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Draft guideline on quality and equivalence of topical products

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Annexes I and II of this guideline replace Annex 1 of the Guideline on Quality of Transdermal Patches (EMA/CHMP/QWP/608924/2014)

The guideline replaces Questions and Answer on Guideline: Clinical Investigation of Corticosteroids Intended for Use on The Skin CHMP/EWP/21441/2006.

Comments should be provided using this template. The completed comments form should be sent to QWP@ema.europa.eu

Keywords	***Medicinal products for cutaneous use, topical products, locally applied locally acting medicinal products, skin permeation, in vitro release, stratum corneum sampling, tape stripping.***

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Draft Guideline on quality and equivalence of topical products

Contents

Executive summary

The guideline relates to locally applied and locally acting medicinal products for cutaneous use and is also relevant for other medicines e.g. preparations for auricular or ocular use.

Specific guidance is provided:

1 On the quality of topical products not covered by other guidelines.

2 On equivalence testing of topical products *in lieu* of therapeutic equivalence clinical trials.

Existing guidelines state that, for topical products, changes in formulation, dosage form, method of administration or manufacturing process may significantly influence the efficacy and/or safety. Clinical therapeutic equivalence studies are in principle necessary, but other models may be used or developed.

Guidance is provided on other models and studies that may be used to independently determine equivalence with respect to (i) quality, (ii) efficacy, and (iii) safety that taken together support a claim of therapeutic equivalence, when the method of administration is the same and risks of inequivalence to the patient are minimal.

Guidance is provided on situations where therapeutic equivalence clinical trials will be expected.

Scope, limitations and acceptance criteria of this approach are described.

The guidance should be used to develop and justify topical product-specific equivalence protocols.

In addition, equivalence test protocols are provided for:

- *in vitro* release
- *in vitro* human skin permeation
- *in vivo* stratum corneum sampling (tape stripping)
- *in vivo* vasoconstriction assay for corticosteroids

The quality guidance applies to new marketing authorisation applications and post approval changes.

The equivalence guidance is applicable to certain cases of demonstration of equivalence of a new topical medicinal product with an existing medicinal product.

1 Introduction and Background

The diversity of topical products is very wide given the complex nature of skin, the range of conditions to be treated and the variety of patients and their needs.

The guideline cannot present a single procedure to address such diversity, instead general recommendations are provided. These can be applied to any given product on a case-by-case basis.

The guideline elaborates existing regulatory guidance and is informed by current scientific knowledge.

1.1 Quality of Topical Products

Guidance on the quality of topical products, not covered by other general quality guidelines, is provided.

The indication, target population and site of action need to be understood to enable informed choices 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.

The quality target product profile should consider patient acceptability, ease of removal from the container and administration, bulk aesthetic properties such as appearance, spreadability, feel, the microstructure/physical properties, evaporation of volatile excipients, and occlusion if appropriate. These elements need to be characterised and, when necessary, controlled as critical quality attributes.

The product formulation should be developed using sound prior knowledge, established scientific rationale and evidence. The resultant quality characteristics should be determined from multiple batches representative of the product to be marketed.

A robust manufacturing process is required to assure consistent product quality through its marketing life-cycle. Marketed products should have the same quality as those batches for which satisfactory evidence of efficacy and safety or equivalence has been demonstrated.

Stability is shown when batches at release and at the end of their shelf life have equivalent physical, chemical and microbiological quality characteristics, and includes *in vitro* performance if appropriate.

The control strategy should ensure that the product is fit for its intended purpose and complies with relevant pharmacopoeial standards. Inadequate product development or quality cannot be justified by reference to clinical trials.

1.2 Equivalence of Topical Products

Demonstration of equivalence of a new topical medicinal product with an existing medicinal product may be required in the context of marketing authorisation applications relying on the dossier of an existing medicinal product, and in case of product changes during pharmaceutical development or post-approval, which could have a potentially significant impact on the safety, quality or efficacy of the medicinal product.

Furthermore in the case of applications which rely on literature to demonstrate the safety and efficacy of the medicinal product the relevance of the literature should be supported by equivalence bridging data between the test product and the product described in the literature. This is because the effect of quality differences in formulation, manufacture and method of administration is not predictable.

Existing guidelines state that, for topical products, changes in formulation, dosage form, method of administration or manufacturing process may significantly influence the efficacy and/or safety. Clinical therapeutic equivalence studies are in principle necessary, but other models may be used or developed.

This guideline provides further detail on how *in vitro* and *in vivo* models may substitute for clinical data for the purpose of establishing therapeutic equivalence.

Demonstration of equivalence with respect to quality is normally not sufficient to predict therapeutic equivalence. 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 method of administration is the same.

Equivalence with respect to quality can, where appropriate, be established using comparative data with the comparator medicinal product (i.e. existing medicinal product) comprising pharmaceutical form; qualitative and quantitative composition; microstructure/physical properties; product performance; administration. This is termed *"extended pharmaceutical equivalence"* for the purpose of this guideline.

Equivalence with respect to efficacy requires comparative permeation kinetic and, where possible, pharmacodynamic studies with the comparator medicinal product. Suitable permeation kinetic methods are in vitro human skin permeation and in vivo stratum corneum (S.C.) sampling (tape stripping) of human volunteers and pharmacokinetic bioequivalence. Suitable pharmacodynamic studies include the in vivo vasoconstriction assay for corticosteroids and in vivo microbial decolonisation studies for antiseptics, undertaken on human volunteers. If permeation kinetics and pharmacodynamic studies are not applicable or are considered insufficiently predictive of clinical response, clinical efficacy data will normally be required.

