exposure levels from cutaneous products can usually be considered much less than from routes with systemic exposure. Deviations from standard calculations should be justified from a safety perspective. For further information around exposure and maximum daily dose of potential genotoxic or carcinogenic impurities, please consult ICH M7: ASSESSMENT AND CONTROL OF DNA REACTIVE (MUTAGENIC) IMPURITIES IN PHARMACEUTICALS TO LIMIT POTENTIAL CARCINOGENIC RISK".		
45	512 - 516	4	**Comment:** This text on calculation of exposure levels and limits for impurities and degradation products is helpful to some degree. However, it would be considerably more useful if some additional considerations could be provided to show how this quality aspect of the product will be expected to be addressed by the applicant (e.g., what considerations to include) such that consistent practices for development and assessment can result.	4	New text introduced that elaborates more.
46	519 – 522	1	*Similar to comments on lines 418 – 419* **Comment:** For cream and gel that the API(s) are dissolved in the solvent system, the drug release is evaluated during the product development stage. A correlation between the drug release rate and the apparent viscosity/rheologic behaviour will be established during the product development and clinical study. With the product quality limits established for the tests such as appearance, pH, and rheology data, the drug release	4	Text has been revised. "Limits for performance tests, i.e. dissolution, in vitro release test (IVRT), if included in the specification, should be justified by reference to clinical batches for which satisfactory efficacy and safety has been demonstrated. Release and shelf life

Comment no.	Line no.	Stakeholder no.	Comment and rationale; proposed changes	Level	Outcome
			rate for the product should be well under control and the IVRT test may be waivered for the product specification with justification. Please see page 1 general comments. **Proposed change**: "~~Limits for performance tests, i.e. dissolution, drug release using a synthetic membrane and, if appropriate skin permeation testing, if included in the specification should be justified by reference to clinical batches for which satisfactory efficacy and safety has been demonstrated. The limits should be the same at release and shelf life, unless justified and qualified by clinical data.~~ Appropriate tests to characterise product performance such as dissolution of suspensions and in vitro drug release (Annex I) should be developed and shown to be stable during storage during the product development of new products.""		limits should normally be the same, unless the reasons for the differences are satisfactorily explained on quality grounds and justified. Justification should be based on clinical batches or batches used in the pharmaceutical equivalence study with the reference product. Tighter limits at release may need to be set, to ensure that the product will remain within specification(s) during the approved shelf life." See also response to comment 42.
47	524 - 526	1	**Comment:** The guideline states: "*To assure quality and stable product characteristics throughout storage, the designated shelf life needs to be based on physical, chemical and microbiological stability, and in vitro release or other performance tests.*" The control strategy which is based on a technical risk analysis defines what the Critical Quality Attributes are and therefore defines what needs to be tested at release and in stability. The way it is currently written suggests that every testing is mandatory. **Proposed change**: "To assure quality and stable product characteristics throughout storage, the designated shelf life needs to be based on the product specifications e.g. physical, chemical and microbiological stability~~, in vitro release or other performance~~ tests."	3,4	Text has been revised. "To assure quality and stable product characteristics throughout storage, the designated shelf life needs to be based on the product specifications, e.g., physical, chemical and microbiological stability, and *in vitro* release or other performance tests, as required."

Comment no.	Line no.	Stakeholder no.	Comment and rationale; proposed changes	Level	Outcome
48	524 - 526	4	**Comment:** There might be cases where performance testing is not applicable, e.g. for some topical ocular products where the residence time of the product in the pre-corneal area is very short, less than a few minutes, and ocular bioavailability is much less than 10%. It is therefore suggested to add a few words. **Proposed change**: To assure quality and stable product characteristics throughout storage, the designated shelf life needs to be based on physical, chemical and microbiological stability, and in vitro release or other performance tests **as required**.	1	Accepted.
49	539 - 540	1	**Comment:** The statements "*unnecessary wastage*" and "*too short in use shelf-lives*" are not clear. **Proposed change**: "~~Unnecessary wastage or too short in use shelf-lives should not be proposed"~~. A reasonable in-use shelf-life should be proposed based on the duration of treatment and the product stability. The amount of product delivered should be sufficient to cover the duration of treatment as specified on the product label, with a goal to also minimize unnecessary waste."	2	Text has been revised. "A reasonable in-use shelf-life should be proposed based on the duration of treatment and the product stability."
50	547	4	**Comment:** The definition of a 'simple product' is not sufficiently clear. For example, it is questioned that 'simple' may not be the correct term here considering that sections 5.2 and 5.2.1 give guidance on investigating quality equivalence by extended pharmaceutical assessment that would seem to be very reasonable to apply to 'non-simple' product formulae.	2	The guideline has been revised and provides: "For the purpose of this guideline, simple formulations are formulations with a single-phase base (matrix or vehicle) in which the active substance is in solution or suspension, e.g., solutions and suspensions in single

Comment no.	Line no.	Stakeholder no.	Comment and rationale; proposed changes	Level	Outcome
			Proposed change: Consider providing better definition of what constitutes a product that can be managed using comparison of quality alone.		phase liquids, -gels, or -ointments, and, do not contain excipients that are intended to enhance drug permeation or are difficult to characterise (e.g. of biological origin). For the purpose of this guideline, complex formulations are multiphase systems, which are difficult to characterise structurally (e.g. emulsions), or formulations with excipients that are difficult to characterise, and formulations containing excipients that are intended to enhance drug permeation."
51	562	4	**Comment:** It is unclear what is meant by "method of administration". If this is the same as "route of administration", it should be stated. Otherwise, please provide one or two examples.	1, 3	"method of administration" as stated in SmPC 4.2. "method of administration" is not the same as "route of administration".
52	572 - 573	4	**Comment:** Whilst this level of rigor may be acceptable for commercial products, it is difficult to fully characterise products in development to this degree.	3	Not agreed. Equivalence has to be shown for quality attributes of the applied formulation. Characterisation is part of development and should inform and support claims for equivalence. See section 5.2.

Comment no.	Line no.	Stakeholder no.	Comment and rationale; proposed changes	Level	Outcome
			Proposed change: "Equivalence requires comparative **stage-appropriate** quality data with the relevant comparator medicinal product…"		
53	581	5	**Comment:** "Changes in the manufacturing process and equipment" should be specified; the guideline should state that a technical transfer or scale up to a larger equipment size is not a relevant manufacturing process change if the equipment is of the same technology and has a reasonably similar design. **Proposed change**: Here reference to the Critical Quality Attributes should be possible.	1,4	The manufacturing process and equipment should be the same in principle. A change of scale should be justified. Refer also to Comment 38. A risk assessment needs to be performed for the proposed changes in scale to determine the impact of the changes in quality, safety and efficacy.
54	581 - 582	1	**Comment:** If there are minor changes moving to commercial scale/site, but they are justified by demonstrating equivalence of CPPs and CQAs, this should be reasonable to bridge pilot and commercial scale batches in most cases. **Proposed change**: "Product quality equivalence should be undertaken on batches representative of the product to be marketed and the manufacturing process – i.e. batches at or near production scale. Alternatively, pilot scale batches, at least 1/10 production scale may be used for characterisation and comparative purposes, ~~if there are no changes in the manufacturing process and equipment, and evidence provided that scale up does not affect product quality~~ however, evidence should be provided that scale up does not affect product quality."	2	See above response to comment 53. Slight amendment of text.