Equivalence with respect to safety and local tolerance may be inferred from knowledge of the active substance and the choice of well-established excipients.

Biowaivers from permeation kinetic or pharmacodynamic equivalence studies are described for simple formulations, i.e. in cases where demonstration of equivalence with respect to quality alone would be sufficient.

The general guidance should be used to develop product-specific protocols to demonstrate equivalence, facilitated by obtaining scientific advice, as necessary.

2 Scope

The guideline applies to locally applied and locally acting medicinal products for cutaneous use and may also be relevant for other medicines, e.g. preparations for auricular or ocular use.

Guidance is provided on the quality of topical products, containing chemical active substance(s), not covered by other general quality guidelines and on equivalence testing of topical products to support a claim of therapeutic equivalence with comparator medicinal products, *in lieu* of therapeutic equivalence clinical trials.

The quality guidance applies to new marketing authorisation applications and post approval changes.

The equivalence guidance is applicable to certain cases of demonstration of equivalence of a new topical medicinal product with an existing medicinal product.

The equivalence guidance does not apply:

- To biological medicinal products, see guidelines on similar biological medicinal products.
- To herbal medicinal products.
- When equivalence with respect to efficacy is demonstrated by therapeutic equivalence clinical trials.
- When the pharmaceutical form or qualitative and quantitative composition of the test and comparator products are not the same or equivalent (see section 5.2.1).

3 Legal basis

This guideline should be read in conjunction with Directive 2001/83/EC and relevant Pharmacopoeial monographs and Guidelines.

Quality Guidelines

- Ph. Eur. Dosage Form Monographs: Liquid Preparations for Cutaneous Application; Powders for Cutaneous Application; Semi-Solid Preparations for Cutaneous Application; Ear Preparations; Eye Preparations; Pressurised Pharmaceutical Preparations.
- Pharmaceutical Development, ICH Q8 (R2), EMEA/CHMP/167068/2004;
- Manufacture of the Finished Dosage Form, EMA/CHMP/QWP/245074/2015;
- Guideline on Process Validation for finished products. Information and data to be provided in Regulatory Submissions EMA/CHMP/CVMP/QWP/BWP/70278/2012-Rev1;
- Excipients in the Dossier for Application for Marketing Authorisation of a Medicinal Product CHMP/QWP/396951/06;
- Q 6A Specifications: Test Procedures and Acceptance Criteria for New Active substances and New Drug Products: Chemical Substances CPMP/ICH/ 367/96-ICH Q6A;
- Q 2(R1) Validation of Analytical Procedures: Text and Methodology, CPMP/ICH/381/95 - ICH Q2 (R1);
- Stability Testing of New Active substances and Drug Products (ICH Q1A (R2)), CPMP/ICH/2736/99-ICH Q1A (R2);
- Stability Testing of Existing Active Ingredients and Related Finished Products, CPMP/QWP/122/02 Rev. 1 corr.;

Equivalence Guidelines

- Note for Guidance on the Clinical Requirements for Locally Applied, Locally Acting Products containing Known Constituents CPMP/EWP/239/95 Final
- Guideline on the Investigation of Bioequivalence CPMP/EWP/QWP/1401/98 Rev. 1/ Corr

- Guideline on bioanalytical method validation EMEA/CHMP/EWP/192217/2009 Rev. 1 Corr. 2
- General Considerations for Clinical Trials (ICH topic E8, CPMP/ICH/291/95)
- Guideline for Good Clinical Practice (ICH E6 (R1), CPMP/ICH/135/95)
- Statistical Principles for Clinical Trials (ICH E9, CPMP/ICH/363/96)
- Reflection Paper on advice to Applicants / Sponsors/ CROs of Bioequivalence Studies EMEA/INS/GCP/468975/2007
- Reflection paper on statistical methodology for the comparative assessment of quality attributes in drug development Draft (EMA/CHMP/138502/2017). Although a draft document, this paper provides current regulatory considerations regarding statistical aspects for the comparative assessment of quality attributes.

Equivalence trials conducted using human volunteers in the EU/EEA should be carried out in accordance with Directive 2001/20/EC.

In vitro human skin permeation kinetic equivalence trials, which are pivotal to product approval, are subject to National Competent Authority inspection and should also be carried out in accordance with Directive 2001/20/EC.

Trials conducted outside of the Union and intended for use in a Marketing Authorisation Application in the EU/EEA should be conducted to the standards set out in Annex I of the community code, Directive 2001/83/EC.

Companies may apply for CHMP and NCA Scientific Advice for specific queries not covered by existing guidelines.

4 Quality of Topical Products

4.1. Description and composition of the drug product

The drug product composition and excipient functions should be described in detail.

The names of excipients should be specific and distinct. The recommended international non-proprietary name (INN or INN modified (INNM)) accompanied by the salt if relevant, or the European Pharmacopoeia name, or their usual common name, or the chemical name, otherwise the proposed name should be justified.

The name should include the grade or brand (commercial) name, if required for consistent manufacturability and product quality.

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 applied dose, in terms of mass of active substance per unit area, based on the SmPC instructions for use, and maximum daily dose, should be stated.

The primary packaging and, if necessary, secondary packaging or other materials or components required for reasons of stability or administration, should be described.

4.2. Pharmaceutical development

The pharmaceutical development component of the dossier should form a sound scientific basis for the topical product for its intended use, providing a clear narrative of product development, and include all relevant data.

4.2.1. Therapeutic objectives and topical product design

The Quality Target Product Profile (QTPP) should identify the intended therapeutic objectives and purpose of the drug product and explain how these objectives are achieved by the product design.

A patient-focussed approach should consider: 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 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).

The means and permeation kinetics by which the active substance reaches the local site of action should be explained. As applicable, this should address administration, the solution state of the active substance, dissolution, release from the product and diffusion through human skin.

In some cases, e.g. skin antiseptic cutaneous solutions, consideration of the method of administration only is appropriate. In others, e.g. NSAID creams, all elements should be considered.

The inclusion of excipients to enhance bioavailability and for emolliency should be explained and justified. The choice of formulation, e.g. aqueous gel, cream, ointment, should be explained and justified.

If applicable, the proportionality of different strengths should be discussed.

Cross references to relevant non-clinical and clinical sections of the dossier should be provided, as appropriate.

4.2.2 Active substance (P.2.1.1)

Active substance physicochemical properties that are important for bioavailability, the formulation, performance and stability of the drug product should be identified and discussed. Such properties may include molecular weight, partition coefficient, melting point (boiling point if applicable), pKa, sensitivity to light, air or moisture, degradation pathway, solubility and pH effects, as well as particle size and polymorphism, if the active substance is present in the solid state in the drug product. Critical quality attributes should be identified and controlled in the Drug Substance Specification.

4.2.3 Excipients (P.2.1.2)

Excipients used in topical products often show batch and source variation e.g. homologue composition of hydrocarbon chains, the degree of unsaturation, molecular weight, polymorphism. This in turn may lead to unforeseen variability in the product rheological properties, microstructure/physical properties, crystallisation of the active substance or other ingredient, stability, or bioavailability.

Batch and source variation of excipients should be considered and addressed during development.

The choice and quantity of each excipient, and relevant critical quality attributes (CQAs), should be discussed and justified in relation to its function(s), including an emollient function, if applicable.

The grade of the excipient should be specified, when active substance bioavailability, product manufacturability and / or quality is altered if other grades are used.

CQAs of the excipients should be controlled in their specifications and their limits justified (P.4.).

Detailed information on those excipients which might have an influence on the active substance permeation and bioavailability, e.g. solubiliser, penetration enhancer, should be provided, including their ability to provide their intended function and to perform throughout the intended drug product shelf life.

In the case of excipients presented as a mixture of compounds, details of the composition should be provided in qualitative and quantitative terms and characterised, including rheological properties if appropriate.

For novel excipients, full details of manufacture, characterisation and controls with cross references to supporting safety data should be provided.

For excipients also used in cosmetics, data showing compliance with Regulation 1223/2009 on Cosmetic Products, would be supportive.

Processing aids should be identified and described.

Some excipients traditionally used in topical products may cause irritation or sensitivity reactions and should if possible be avoided, or minimised if unavoidable, in the development of a new product. For reference, see the guideline on "Excipients in the label and package leaflet of medicinal products for human use".

4.2.4. Formulation development

The development of the drug product should be described with respect to the defined QTPP, employing suitable tests to characterise and control CQAs, factors affecting ease of administration and duration of use, and product performance e.g. dissolution, *in vitro* drug release and if appropriate *in vitro* skin permeation. Evidence of the suitability of the test methods and acceptance criteria used to assess the product should be provided (see also Annexes I and II).

The presentation of the active substance in the drug product e.g. as a solute or in a suspension, and the degree of saturation are CQAs, which should be justified in terms of product efficacy and safety, supported by evidence of how the target state is achieved during manufacture and maintained during storage.

The risks of precipitation / particle growth / change in crystal habit, or changes to other active substance characteristics likely to affect bioavailability, arising from changes in temperature and on storage should be assessed and appropriate tests included in the stability studies.

The delivery of the active substance to the site of action needs to be discussed. Solvents and enhancers can be used to aid transport through the different layers of the skin. Ointments may function to occlude the skin and thus facilitate permeation. The concentration gradient of the active substance between the drug product and the site of action is a driving force for delivery and achieving a saturated status of the active substance in the drug product can therefore be crucial.

Patient acceptability and usability of the drug product should be considered e.g. ease of administration, spreadability, which can be of importance for dose per surface area, and feel (dry or greasy).

Where appropriate, the type of the pharmaceutical form should be identified e.g. hydrophobic ointment (hydrocarbon base, absorption base), water emulsifying ointment, hydrophilic ointment.

Product microstructure/physical properties, which may be complex for semisolid products, and mechanisms responsible for its formation during processing, should be understood e.g. in terms of excipient interactions, batch variation and scale-up, so that the manufacturing process can be optimised to give a consistent quality product.

Transformation of the topical product on administration should be discussed. Particularly in those cases where evaporation of volatile solvents and excipients, or other phenomena, are necessary for effective drug delivery to the site of action.

The clinical trial formulation and the batches used in the comparative studies should be described in detail. Any differences in formulation and manufacturing processes between pivotal clinical batches and the drug product to be marketed should be justified. Results from comparative extended pharmaceutical equivalence studies, *in vitro* studies or *in vivo* studies should be provided.

When the formulation composition is decided, up-scaling of the manufacturing process will start and the critical process parameters should be identified and controlled.

During this period, it is reasonable to expect that necessary adjustments will be made to reach and optimise full-scale production. These adjustments might be changes in composition, manufacturing processes, equipment or manufacturing site. In some cases, the potential impact of these adjustments on the functions of the drug product, e.g. with respect to bioavailability and usability, should be assessed.

Evidence of compliance with Ph. Eur. requirements for the topical dosage form should be provided.

The relationship between the QTPP, critical quality attributes and the drug product specification should be fully discussed.

Where the drug product vehicle contains flammable volatile solvents, e.g. isopropyl alcohol and ethanol, the flash point should be determined in compliance with relevant ISO standards and appropriate warnings included in the product information (see also section 4.2.6).