Comment no.	Line no.	Stakeholder no.	Comment and rationale; proposed changes	Level	Outcome
55	586 - 587	4	**Comment:** It is unclear from where the number of 12 samples originates. **Proposed change:** Please clarify text, e.g. by reference to literature, or rephrase "To enable statistical evaluation, the number of samples should be representative, ~~with at least 12 units per batch~~ for each experiment...".	2,3	Text has been amended but 12 samples is retained in principle.
56	588 - 589	4	**Comment:** It is unclear whether extrapolation is allowed or real time data for full shelf-life is needed. **Proposed change:** Please clarify text.	3	Standard Stability Guidelines apply.
57	595	4	**Comment:** It is unclear what is meant by "same immiscible phases"? Oil and water? Or the exact water phase and oily phase? **Proposed change:** Please clarify text.	3	Acceptable to delete immiscible. Text amended.
58	597	1	**Comment:** The guideline states "*The active substance content, and its salt form should be the same.*" The statement "salt form" should be clarified, ie. polymorphism of a same salt or a different salt. **Proposed change**: Either "The active substance content, and its salt form <u>(i.e. polymorphic form)</u> should be the same." Or "The active substance content, and its salt form <u>(i.e. ionic form)</u> should be the same."	3	Text amended and clarified.
59	624 - 625	1	**Comment:** It is suggested to mention as well that fragrance and sensates (eg, cooling/warming/tingling agents) quantitative change >±10% is acceptable (in addition to the listed emollients, antioxidants, antimicrobials, colours),	3	Refer to the revised guideline.

Comment no.	Line no.	Stakeholder no.	Comment and rationale; proposed changes	Level	Outcome
			provided justification is given that they do not interfere with transdermal delivery or subsequent biodistribution. **Proposed change**: "For excipients whose function is not related to product performance or administration, i.e., antioxidants, antimicrobial preservatives, colorants, fragrances, skin sensates (i.e., agents creating cooling/warming/tingling skin sensations)."		
60	630 - 632	1	**Comment:** The confidence interval limits of 90 to 111% are very tight for IVRT (USP quotes 75%-133%, see further comments in the method validation section lines 914-915). Also, this does not account for other types of testing that could be applied. **Proposed change**: "~~For quantitative quality characteristics, the 90% confidence interval for the difference of means of the test and comparator products should be contained within the acceptance criteria of +/- 10% of the comparator product mean, assuming normal distribution of data.~~ For quantitative quality characteristics, appropriate statistical acceptance criteria should be applied based on the precision of the quantitative methods used for example Mann Whitney U tests for IVRT or t-tests for other methods. the 90% confidence interval for the difference of means of the test and comparator products should be contained within the acceptance criteria of +/-10% of the comparator product mean, assuming normal distribution of data."	3	This limit is in line with the Bioequivalence guideline F2 requirement. In principle in vitro acceptance ranges should be narrower than the in vivo acceptance ranges taking into account variability in the reference product; comparisons should be conducted with batches of the similar age. Refer to the revised guideline. The text has been revised and elaborated.
61	630 - 633	4	**Comment:** The intent of this section is unclear; please clarify. More specifically, the text's stated acceptance criteria for quantitative quality characteristics (of ±10% of the comparator product mean) may be a reasonable approach to		Partially accepted. Refer to the revised guideline.

Comment no.	Line no.	Stakeholder no.	Comment and rationale; proposed changes	Level	Outcome
			apply for the assessment of a proposed generic product but the innovator may have established a more comprehensive understanding of quality impact and wider specifications for some of these quality characteristics (or the methodological variability may be too wide to establish a ±10% criteria, as described in section 5.3.2. See also line 901 where a CV of 10% is described; this CV would preclude a ±10% specification being set for such a test). Thus, some wider allowance should be accommodated 'when justified' by a wider scientific understanding of the specific product. This is further supported by line 848 where the text states "*in vitro* release limits should be justified by reference to the *in vitro* release rates observed with clinical batches for which satisfactory efficacy or equivalence has been demonstrated". This again could justify acceptance criteria beyond ±10%. **Proposed change**: Change text to read "For quantitative quality characteristics, the 90% confidence interval for the difference of means of the test and comparator products should be contained within the acceptance criterion of ± 10% of the comparator product mean, assuming normal distribution of data, **unless otherwise justified**".		The text has been revised and elaborated. In principle in vitro acceptance ranges should be narrower than the in vivo acceptance ranges taking into account variability in the reference product and the understanding of the clinical consequences of the differences in the critical quality attributes.
62	630 - 632	5	**Comment:** The requirement to demonstrate comparable quantitative product characteristics with acceptance limits within ±10 % for each parameter results in a high probability of product failure due to multiple testing associated with a defined risk of failure for each test so that finally the probability of not matching one or few criteria is high even for nearly identical products.		Partially accepted. It is necessary to identify the critical quality attribute for which similarity has to be demonstrated and the acceptance range should be defined taking into account the variability of the reference product.

Comment no.	Line no.	Stakeholder no.	Comment and rationale; proposed changes	Level	Outcome
			Proposed change: One solution could be to introduce generally wider acceptance criteria however a "one-size-fits-all" approach was generally not favoured by the majority of the participants of the EUFEPS meeting. A better solution could be to allow for case-by-case widening of acceptance criteria based on variability of the originator in the sense of a scaling procedure. Alternatively, a Principal Component Analysis has been proposed by a speaker from the auditorium in Bonn summarising all parameters to just one or two. The latter solution was considered an innovative approach which finally might be a good option. It requires further discussion but seems promising.		Refer to the revised guideline. The text has been revised and elaborated.
63	645	5	**Comment:** As alternative method for in-vitro skin permeation studies confocal Raman spectroscopy was recommended to be mentioned in the guideline, as validation has been realised in single cases and the technique offers promising alternatives (Franzen et al 2015, Paper attached); it was recommended during the meeting to consider Raman spectroscopy as future option provided that adequate validation is presented.		See response to comment #64.
64	654 - 655	1	**Comment:** The guideline states: "*Other techniques, such as Microdialysis and Confocal Raman spectroscopy are not sufficiently established to provide pivotal equivalence data but may be supportive.*" The options to use these methods should remain open if the applicant demonstrates that the method has been validated. **Proposed change**: "Other techniques <u>evidencing the drug diffusion and content at the site of action,</u> such as Microdialysis and Confocal Raman spectroscopy are not <u>currently</u> sufficiently		This following wording proposal is acceptable and is implemented. Other techniques evidencing the drug diffusion and content at the site of action, such as Microdialysis/ open flow microperfusion and Confocal Raman spectroscopy are not currently sufficiently established to provide

Comment no.	Line no.	Stakeholder no.	Comment and rationale; proposed changes	Level	Outcome
			established to provide pivotal equivalence data but may be supportive. They could be considered pivotal if appropriately validated."		pivotal evidence but may be supportive. They could be considered as pivotal evidence if appropriately qualified as suitable method for equivalence testing. These new approaches should preferably be confirmed by a CHMP qualification opinion (please refer to Qualification of novel methodologies for drug development: guidance to applicants, EMA/CHMP/SAWP/72894/2008).
65	654 - 655	4	**Comment:** What is meant by that these studies "may be supportive"? Can they be used if one of the other tests do not fulfil requirements? Or must they be used in addition, if applicable for the relevant drug products? **Proposed change**: Please clarify text.		Supportive means providing additional reassurance to the data from the pivotal study. See response to comment #64.
66	654 - 655	5	**Comment:** The whole sentence should be deleted as the guideline now discourages further scientific development. Instead, other alternative methods should be encouraged to be further validated In general skin-PK-based methods should be addressed as very sensitive methods in regards to detection of product differences, provided the validation of the method in question has demonstrated that product differences can adequately be detected. Alternative methods for characterising skin penetration based on pharmacokinetic data should explicitly be allowed in the guideline, such as microdialysis and related methods such as		Comment considered and text has been revised. See response to comment #64.

Comment no.	Line no.	Stakeholder no.	Comment and rationale; proposed changes	Level	Outcome
			open flow microperfusion, particularly since the latter has undergone intensive testing during the last years. Furthermore, there are increasing activities to establish Confocal Raman Spectroscopy also for in-vivo PK studies. So, provided that adequate validation of the method in question has been shown, certain evidence of sensitivity towards product differences can be presented and the site of determination is predictive for the site of action - directly or indirectly - these methods should be allowed. The auditorium of the EUFEPS meeting in Bonn strongly emphasized that future scientific investment into these alternative but very promising methods will only occur if they are principally allowed in the guidance. **Proposed change**: Instead of excluding them, the auditorium recommended to allow Microdialysis, Open Flow Microperfusion and Confocal Raman Spectroscopy but to define validation criteria for all PK methods. There is reason to assume that comparable to the systemically available drugs skin PK methods may even be superior to PD methods for detection of product quality differences; on the other hand for the PD methods detected differences will presumably be of clinical relevance and thus they may be applied in those cases when PK equivalence could not be demonstrated, e.g. in hybrid applications.		
67	656 - 658	5	**Comment:** The whole sentence should be deleted as the guideline now discourages further scientific development. Instead, other alternative methods should be encouraged to be further validated. As additional pharmacodynamic method in patients the psoriasis microplaque assay should be mentioned. There the		Comment considered and text has been revised.

Comment no.	Line no.	Stakeholder no.	Comment and rationale; proposed changes	Level	Outcome
			intraindividual assessment is useful to minimise variability. The sensitivity of the method and the impact of reduced sensitivity regarding product difference related to study design issues intended to maximize effectiveness, for example occlusive application, should be addressed. Non-occlusive application should be favoured, unless adequate sensitivity towards product differences has also been demonstrated for the occlusive testing. Sonographic assessment or alternative non-invasive imaging method of the inflamed layer is recommended to reduce investigator bias with clinical scoring. In order to apply any imaging method or other biophysical measurement method, the variability of the measurement method itself with different operators and assessors must be assessed and adequate steps undertaken to ensure that variability of the measurement method itself is within acceptable limits. As endpoint for evaluation AUC is recommended. In cases where the API itself leads to a clear effect such as increased blood flow, and this effect can be considered a surrogate endpoint, biophysical measurements which quantify the effect should be allowed as a pharmacodynamic endpoint in study designs with healthy volunteers or patients. For example, in the case of increased blood flow from an API such as capsaicin, Laser Speckle Contrast Imaging should be allowed as pharmacodynamic endpoint. The technique allows quantifying perfusion as well as erythema on a very high level of precision and accuracy so that for example capsaicin effect might be quantifiable. In healthy volunteers histamine or other adequately validated challenge models can be also considered as PD models for anti-inflammatory drugs. However, for topical drugs this will most likely only apply for methods inducing the inflammation by intradermal injection, external induction such as UV erythema,		

Comment no.	Line no.	Stakeholder no.	Comment and rationale; proposed changes	Level	Outcome
			or methods where it can be demonstrated that induction of the challenge does not result in an interaction with the topical application of test product. Methods such as Laser Speckling Imaging can then be used to quantify inflammation. In such study designs the variability of the measurement method itself with different operators and assessors must be assessed and adequate steps undertaken to ensure that variability of the measurement method itself is within acceptable limits. As endpoint for evaluation AUC is recommended.		
68	669	1	**Comment:** The guideline states "*Because the studies are single-dose, product application is a significant source of variability.*" Depending on the posology, more than one dose may be applied in 24 hours, therefore this statement should be deleted. **Proposed change**: "~~Because the studies are single-dose, product application is a significant source of variability~~."		Not agreed. The IVRT, IVPT, PK BE, TS are single dose studies.
69	679 - 680	1	**Comment:** The last sentence seems redundant as it refers to general GMP criteria. **Proposed change**: "The studies should be conducted following strict protocols ~~by experienced trained staff, with quality assurance in place~~."		Agreed.
70	681 - 682	1	**Comment:** The guideline states "*In vitro skin permeation and stratum corneum sampling (tape stripping) studies should include negative controls that are not equivalent to the test and comparator products.*" This is included to discriminate between true positive (identical) and true negative (different API contents) formulations. This cannot be called a negative control, which refers to "no detection", "no signal", "no effect".		Accepted. The word "negative " has been removed to avoid confusion. Text amended.