Drug products with a paraffin vehicle are not in themselves flammable, but when clothing, bedding and dressings become impregnated with these, the material acts as a wick and the paraffin acts as an accelerant when ignited. The patient risks should be assessed, and appropriate warnings included in the product information (see also section 4.2.6).

4.2.5 Product characterisation

A detailed product characterisation should be developed to facilitate life-cycle management and, where applicable, to support a claim of equivalence to original or comparator medicinal products.

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.

Pharmaceutical Form

The diverse topical dosage forms include cutaneous solutions, foams and sprays, shampoos, ointments (hydrocarbon, absorption, water-removable and water-soluble bases), creams (oil in water or water in oil), gels, pastes, poultices, medicated plasters and cutaneous patches.

Evidence should be provided that characterises the pharmaceutical form in terms of the solution state of the active substance, disperse and immiscible phases and dosage form type.

For example:

Active substance in solution, single phase vehicle: e.g. cutaneous solution, single phase gel or ointment.

Active substance in suspension, single phase: e.g. cutaneous suspension.

Active substance in solution, two phase vehicle: e.g. o/w cream, active substance in solution in oily phase.

Active substance in suspension, two phase vehicle: e.g. o/w cream, active substance insoluble in either phase in suspension.

For suspensions, additional characterisation in terms of active substance particle size distribution and polymorphic form, including photomicrographs, is required.

For immiscible phase formulations, additional characterisation in terms of globule size distribution and appearance, including photomicrographs, is required.

Particle size analysis by diverse methodologies should be employed, if possible e.g. laser light diffraction, Raman chemical imaging, as well as microscopy.

Appearance

This should be characterised visually and with microphotography - particularly for dispersed systems.

Microstructure / Physical Properties

Evidence should be provided to characterise the microstructure/physical properties in terms of bulk physical CQAs that influence bioavailability, usability or indicate variability in the manufacturing process and product instability.

e.g. for solutions and suspensions – pH, buffering capacity, viscosity, density, surface tension, osmolality.

e.g. for semisolid formulations – pH, density, rheological behaviour.

Non-Newtonian rheological behaviour should be characterised using an appropriate absolute rheometer and include:

- 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. The resulting curves should be

characterised by fitting to (modified) power law equations so that numerical data can be produced.

- Yield stress and creep testing
- The linear viscoelastic response (storage and loss modulus vs. frequency)

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. ŋ100); plastic flow yield stress values; thixotropic relative area (S_R); viscoelastic storage and loss moduli (G' and G"), apparent viscosity, loss tangent (tan δ).

Appropriate characterisation of rheological properties may enable the identification or design of a simpler test to be used in the Finished Product Specification.

Product Performance

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.

In vitro skin permeation (Annex II) testing may also be of value.

4.2.6 Administration

The SmPC and product information should include instructions for use and any necessary warnings for the safe use of the drug product.

Where relevant, transformation of the drug product on administration should be described.

The following should be considered:

Site of administration;

The necessity to avoid damaged or undamaged skin;

The requirements for skin pre-treatment;

Effect of exposure to environmental extremes of heat, cold, sunlight;

Effect of normal human behaviour such as washing, showers, use of sun screens and moisturisers;

Any necessary restrictions e.g. avoidance of occlusion;

The practical suitability of any special storage conditions;

Avoiding inadvertent use by children;

For drug products containing flammable volatile solvents, appropriate flammability safety warnings.

For example:

Danger: Flammable.

Keep away from heat, hot surfaces, sparks, open flames and other ignition sources.

No smoking. Protect from sunlight.

Do not expose to temperatures exceeding 50°C.

Do not spray on flames or other sources of ignition.

Patients being dispensed or treated with large quantities (> 100g) of any paraffin-based product should be advised to regularly change clothing, bedding or dressings impregnated with the product and keep away from naked flames.

For example:

When this paraffin-based product is covered by a dressing or clothing, there is a danger that smoking, or using a naked flame could cause your dressing or clothing to catch fire.

Do not smoke, use naked flames (or be near people who are smoking or using naked flames) or go near to anything else which may cause a fire whilst these products are in contact with your clothes, dressing or bandages.

Ensure that your clothes and bedding are changed regularly (preferably daily) as the paraffin soaks into the fabrics and can potentially be a fire hazard. You should also be careful to make sure that the paraffin does not soak into chairs, seating or other furniture.

Tell your relatives or carers about your treatment and show them this leaflet.

Tell your doctor, nurse or pharmacist if you normally smoke. They will be able to offer you help and advice to stop smoking.

4.2.7 Manufacturing process development and Manufacture (P.2.3 and P.3)

For dispersed drug products, e.g. two-phase emulsions, changes in formulation or manufacturing process may 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.

Module 3.2.P.3.3 and 3.2.P.3.4 should be sufficiently detailed and include both critical and non-critical process parameters and justified by reference to the manufacturing process development undertaken.

Hold times and storage conditions of different solutions and intermediate materials should be stated and justified, supported by appropriate stability studies and other relevant data.

Many bulk topical products exhibit shear thickening in the days following manufacture. The time between product manufacture and assembly may need to be optimised.

The suitability of the packaging for intermediates, bulk storage, and transportation (shipping) should also be discussed.

4.2.8 Container closure system (P.2.4)

The suitability of the container closure system (described in 3.2.P.7) should be discussed and justified. This should include the choice of materials, protection from moisture, oxygen and light where applicable, drug product compatibility, dosing, usability and safety.

Drug products having sterile requirements should be packaged in single-use containers.