Comment no.	Line no.	Stakeholder no.	Comment and rationale; proposed changes	Level	Outcome
			Proposed change: "In vitro skin permeation and stratum corneum sampling (tape stripping) studies should include true negative controls that are not equivalent to the test and comparator products."		
71	682	4	**Comment:** A more precise explanation of what an appropriate negative control is could be useful – e.g. as described in line 924.		As above in response to comment #70.
72	701 and 950	1	**Comment:** The guideline states "*For in vitro skin permeation studies, the number of donors may be less than 12, if justified*". It conflicts with line 950 which states "*The number of skin donors should not be less than 12, with at least 2 replicates per donor*." **Proposed change**: "For in vitro skin permeation studies, the number of skin donors ~~may~~ should not be less than 12, except if justified, with at least 2 replicates per donor."		Agreed and revised: "For in vitro skin permeation studies, the number of skin donors should not be less than 12, unless otherwise justified, with at least 2 replicates per donor. A larger number of replicates may be needed in case of high intra-donor variability."
73	707—715 and 1004	1	**Comment:** The Guideline speaks of using ratio of means. It is suggested to change it to geometric means since skin permeability shows log-normal (and not normal) distribution (there is literature data in support, see, for example, Meidan and Roper, Tox in vitro, 22 (2008) 1062-1069; Lehman et al, Pharm Res, 34 (2017) 217-228). **Proposed change**: "The acceptance criteria for equivalence parameters is that the 90% confidence interval for the ratio of geometric means of the test and comparator products should be contained within the acceptance interval of 80.00-125.00%, unless justified."		Agreed. Added in the text.

Comment no.	Line no.	Stakeholder no.	Comment and rationale; proposed changes	Level	Outcome
74	708 - 710	4	**Comment:** The criterion of "that the 90% confidence interval for the ratio of means of the test and comparator products should be contained within the acceptance interval of 80.00 - 125.00%" are considered too tight for IVPT given the inherent variability in the donor skin permeability. **Proposed change**: Please provide a rationale for this criterion.		20% like for PK BE studies. Widening based on variability like Cmax may be applicable. Replicates should be used to determine intra-subject CV.
75	727	5	**Comment:** We propose to add the following line to the guideline: "Continuous skin interstitial fluid sampling methods (dOFM and dMD) Annex IV of this guideline".		Additional methods may be a promising alternative and have been included in the revised guideline as possible methods if validated. See section 5.3.1.
76	738	4	**Proposed change**: Change "ATSM" to "ASTM"		OK ; it is a typo.
77	752 - 753	1	**Comment:** The guideline states "*For topical products, with a regional site of action, where the active substance has systemic bioavailability, bioequivalence studies provide evidence of both efficacy and safety*." For products with regional site of action, where effect compartment concentrations are more correlated with efficacy, systemic concentrations are useful to establish safety but not efficacy. **Proposed change**: "For topical products, with a regional site of action, where the active substance has systemic bioavailability, bioequivalence studies provide evidence of ~~both efficacy and~~ safety."		Not agreed. The amount/concentration in plasma that is due to absorption from the skin also reflects efficacy because the amount available to go into the circulation is also available to go to the site of action and equilibrium does not depend on the formulation once in the dermis. Furthermore, the formulation is practically the same. So, if there is an effect due to excipients, it is similar in both products.

Comment no.	Line no.	Stakeholder no.	Comment and rationale; proposed changes	Level	Outcome
78	776	4	**Comment:** It is unclear which novel studies the text refers to. **Proposed change**: Please clarify text.		For example psoriasis microplaque assay or Laser Speckle Contrast Imaging. These have been added to the revised guideline.
79	778 - 785	1	**Comment:** it is suggested to add a bullet point for site changes, where no change in equipment or process are proposed, and it can be shown the CPPs/CQAs have been met. Some minor process changes can be justified in certain cases with appropriate data. **Proposed change**: "A waiver of the need to provide permeation kinetic or pharmacodynamic equivalence data can in principle be acceptable for: • Simple formulations with a single-phase base in which the active substance is in solution or suspension e.g. cutaneous solutions, single phase gels and ointments; cutaneous suspensions. • If the objectives and purpose of the drug product is only administration of the active substance to the surface of the skin (see section 4.2.1), then extended pharmaceutical equivalence, including in vitro drug release for gels, ointments and suspensions, and equivalence in administration should normally be sufficient • Site changes, where minimal change in equipment or process are proposed, and it can be shown the CPPs/CQAs have been met."		Text has been revised. See definitions of "simple" and "complex" formulations in section 5.1 Regarding post approval changes see revised section 6.
80	778 - 794	4	**Comment:** Following on from the comment to line 547 above, the products suitable for 'biowaiver' should be aligned with those that can be underwritten by extended pharmaceutical		Text has been revised.

Comment no.	Line no.	Stakeholder no.	Comment and rationale; proposed changes	Level	Outcome
			assessment (and the product control strategy applied). The section on biowaiver allowance currently does not seem well-aligned to the sections on extended pharmaceutical assessment. **Proposed change**: Please align the guidance content better between extended pharmaceutical assessment (and controls applied) and biowaiver allowance.		See definitions of "simple" and "complex" formulations in section 5.1
81	784	4	**Comment:** Gels, ointments and suspensions are mentioned. Is there a reason that creams are not included here?		Emulsions are considered complex products.
82	786	4	**Comment:** The text states an expectation for an equivalence study to be conducted when "the formulation has a qualitatively different excipient composition from the comparator". This is considered too conservative – e.g., if a low-level excipient (such as a colorant or perfumant) is qualitatively changed, this small change would not seem to be significant enough to product quality to drive an *in vivo* study. Similarly, the lowering (or removal) of an anti-oxidant or preservative should also be capable of acceptance without the need for an *in vivo* study. **Proposed change:** Modify the text to read "[h]as a qualitative **and significantly** different composition **in significant** excipients (i.e. excipients apart from colorants, perfumants, anti-oxidants, preservatives etc., if justified) from the comparator product."		Qualitative and quantitative differences in colours, antimicrobials, antioxidants, fragrance can be accepted, see section 5.2.1
83	793 - 794	1	**Comment:** The guideline states "*Bioequivalence studies should usually be provided if the products have a regional site of action, where the active substance has quantifiable systemic*		Not agreed. The amount/concentration in plasma that is due to absorption from the skin also reflects efficacy

Comment no.	Line no.	Stakeholder no.	Comment and rationale; proposed changes	Level	Outcome
			bioavailability." This should relate to products with regional site of action where systemic bioavailability is related to efficacy. For products with regional site of action, where effect compartment concentrations are more correlated with efficacy, systemic concentrations can still be useful to establish safety (see line 753). For such situations, a relative bioavailability study seems more appropriate. **Proposed change**: "Bioequivalence studies should usually be provided if the products have a regional site of action, where the active substance has quantifiable systemic bioavailability. <u>The bioequivalence study will inform on safety but not on efficacy when plasma compartment is not the site of action.</u>"		because the amount available to go into the circulation is also available to go to the site of action and equilibrium does not depend on the formulation once in the dermis. Furthermore, the formulation is practically the same. So, if there is an effect due to excipients, it is similar in both products.
84	793 - 794	4	**Comment:** The meaning of the text: "Bioequivalence studies should usually be provided if the products have a regional site of action, where the active substance has quantifiable systemic bioavailability" is unclear. The scope of this guideline is locally applied locally acting products, which often are without quantifiable systemic bioavailability. How should equivalence with respect to effect be shown for these products? **Proposed change**: Please clarify text.		See revised text in section 5.5: "For cutaneous products, with a regional site of action, where the active substance has systemic bioavailability, bioequivalence studies provide evidence of both efficacy and safety." See also response to comment #83.
85	801	1	**Comment:** it should be clarified that some minor changes in qualitative or quantitative composition of excipients can be justified in some cases (per text included on line 598). **Proposed change**: "b) the different strengths of the test products have the same qualitative composition. <u>Refer to Section 5.2.1, for permitted exceptions to the need for qualitative equivalence of excipients."</u>		Guideline text has been revised. Differences that can be accepted are described in other sections of the guideline.