If any device is co-packaged to facilitate e.g. the measuring or application of the product, the device should be CE-marked. Compatibility between the device and the medicinal product should be shown and if it is a measuring device, the dose accuracy should be demonstrated with the applied product.

4.2.9 Microbiological Attributes (P.2.5)

Microbiological aspects should be considered in the same manner as for other administration routes, bearing in mind that cutaneous products are sometimes applied to damaged skin. Reference should be made to European Pharmacopoeia 5.1.4., Microbiological quality of non-sterile pharmaceutical preparations.

Sterility of the drug product is required if it is to be used on large open or deep wounds or on severely injured skin, and products used prior to invasive procedures (e.g. preoperative skin antiseptic) and for preparations for irrigation.

For non-sterile drug products in multiple-use containers the need to include an antimicrobial preservative should be addressed and justified. The concentration used should be at the lowest feasible level. Reference should be made to European Pharmacopoeia 5.1.3., Efficacy of antimicrobial preservation. For multi-phase formulations, the solubility of the preservative in the different phases needs to be considered.

4.3 Control strategy

General regulatory guidance on the establishment and justification of a control strategy for the drug product 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, 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.

4.3.1 Drug product specification (P.5)

General guidance on the drug product specification is given in ICH Q6A, Q3B, Q3C and Q3D and the European Pharmacopoeia lists dosage form monographs.

The drug product specification should contain tests for the physical, chemical and microbiological quality, and product performance i.e. the established product characteristics (see 4.2.5) are controlled.

Crystal formation is a quality deficiency likely to adversely influence efficacy. Syneresis, the extraction or expulsion of a liquid from a semisolid, is another deficiency. Uniformity of the finished product in the container should be considered to detect sedimentation phenomena.

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.

Specific precautions in calculating acceptance limits for impurities should be made for cutaneous products applied to damaged skin or products containing penetration enhancers.

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.

4.4 Stability program (P.8)

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 risk factors to product stability should be assessed e.g. precipitation, particle growth, change in crystal habit, or other active substance characteristics likely to affect the thermodynamic activity, changes in emulsion characteristics. Appropriate tests, additional to those in the product specification, should be included in the drug product stability study quality specification.

Shear thickening and changes in the product microstructure are also risk factors that should be considered.

The stability programme should include stress testing to assess the effect of severe conditions on the drug product e.g. temperature cycling for creams and emulsions.

The stability study quality specification should include tests to monitor the suitability of the container closure system.

Requirements for special storage conditions e.g. do not refrigerate, should be addressed.

An in-use stability programme should be undertaken. It is important that these tests have a reasonable length considering dosage regimen and package size. Unnecessary wastage or too short in-use shelf-lives should not be proposed.

5 Equivalence of Topical Products

5.1 Scope

This section addresses equivalence testing of topical products to support a claim of therapeutic equivalence with comparator medicinal products, *in lieu* of therapeutic equivalence clinical trials. Aspects relating to quality, efficacy, and safety are discussed.

For simple formulations (e.g. single-phase solutions, gels, ointments) demonstration of equivalence with respect to quality, i.e. extended pharmaceutical equivalence, may be sufficient.

For more complex formulations, or those containing excipients that might directly influence the active substance bioavailability or product performance, then additional permeation kinetic and, if possible, pharmacodynamic equivalence tests are normally required.

The formulation and strength of the drug product must also be such that the equivalence tests and associated analytical methods are sufficiently sensitive, discriminating, accurate and precise to measure a quantifiable permeation kinetic or pharmacodynamic event.

This approach is not applicable and clinical therapeutic equivalence studies are in principle required for the following drug products:

- With a narrow therapeutic index.
- With dose related, systemic toxicity, except in those cases where equivalent systemic exposure is shown by conventional pharmacokinetic bioequivalence studies.
- Where the means e.g. dissolution, release, diffusion, and permeation kinetics by which the active substance reaches the local site of action is not established or understood.
- Where the method of administration is not the same.
- That cannot be fully characterised with respect to quality attributes e.g. due to complex formulation, methodological limitations.
- Where it is not possible to measure a quantifiable permeation kinetic or pharmacodynamic event e.g. due to limited diffusion or insensitive tests.
- Where *in vitro* and *in vivo* permeation kinetic and pharmacodynamic studies are not applicable or considered insufficiently predictive of clinical response e.g. products indicated for the treatment of open wounds and ulcers.

5.2 Equivalence with respect to quality (extended pharmaceutical equivalence)

Equivalence requires comparative quality data with the relevant comparator medicinal product. The products should be characterised (see sections 4.2.5 and 5.5).

Pharmaceutical form, qualitative and quantitative composition, microstructure/physical properties, product performance e.g. dissolution, *in vitro* release test, and method of administration should be compared. For volatile solvent based topical products, product transformation on administration should also be compared.

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.

It is acknowledged that there may be only a limited number of representative batches available at the time of submission, and at least three different batches of both the test and comparator products should be compared.

To enable statistical evaluation, the number of samples should be at least 12 units per batch for each experiment.

Data are also required to show that the product characteristics remain consistent and equivalent throughout the designated shelf-life.

5.2.1 Extended pharmaceutical equivalence acceptance criteria

The extended pharmaceutical equivalence acceptance criteria between the test and comparator medicinal product are:

Pharmaceutical form

- The drug product should be the same pharmaceutical form, with the same solution state of the active substance in the same immiscible phases.

Qualitative and Quantitative Composition

- The active substance content, and its salt form should be the same.
- In general, the excipients qualitative composition, including grade, if necessary, and quantitative composition of excipients should be the same, although some exceptions are permitted.

  In particular, excipients whose function is to influence the active substance solubility, thermodynamic activity or bioavailability and product performance should be qualitatively the same.

  The nominal quantitative composition of the excipients should be the same or differences not greater than ±5%. For example, for an excipient present in the comparator medicinal product at 2%w/w, the permitted range in the test product is 1.9 – 2.1%w/w.
- A permitted exception for a *qualitatively* different excipient may be acceptable for:
  - Excipients whose primary function is not related to product performance or administration, i.e. antioxidants, antimicrobial preservatives, colours, and do not have any other functions or effect that influences the active substance solubility, thermodynamic activity or bioavailability and product performance.

    Well-established excipients in usual amounts should be employed and possible interactions affecting drug bioavailability and/or solubility characteristics should be considered and discussed.
  - Excipient paraffin homologues may be acceptable for excipients whose function relates to the vehicle or emolliency, and do not influence the active substance solubility, thermodynamic activity or bioavailability and product performance.

  The different excipient should have no effect on local tolerance or safety. It should be shown that the excipients do not have any other functions or effect that influences the active substance solubility, thermodynamic activity or bioavailability and product performance. In these cases, a biowaiver (section 5.5.1) cannot be justified and is not permitted.
- A permitted exception for a *quantitative* difference of not greater than ±10% is acceptable:
  - For excipients whose function only relates to the vehicle properties or emolliency.
  - For excipients whose function is not related to product performance or administration, i.e. antioxidants, antimicrobial preservatives, colours.

It should be shown that the excipients do not have any other functions or effect that influences the active substance solubility, thermodynamic activity or bioavailability and product performance.

Acceptance Criteria

- 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.
- Qualitative quality characteristics should be essentially the same.

Administration

- The method of administration and administration devices should be similar and achieve the same dose on application.
- If applicable, when product transformation occurs following administration, the test and comparator medicinal product residues are equivalent with respect to quality i.e. in terms of extended pharmaceutical equivalence.

5.3 Equivalence with respect to efficacy

5.3.1 Methods

The following methods are considered suitable for equivalence testing, *in lieu* of a clinical therapeutic study:

Permeation Kinetics Studies

- *In vitro* skin permeation
- Stratum Corneum Sampling (Tape Stripping)
- Pharmacokinetic bioequivalence

These tests provide a means of measuring equivalence in active substance permeation kinetics of drug products applied to intact skin.

Human bioequivalence studies are appropriate when the active substance has quantifiable systemic bioavailability. *In vitro* skin permeation studies are suitable when the active substance diffuses through the skin to permit quantification in the receptor cell. Stratum Corneum Sampling (Tape Stripping) is suitable when there is sufficient quantifiable drug diffusion across the stratum corneum.

Other techniques, such as Microdialysis and Confocal Raman spectroscopy are not sufficiently established to provide pivotal equivalence data but may be supportive.

Pharmacodynamic Studies

- Vasoconstriction Assay for corticosteroids.
- Antiseptic and anti-infective studies.

These studies provide a means of measuring equivalence in active substance pharmacodynamic activity of drug products applied to intact skin.

Pharmacodynamic studies for other drugs are not sufficiently established to provide pivotal equivalence data but may be supportive. The model should be suitably valid and its relationship with the therapeutic situation must be demonstrated.

5.3.2 General Considerations

Managing Variability

The test conditions should be standardised to minimise the variability of all factors involved except those of the products being tested. Pilot studies are recommended to develop and optimise procedures.

Because the studies are single-dose, product application is a significant source of variability. The dose application procedure (and removal procedure for stratum corneum sampling (tape stripping)) should be practical and carefully described, in accordance with the SmPC of the comparator product, and strictly controlled, e.g. use of administration templates or aids by a single or limited number of trained personnel. The procedure should enable determination of the actual dose applied. The procedure should be validated.

The study duration should be sufficient to permit quantitative observation of diffusion, but optimally limited to minimise changes in test conditions that may naturally occur, which introduce bias to kinetic profiles, e.g. desquamation, loss in skin integrity, back diffusion, accidental loss or transfer of applied dose.

The methods involve multiple complex steps. The studies should be conducted following strict protocols by experienced trained staff, with quality assurance in place.

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.

Inter-subject or inter-donor skin variability should be minimised by a cross-over study design.

For *in vitro* skin permeation and stratum corneum sampling (tape stripping) studies, the test, comparator and negative control formulations should each be tested on the same set of volunteers or donor skin.

For low strength and limited diffusion drug products, the very low active substance concentrations expected in samples may be a significant source of variability. Sensitive analytical methods should be used, e.g. coupled chromatography – mass spectroscopy systems.

The analytical methods should comply with the Guideline on bioanalytical method validation.

Dose

The dose, in terms of (a) mass of active substance, (b) application area, and (c) mass or volume of drug product used, should be specified and based on the comparator product SmPC instructions for use.

The application area should be at least sufficient to achieve quantifiable results. If necessary, the area may be greater than normally indicated, if without safety concerns.

For *in vivo* studies, the skin site should be justified.

Sample sizes

The number of human volunteer subjects should be based on an appropriate sample size calculation and not less than 12.

For in vitro skin permeation studies, the number of donors may be less than 12, if justified.

For *in* vitro skin permeation and stratum corneum sampling (tape stripping) studies, a replicate design is required. The minimum number of experiments for each of the test, comparator and control products should not be less than 24.

The number and frequency of sample time points, per subject or replicate, should be sufficient to characterise the active substance kinetic profile and determine equivalence parameters.

Acceptance Criteria

The acceptance criteria for equivalence parameters is 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%, unless justified.