Comment no.	Line no.	Stakeholder no.	Comment and rationale; proposed changes	Level	Outcome
86	802-803	1	**Comment:** The use of "equivalent" is absolute here and should be clarified. There are exceptions where minor differences can be justified between the test and comparator product, depending on the dosage form (i.e., solutions/excipients with no influence on drug permeation/absorption, etc.). **Proposed change**: "c) the qualitative and quantitative compositions of the different strengths of the test products are equivalent to the different strengths of the comparator medicinal products. • Where there are minor differences in quantitative excipient levels (+/- 10% for excipients whose only function relates to vehicle properties or emolliency, and +/- 5% for all other excipients), these should be justified."		Guideline text has been revised. Differences that can be accepted are described in other sections of the guideline.
87	806 - 827	4	**Comment:** It should be made more clear which level of post approval changes are in scope of the guideline. Also, many topical drug products approved for decades have not been characterised according to this draft guideline, but there is a thorough product and process knowledge and long clinical experience from the markets. These situations are not clearly acknowledged and described in this draft guideline. There may be instances with respect to post approval changes where IVRT is not suitable, and do not discriminate between batches. **Proposed change**: In line with section 5.5.1, include and describe situations were waivers in respect to post approval		It is highlighted that for a post authorisation change a risk assessment should be performed to determine its impact on quality, safety, or efficacy of the product. The guideline applies in post authorisation changes and in order to apply the guideline it is emphasised that a discriminative IVRT method should be developed if not available. Text has been modified.

Comment no.	Line no.	Stakeholder no.	Comment and rationale; proposed changes	Level	Outcome
			changes are applicable e.g. categorization of acceptable minor formulation and process changes. Include the possibility of measuring sameness by other physical and chemical means than IVRT, in cases where IVRT is not discriminative.		
88	806 - 827	4	**Comment:** To provide guidance on the level of information needed to be submitted in connection with post approval change on topical products and the category of change, EFPIA sees a need for updating and align the variation guideline with the draft guideline.		The classification of changes is not in the scope of this guideline. The justification of the proposed classification is up to the applicant and should be supported by suitable data.
89	810 - 816	1	**Comment:** The exclusion of manufacturing scale and site change here should be commented on in the guidance, so it is clear whether all things being the same, scale or site should in itself trigger anything beyond extended pharmaceutical equivalence. **Proposed change**: ”The following changes are considered to have a potential significant impact on the safety, quality or efficacy of the drug product: • A change in the physicochemical state and / or thermodynamic activity of the active substance; • A change that affects dissolution, in vitro release, in vitro permeation kinetic characteristics of the drug product. • A change in the manufacturing process e.g. a change in a critical process parameter. For site change or scale-up, minor changes in process and equipment may be proposed, but must be fully justified.”		Not accepted. IVRT is needed for minor variations in the same way that an in vitro dissolution profile is needed for a tablet.

Comment no.	Line no.	Stakeholder no.	Comment and rationale; proposed changes	Level	Outcome
90	817 – 818	4	**Comment:** When an IVRT method is included in the drug product specification, and the limits are established based on the release rate observed on the clinical batches, it should be sufficient to show that the post-change batches comply with the specification limits for in vitro release. In other words, the "comparative medicinal product" is not the latest manufactured pre-change batches in the case of comparing the parameters already specified on the drug product specification. A prerequisite for this approach is of course that both the latest pre-change batches and the post-change batches fulfil the original drug product specification.		Not agreed. Compliance with the specification alone is not enough to demonstrate equivalence when post approval changes to the product are considered. In that case equivalence pre- and post-approval change should be demonstrated as per this guideline.
91	837 (Annex I)	1	**Comment:** For IVRT, immersion cells described in the USP1724 Semisolid drug products – performance tests could be an alternative method easier to use in case of post approval product changes on a manufacturing site. **Proposed change**: An IVRT with pseudo-infinite dosing using diffusion cells **or immersion cells** evaluates the rate and extent of release of an active substance in the proposed formulation.		Acceptable. "Other equipment may be used (e.g. immersion cells)."
92	846 – 849 (Annex I)	1	**Comment:** IVRT is not necessary for routine batch control. Please see page 1 general comments. **Proposed change**: "~~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~~. Generation of IVRT data on clinical batches is encouraged to support post approval changes to support a claim of therapeutic equivalence with the comparator medicinal product."		Refer to 4.3 and 4.3.1, which have been revised.

Comment no.	Line no.	Stakeholder no.	Comment and rationale; proposed changes	Level	Outcome
93	846 – 847 (Annex I)	5	**Comment:** In the auditorium it was recommended not to ask for IVRT as routine test. This is in accordance with the USP Pharmacopeia (Forum 44(5) General Chapter < 3 > "For semisolid dosage forms, in vitro drug release testing is currently not required for batch release".) For routine QC batch release and stability testing IVRT has certain operational constraints, e.g. need for repeated requalification. Requalification could result in a drift over product lifetime. Instead alternative techniques such as microscopy, DSC, rheology etc. should be favoured.		Refer to 4.3 and 4.3.1, which have been revised.
94	855 – 856 (Annex I)	5	**Comment:** As the type of membranes chosen might influence the outcome adequate justification of membrane selection is to be provided.		Agreed, covered by section 2a of the Annex I.
95	865 - 868 (Annex I)	1	**Comment:** Ensuring receptor fluid solubility of the drug by increasing the volume only, does not take into account the inherent solubility of the drug in the medium. **Proposed change**: "Sink conditions should be confirmed. An acceptable sink condition is one where the maximum concentration of the active substance in the receptor medium achieved during the experiment does not exceed 30% of its maximum solubility in the receptor medium. ~~Sink conditions normally occur in a volume of medium that is at least 3-10 times the saturation volume~~."		Partially accepted. Text has been revised.
96	872 (Annex I)	4	**Comment:** It is not clear why sampling time points should be at least hourly. In case of very slow release this does not make sense. **Proposed change**: Delete "(at least hourly)"		Not agreed. The number of timepoints and the duration of the test should be selected to sufficiently characterise the

Comment no.	Line no.	Stakeholder no.	Comment and rationale; proposed changes	Level	Outcome
					release profile. Study durations of more than 6 hours are rare.
97	874 (Annex I)	5	**Comment:** Several participants were of the opinion that there is no need to ask for a minimum release of 70%.		Agreed. Text has been revised.
98	877 – 880 (Annex I)	4	**Comment:** The amount of drug product applied is determined by the volume of the donor chamber. It is however not possible to measure the exact amount applied and thereby documenting a variation within ±5%. **Proposed change**: Delete "(±5% between samples)"		Partially accepted, text has been revised to ±10%.
99	884 – 901 (Annex I)	5	**Comment:** Validation of IVRT should include placebo control.		Not agreed. Discriminating against placebo has no added value.
100	886 (Annex I)	4	**Comment:** The text states "testing conditions providing the most suitable discrimination should be chosen." This is understood but is too stringent – what should be needed is 'suitable' discrimination, not an endless search for the 'MOST' discriminating. **Proposed change**: Modify this text to "Testing conditions providing suitable discrimination should be chosen."		Agreed.
101	890 – 894 (Annex I)	1	**Comment:** Validating IVRT at 3 or more strengths is problematic for post-approval change equivalence testing. This is because it would require manufacture of 3 production or at least pilot scale batches which is wasteful and at a different concentration may potentially not be representative of true product drug release. Better would be to do a 'dose discrimination' test where a production scale batch is diluted		Not agreed. The IVRT method should be able to discriminate drug release rates from lower and higher strength formulations. This requirement is irrespective of whether the method is used pre- or post- approval.

Comment no.	Line no.	Stakeholder no.	Comment and rationale; proposed changes	Level	Outcome
			with placebo to 50% and then IVRT done to show that the test can discriminate between gross changes in the product. **Proposed change**: "~~The release rate as a function of drug concentration (at least three strengths) in the formulation should be investigated. The linearity (r2>0.90) of the correlation of formulation concentration to rate of drug release (R) should be confirmed when the drug is fully dissolved. For suspensions, the relation between drug concentration and rate of drug release (R) should also be understood and discussed.~~ Perform a dose discrimination test where a test batch is made with 50% of the active concentration and demonstrate that the 50% is not equivalent to the on target 100% reference product to show that the test can discriminate between gross changes in the product."		The different strengths should be manufactured by the same manufacturing process.
102	891 (Annex I)	4	**Comment:** EFPIA notes that the validation requirement to linearity (r^2>0.90) is not identical to, for instance, the requirement in the FDA *Draft Guidance on Acyclovir (Recommended Dec 2014 – Revised Dec 2016),* where r^2≥0.90 is asked for. Global harmonisation of such requirements would be a huge benefit for industry. **Proposed change**: Change "r^2>0.90" to "r^2 ≥0.90".		Agreed. Amended.
103	900 – 901 (Annex I)	4	**Comment:** EFPIA notes that the validation requirement to intermediate precision (CV<10%) is not identical to, for instance, the requirement in the FDA *Draft Guidance on Acyclovir (Recommended Dec 2014 – Revised Dec 2016),* where CV<15% is asked for. Global harmonisation of such requirements would be a huge benefit for industry.		Text amended to "CV<10 % preferably".

Comment no.	Line no.	Stakeholder no.	Comment and rationale; proposed changes	Level	Outcome
			Proposed change: Change "CV<10%" to "CV<15%".		
104	905 – 906 (Annex I)	1	**Comment:** The guideline states "*A minimum of 12 samples per batch should be used for initial method validation or to demonstrate equivalence. For routine release, a minimum of 6 samples would be accepted*." For routine release testing where development/validation has shown the product to be homogenous, a statistically relevant number of samples could be used. **Proposed change**: "A statistically relevant number of samples per batch ~~minimum of 12 samples per batch~~ should be used for initial method validation, routine release or to demonstrate equivalence. ~~For routine release, a minimum of 6 samples would be accepted.~~ "		Not agreed. A minimum of 12 is consistent with the requirement for in vitro dissolution comparison of oral solid dosage forms.
105	914 – 915 (Annex I)	1	**Comment:** The 90% confidence interval limits of 90-111% are too tight for equivalence. USP <1724> uses the Mann-Whitney U test to calculate the 90% confidence interval and applies limits of 75-133.33%. Furthermore, if the test fails at Stage 1, further cells can be analysed for Stage 2 testing and included in the calculation of confidence intervals. **Proposed change**: "~~The 90% confidence interval for the ratio of means of the test and comparator products for the parameters (R), (A) should be contained within the acceptance interval of 90 – 111%.~~ The Mann-Whitney U test 90% confidence interval for the ratio of means …should be contained within the acceptance interval of 75-133.33%. Should the testing fail at Stage 1 with 6 samples then perform Stage 2 testing. This consists of an additional 2 sets of 6 cells for the test and reference product to generate 12 new slopes and generate confidence interval		Not accepted. In the EU the acceptance range for in vitro parameters has been traditionally narrower than in vivo parameters. In order to be consistent with other guidelines (in vitro dissolution test, OIP) a 10% acceptance range has been defined. The sample size should be increased to comply with this narrow acceptance range. If variability is very high, the acceptance range might be widened. Explanation included in the revised guideline text.

Comment no.	Line no.	Stakeholder no.	Comment and rationale; proposed changes	Level	Outcome
			data from all 18 slopes."		
106	914 – 915 (Annex I)	4	**Comment:** It is questioned on which principle the 90% confidence interval for the ratio of means of the test and comparator products for the parameters (R), (A) of 90-111% is proposed. Please provide justification and an example of the calculations for clarification. Furthermore, EFPIA notes that the 90% confidence interval for the ratio of means of the test and comparator products for the parameters (R), (A) is not identical to, for instance, the requirement in the *FDA Guidance for Industry, Nonsterile Semisolid Dosage Forms, Scale-Up and Postapproval Changes: Chemistry, Manufacturing, and Controls; In Vitro Release Testing and In Vivo Bioequivalence Documentation,* in which the requirement is 75%-133.33% based on detailed descriptions and calculations of the methods. Global harmonisation of such requirements would be a huge benefit for industry.		Explanation included in the revised guideline text.
107	923 – 924 (Annex II)	1	**Comment:** The guideline states "*For equivalence studies, test and comparator products, together with a negative control such as a formulation with 50% of the proposed product strength, are compared.*" **Proposed change**: "For equivalence studies, test and comparator products, together with a true negative control such as a formulation with 50% of the proposed product strength, are compared."		The word "negative" has been removed to avoid confusion. Text amended.
108	934 (Annex II)	5	**Comment:** IVPT: objections were raised against the requirement to allow only human skin. Data in literature indicate that pig ear skin may result in highly comparable		"Use of *ex vivo* animal skin is not currently sufficiently established to provide pivotal evidence."