Wider acceptance criteria for the 90% confidence interval, to a maximum of 69.84 – 143.19, may be accepted in the case of high within-subject or within-donor variability observed with low strength and limited diffusion drug products, and if clinically justified. The procedure in the Guideline on Investigation of Bioequivalence, "Section 4.1.10 Highly variable drugs or drug products" should be followed.

Accreditation

It should be ensured that the performing laboratory is qualified to undertake the studies and that an effective quality system is in place. This should include:

- A declaration of compliance with a suitable quality system.
- The technical ability of the performing laboratory and the validity of the method used should be internally assessed at regular intervals and recent results provided;
- External audit by a National Competent Authority.

5.3.3 Permeation Kinetic Studies

Specific guidance for each of the three methods is available:

- *In vitro* skin permeation (Annex II of this guideline)
- Stratum Corneum Sampling (Tape Stripping) (Annex III of this guideline)
- Bioequivalence Guideline on Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1)

5.3.4 Pharmacodynamic Studies

Corticosteroids

The vasoconstriction assay for corticosteroids is accepted for equivalence testing.

The study should comply with the methodology described in Annex IV.

Skin Antiseptics

Skin antiseptics should comply with Ph Eur 5.1.11. *Determination of bactericidal, fungicidal or yeasticidal activity of antiseptic medicinal products*.

Where the method of administration is poorly defined or new then *in vivo* volunteer tests should be undertaken. In these studies, volunteer's indigenous flora are recovered before and after skin antisepsis, with justified criteria for microbial recovery log reduction.

For skin antiseptics for use prior to invasive procedures, a study in compliance with ATSM E1173 – 15 *Standard Test Method for Evaluation of Pre-operative, Pre-catheterization, or Pre-injection Skin Preparations* would be acceptable.

Antimicrobial drug products for treatment of skin infections

I*n vitro* skin infection and decolonisation equivalence studies, if satisfactorily validated, may be acceptable to provide an assurance of equivalence in efficacy, in conjunction with other equivalence studies.

5.4 Equivalence with respect to safety

In general, safety and local tolerance may be guaranteed by knowledge of the active substance and the choice of well-established excipients.

Equivalence with respect to quality, when shown, provides an assurance of safety and local tolerance.

In addition, equivalence seen with permeation kinetic equivalence studies would show that the same amount of active substance is expected to reach the site of action and/or the systemic circulation as the comparator medicinal product.

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.

As discussed in section 5.1, drugs with dose related, systemic toxicity are out of scope and require local tolerance and clinical safety studies. However, if systemic exposure is measurable, a bioequivalence study showing a similar systemic pharmacokinetic profile would be sufficient to conclude that systemic exposure is not higher for the test product than for the comparator product.

5.5 Topical Product Specific Equivalence Protocols

The development of topical product specific equivalence protocols and choice of equivalence tests should consider the following key factors: pharmaceutical form; product formulation; drug dissolution and release; drug diffusion in the skin and site of action.

A formal topical product specific equivalence protocol, with test methods and their acceptance criteria, should be provided and justified. The protocol should be prepared before commencing the equivalence studies. All data available, positive and negative, should be provided.

Equivalence may be concluded if results comply with the protocol criteria specified *a priori*.

In general, the product-specific equivalence protocol should comprise:

- Justification for the absence of a clinical therapeutic equivalence study; that the drug product is within and not out of the scope of this guideline (Section 5.1).
- Justification for the absence of safety studies (section 5.4).

- Extended pharmaceutical equivalence studies and equivalence in the method of administration (Section 5.2).
- An appropriate permeation kinetic equivalence study, if diffusion through the skin is relevant to efficacy (Section 5.3.3) and justification of the choice of study or studies. Alternatively, if applicable, justification for the absence of kinetic equivalence studies.
- Pharmacodynamic studies should also be performed, if possible and relevant. The development, validation and conduct of novel studies is encouraged (Section 5.3.4).

5.5.1 Biowaivers

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

Equivalence studies with respect to efficacy (Section 5.3) are *always* required if the formulation:

- Includes excipients whose function is to influence the active substance bioavailability, product performance or enhance drug penetration;
- Includes complex excipients where different suppliers or grades may affect the in vivo performance or stability of the active substance;
- Has a *qualitatively* different excipient composition from the comparator product (see section 5.2.1, Qualitative and Quantitative Composition, line 568).

Bioequivalence studies should usually be provided if the products have a regional site of action, where the active substance has quantifiable systemic bioavailability.

5.5.2 Strength Biowaiver

If several strengths of a test product are applied for, it may be sufficient to establish equivalence at only one strength, which is most sensitive to detect potential differences between formulations.

The following requirements must all be met where a waiver for additional strength(s) is claimed:

a) the different strengths of the test products are manufactured by the same manufacturing process.

b) the different strengths of the test products have the same qualitative composition.

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.

d) extended pharmaceutical equivalence (section 5.2) is demonstrated between the test and comparator medicinal product for all strengths.

6 Post-authorisation changes

For any proposed change, a risk assessment should be performed to determine its impact on quality, safety, or efficacy of the product.

Risks arising from cumulation of changes from the original drug product should also be considered.

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.

The comparative medicinal product for use in equivalence studies is usually that authorised under the currently registered formulation, manufacturing process, packaging etc.

If the proposed change meets the extended pharmaceutical equivalence acceptance criteria (section 5.2.1) for pharmaceutical form, and qualitative and quantitative composition, then equivalence should be demonstrated according to this guideline using a product specific equivalence protocol, with justified test methods and acceptance criteria (section 5.5).

If the proposed change does not meet the extended pharmaceutical equivalence acceptance criteria (section 5.2.1) for pharmaceutical form, or qualitative and quantitative composition, then equivalence should be demonstrated using an appropriate clinical study.