Comment no.	Line no.	Stakeholder no.	Comment and rationale; proposed changes	Level	Outcome
			outcome, however of course adequate validation and system calibration is mandatory and needs to be provided; Such testing system would overcome the limited availability of testing material and could help reduce costs; thus, provided adequate sensitivity towards product differences is demonstrated pig ear skin could be introduced as alternative testing system.		When evidence of the same sensitivity to detect differences between formulations (a large variety of formulations) becomes available the guideline can be revised in this regard.
109	943 (Annex II)	1	**Comment:** The guideline states "*The skin integrity should be checked prior to and after each experiment*." Skin integrity is never tested AFTER the experiment. It is monitored PRIOR to the application to withdraw membranes exhibiting unacceptable skin integrity. Moreover, testing skin integrity after the experiment is not compatible with TEER technique since it requires to add buffer on the skin membrane. **Proposed change**: "The skin integrity should be checked prior to ~~and after~~ each experiment."		Accepted.
110	948 (Annex II)	4	**Comment:** Inclusion of negative control is requested for the in vitro skin permeation studies. Can QWP explain the rationale for this requirement and provide some references?		It is noted that "negative" control has been removed; please refer to response to comment 107. A control is required to ensure assay sensitivity.
111	950 (Annex II)	5	**Comment:** All the samples from at least 12 different donors should preferably be investigated on the same day to ensure comparable testing conditions, this was considered as additional argument to allow pig ear skin instead of human skin for testing of comparability of products.		With regard to pig skin refer to comment 108. The revised text throughout the guideline reads: "The number of skin donors should not be less than 12 unless otherwise justified, with at least 2 replicates per donor."

Comment no.	Line no.	Stakeholder no.	Comment and rationale; proposed changes	Level	Outcome
					It is the responsibility of the applicant to determine the number of donors required to adequately power the IVPT pivotal study.
112	958 – 960 (Annex II)	1	**Comment:** This refers to admissible addition of anti-microbial agent in the receptor fluid, however it should also allow the addition of solubilization agents to ensure complete solubilization of the test item in the receptor medium. **Proposed change**: "The inclusion of an anti-microbial agent, to mitigate potential bacterial decomposition of the skin membrane, and of solubilization agent, to ensure complete solubilization of the test item in the receptor medium, is acceptable, but they ~~it~~ should not interfere with the properties of the skin or the assay."		Revised text. *The inclusion of an anti-microbial agent, to mitigate potential bacterial decomposition of the skin membrane,* ***and of a solubilization agent, to ensure sink conditions of the test item in the receptor medium,*** *is acceptable,* ***but it should be demonstrated*** *that they do not interfere with the permeability of the skin or the assay'*.
113	961 – 965 (Annex II)	1	**Comment:** The guideline states "*The number of sampling time points should be sufficient to obtain meaningful profiles, i.e. capturing the maximal rate of absorption and a decline in the rate of absorption […]*". In skin permeation studies, maximal absorption of some active substance is not reached 24 hours after topical application. Therefore, maximal rate cannot be captured, nor decline in rate of absorption within this timeframe. **Proposed change**: "The number of sampling time points should be sufficient to obtain meaningful profiles, i.e. ~~capturing the maximal rate of absorption and a decline in the rate of absorption~~ enabling to conclude on pre-defined endpoints thereafter, with more frequent sampling during the period of greatest change.		Not agreed.

Comment no.	Line no.	Stakeholder no.	Comment and rationale; proposed changes	Level	Outcome
			The duration for testing should be 24 hours. If the study duration is longer than 24 hours, it should be shown that skin barrier function and integrity is adequately maintained."		
114	982 – 1026 (Annex II)	5	**Comment:** Validation of IVPT should include placebo-control.		Not agreed. A control, such as a formulation with 50% of the proposed product strength, is required to ensure assay sensitivity.
115	985 (Annex II)	1	**Comment:** This is the same issue as cited for line 923. **Proposed change**: "The suitability of the test conditions should be demonstrated using batches with different quality attributes (a true negative control), such as a drug formulation with 50% of the proposed product strength, that is shown to be statistically different and non-equivalent to the comparator product."		The word "negative" has been removed and text revised.
116	999 – 1000 (Annex II)	1	**Comment:** The guideline states *"[…] total amount permeated at the end of experiment (A_{total}) […]".* While not explicitly stated, the A_{total} parameter seems to be in mass unit, while the plot represents cumulative amounts permeated in mass unit per unit area. It is suggested to provide mass unit per unit area, for sake of study comparison. **Proposed change**: "Relevant permeation parameters, e.g., the maximal rate of absorption (J_{max}) and total amount permeated per unit area at the end of experiment (A_{total}) should be determined and compared."		Accepted.
117	1020-1024 (Annex II)	1	**Comment:** The usefulness of determining mass balance may depend on the composition of the product. For example, for		Accepted. Text revised.

Comment no.	Line no.	Stakeholder no.	Comment and rationale; proposed changes	Level	Outcome
			products with high alcohol content, mass balance will be affected by the rate of evaporation and therefore mass balance should be determined if appropriate for the formulation under evaluation. **Proposed change**: "The mass balance should be determined when possible. Depending on the type of products and its composition, a justification for not determining mass balance could be accepted. The cumulative amount of the active substance permeated into the receptor medium (A_{total}), the total amount of active substance retained (S_{total}) in the skin samples and amount of active substance retained on the cleaning or experimental equipment (R_{total}) should be presented. The overall recovery of the active substance of 90-110% would be acceptable without justification, larger variation should be fully justified and explained."		
118	1020-1024 (Annex II)	5	**Comment:** The overall recovery of the active substance in IVPT is often below 90%, thus acceptance limits for the confidence interval of the recovery of 90-110% are too tight. For comparative evaluation the requirement that equivalence parameters (Jmax) and (Atotal) should be equivalent (within acceptance limits of 80 - 125) after 24 hours should suffice.		Partially accepted, see comment 117.
119	1028-1197 (Annex III)	4	**Comment:** EFPIA is broadly in agreement with the guidance given in Annex 3. We have some detailed comments below: • measurement of TEWL values for each separate sample, or even after application of each separate piece of tape will be very time consuming. It could be considered if a fixed number of repetitions could be		1. Partially agreed. The first two tapes should not be discarded. It is accepted that the transepidermal water loss does not need to be measured after the removal of every single tape but it is necessary to assess how the transepidermal water loss increases.

Comment no.	Line no.	Stakeholder no.	Comment and rationale; proposed changes	Level	Outcome
			acceptable (e.g. 22), where the first two tape-discs are discarded • Is it possible to be more specific on the applicability of TS when patients with skin diseases are involved (line 1043-45)? EFPIA is opposed to using such tests for, for instance, atopic dermatitis patients. • Weighing of each separate tape-disc before and after use is very difficult and time consuming • Inclusion of negative control is requested for the in vivo clinical tape stripping studies. Can QWP explain the rationale for this requirement and provide some references? • Quantification of surplus drug removed from the surface before tape-stripping and measurement of compound permeating through SC will be necessary for conduct of a mass-balance. However, this will be difficult and time-consuming, and the question is, if it is necessary to conduct a mass balance? • It should be possible to use the back instead of the forearm for this type of study, since drug permeation may be higher on the skin of the back than on the skin of the forearm. Thereby, quantification may be easier.		This is one of the criteria to define the end of tapestriping, which a fixed number of tapes cannot guarantee on its own. 2. The intention is not to use patients but to limit the use of TS to products that are applied on intact skin. 3. It is acknowledged it is difficult but it is considered essential for TS method. the amount of stratum corneum that is removed with every tape need to be quantified. Alternative methods may be used if validated. 4. The objective is to demonstrate that the method is sensitive and discriminative. 5. Mass balance is essential to confirm the methodology is correct. 6. It is possible but we are not interested in the permeation to viable dermis. We are only interested in the SC. For drugs that are permeable to the viable dermis and available to plasma other methods are preferred.
120	1039-1042 (Annex III)	1	*Similar to lines 650-653* **Comment:** Tape-stripping should be restricted only to cases when the site of action is in the Stratum corneum or in the		This is not agreed because we assume that there is equilibrium between skin layers, the dermis with blood vessels and deeper tissues. For drugs that are

Comment no.	Line no.	Stakeholder no.	Comment and rationale; proposed changes	Level	Outcome
			viable skin. Stratum corneum levels are not predictive of drug levels in tissues situated below the viable skin because of the often unknown drug distribution between local tissue and systemic circulation. For this reason, TS is not appropriate for demonstrating equivalence of regionally acting drug products with deeper sites of action. **Proposed change**: "TS data provide direct measurements and information on the local bioavailability of semi-solid drug products that act on or in the S.C. e.g. antifungal products. In cases when the target sites of action are ~~beyond the S.C,~~ in the viable skin (e.g., actinic keratosis, sunburn), TS data may provide a suitable surrogate to characterise the rate and extent of drug absorption to the underlying tissues. The method is not appropriate for demonstrating equivalence of regionally acting drug products with deeper sites of action."		permeable to the viable dermis and available to plasma other methods are preferred.
121	1160 (Annex III)	1	**Comment:** This is the same issue as cited for line 923. **Proposed change**: "The discriminatory power of the TS method should be demonstrated for batches with different quality attributes (a true negative control), such as a drug formulation with ±50% of the proposed product strength, that is shown to be statistically different and non-equivalent to the test and comparator products."		The word "negative" has been removed.
122	1174-1175 (Annex III)	5	**Comment:** The proposed evaluation strategy to build the mean out of the replicate analysis prior to further evaluation should be reconsidered. **Proposed change**: Instead individual values should be kept and as evaluation reference should be made e.g to Proc Mixed for analysing repeated measures.		In the EU, generalised linear model (GLM) is preferred; for this analysis the mean of the replicate measurement is preferred.

Comment no.	Line no.	Stakeholder no.	Comment and rationale; proposed changes	Level	Outcome
123	1199 (Annex IV)	5	**Proposed change:** We propose to add a new Annex IV "Continuous skin interstitial fluid sampling methods (dOFM and dMD)" to the guideline with identic structure as Annex I to III. Joanneum Research would be happy to provide a first draft for the additional Annex IV.		The revised text in section 5.3.1 allows the use of other techniques if appropriately qualified: *"Other techniques evidencing the drug diffusion and content at the site of action, such as Microdialysis/ open flow microperfusion and Confocal Raman spectroscopy are not currently sufficiently established to provide pivotal equivalence data but may be supportive. They could be considered pivotal evidence if appropriately qualified as suitable method for equivalence testing."*
124	1207 (Annex IV)	1	**Comment:** Vehicle is not named in the FDA guidance and will be only available for the test product in VCA Tests for generic products. Vehicle for an approved drug is usually not available on the market. Furthermore, assessment of the blanching of untreated sites provides the requisite information hence including the vehicle would be an unnecessary action and would not provide any useful additional information. **Proposed change**: The same test products as stated in the FDA Guidance for Industry: ("Topical Dermatologic Corticosteroids: in vivo bioequivalence 2 June 1995") which is test product (T), reference product (RLD), shorter and longer dose duration calibrator (D1 and D2), untreated control (UNT) should be named in the guideline.		The vehicle to be used is the vehicle of the test product (ideally the same excipients with the same amount).

Comment no.	Line no.	Stakeholder no.	Comment and rationale; proposed changes	Level	Outcome
125	1207-1208 (Annex IV)	1	**Comment:** The following products should be randomly assigned to application site on the ventral forearms: Test product, vehicle, comparator product and untreated control. The VCA Test can be used to address both newly developed topical corticosteroids (i.e. new substances) as well as topical products which can be considered as generic versions of approved products (which is subject of this draft guideline). In case of comparison of a generic version with an already approved product the denomination "reference product" should be used instead of comparator product. The denomination comparator product might lead to confusion, because comparator is also used as a description for products with stronger and weaker (corticoid) activity which should be used in VCA Tests do describe newly developed topical corticosteroids. These kind of comparators are not necessary for VCA Tests for generics, because if bioequivalence is shown between test and reference product the test product should have also the same corticosteroid activity and belongs therefore to the same class of corticosteroids like the reference product. **Proposed change**: The naming of the products which should be used in a VCA Test for comparison of a generic product with an already approved product should be the same as in the FDA Guidance for Industry ("Topical Dermatologic Corticosteroids: in vivo bioequivalence 2 June 1995") which is test product (T), reference product (RLD), shorter and longer dose duration calibrator (D1 and D2), untreated control (UNT). This would avoid any misinterpretation.		Accepted, see also clarification above.
126	1219-1221 (Annex IV)	1	**Comment:** Regarding the measurement of the vasoconstriction reaction, it is recommended in the draft guideline that a chromameter should be used or other methods		Agreed and amended.

Comment no.	Line no.	Stakeholder no.	Comment and rationale; proposed changes	Level	Outcome
			more sensitive than visual estimation. We highly appreciate this recommendation. But it is also stated that a secondary clinical assessment by an independent observer should be made. This part is not in line with the FDA Guidance and might lead to confusion if only one method (chromameter or clinical assessment) shows bioequivalence. Furthermore, the VCA Test per se has been successfully used for many years without the need for additional clinical assessment (the FDA Guidance was adopted in 1995). It is unclear what important significant additional information would be obtained from the clinical assessment by an independent observer and how this clinical assessment should be performed since visual assessment of the blanching is regarded as less sensitive in the draft guideline. **Proposed change**: Delete the following part in line 1220/1221 "and by a secondary clinical assessment by an independent observer."		