In all cases, the change should be supported by appropriate and representative batch data of the original and proposed change of all critical quality attributes.

Annex I In vitro release test (IVRT)

1. Scope of IVRT

This annex provides information for *in vitro* release rest (IVRT) of semisolid drug products (e.g. creams, gels or ointments) and liquid suspensions.

The following types of topical products are out scope for IVRT, but other *in vitro* tests may be applicable: simple liquid solutions, topical powders and other non-standard topical formulations (such as foams).

2. Rationale for IVRT

An IVRT with pseudo-infinite dosing using diffusion cells evaluates the rate and extent of release of an active substance in the proposed formulation.

The following parameters should be determined:

- Drug release rate (R): The slope of the cumulative amount of active substance released versus the square root of time for the linear portion of the drug release profile. If a linear portion of the drug release profile cannot be obtained, the IVRT is not valid.
- The cumulative amount (A) of active substance released, usually expressed in mass units per surface area, at the last sampling time of the linear portion.
- Lag time (if present)

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.

The *in vitro* release limits should be justified by reference to the *in vitro* release observed with clinical batches for which satisfactory efficacy or equivalence has been demonstrated.

Release and shelf life limits should normally be the same, unless the reasons for the differences are satisfactorily explained on quality grounds and justified by reference to clinical batches, and tighter limits at release are set, to ensure that the product will remain within the shelf life specification.

A validated *in vitro* release test is required to support extended pharmaceutical equivalence.

3. Study design

A pilot IVRT study comparing the test and comparator products is recommended to confirm the suitability of the chosen membrane and to validate the experimental conditions.

The experimental conditions should be justified with respect to the following:

a. Choice of membrane:

i. The membrane should ensure that the product and the receptor medium remain separate to ensure the tested formulation remains unchanged throughout the testing period.

The membrane should not be rate-limiting to active substance release.

ii. The membrane should be compatible with the drug product formulation and not bind to the active substance.

b. Choice of receptor medium:

i. 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.

ii. Back diffusion of the receptor medium should be minimised to avoid transformation of the applied drug product. The pH of the receptor medium should remain constant throughout the release test.

c. The sampling time (at least hourly) and experimental conditions (such as apparatus, temperature, mixing speed) should be defined. The duration of IVRT should be sufficient to characterise the release profile, ideally at least 70% of the active substance applied is released. At least 6 time points should be obtained in the linear portion of the drug release profile, including the first sample immediately after drug diffusion has reached a steady state.

d. The amount and method of formulation application should be described, consistent (±5 % between samples) and validated to ensure homogeneous spreading of the formulation over the membrane and pseudo-infinite dose conditions. The effects of formulation evaporation should be minimised.

e. The analytical methods should be sensitive enough to quantify the amount of drug in the receptor solution at various time points and validated.

4. Method validation

The marketing authorisation application should include documented evidence that the IVRT has been validated and is suitable for the quality control of the drug product. A summary of the development of IVRT should be provided. Testing conditions providing the most suitable discrimination should be chosen.

a. Satisfactory evidence of discrimination should be provided, with respect to both of the following quality modifications:

i. The release rate as a function of drug concentration (at least three strengths) in the formulation should be investigated. The linearity (r^2>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.

ii. Discriminative power of the proposed method should be demonstrated with altered product formulations with changes in critical quality attributes (such as the active substance particle size distribution or drug product rheological profile), critical manufacturing variables or quantitative excipient composition; the complete omission of one or more specific excipients from the altered product formulation is not supported.

b. Method intermediate precision for the same batch should be studied with different operators on different days (CV<10%).

c. Method robustness with respect to variations in mixing rate, amount of formulation applied, receptor mediums and temperature should be studied.

5. Presentation of data

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.

The *in vitro* drug release profile data should be provided in tabular and graphical formats.

For the drug release profiles, the quantity of active substance released in mass units per unit area at a given time should be reported.

For extended pharmaceutical equivalence testing:

- The cumulative amount of active substance released versus the square root of time should be linear.
- The parameter R should be significantly different from zero.
- 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%.
- Lag times should be the same (i.e. within ±10%), if present.

Annex II In vitro skin permeation studies (IVPT)

1. Scope and rationale for IVPT

Establishing the characteristic permeation profile of the drug product, using a discriminative *in vitro* permeation test (IVPT), is of value in change control during life-cycle management and an acceptable permeation kinetic test to demonstrate equivalence.

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.

2. Study design

To minimise risk of bias, the study protocol should specify methods of blinding and randomisation in line with ICH E8.

A pilot IVPT study comparing the test and comparator products is recommended to confirm that the active substance permeates through the skin, to validate the experimental conditions (such as apparatus, dosing amount, sampling times, stirring rate, etc.) and may be of value in estimating sample size required for the pivotal study.

The experimental conditions should be justified with respect to the following:

a. Choice of skin membrane:

i. It is recommended to use *ex vivo* adult human skin. The study protocol should specify the inclusion/exclusion criteria for skin sections, the anatomical region, condition and duration of skin storage. Skin with tattoos, any signs of dermatological abnormality or exhibiting a significant density of terminal hair should be excluded.

ii. Different skin preparation techniques can be used. Evidence should be provided to demonstrate that the skin preparation technique and storage does not introduce artefacts, nor alter the skin barrier function. The use of full-thickness skin may artificially delay drug permeation and should be avoided unless otherwise justified. The skin thickness and separation technique should be described.

iii. The skin integrity should be checked prior to and after each experiment. The choice of the skin integrity test and its acceptance criteria should be explained. Different acceptance criteria maybe proposed for before and after the experiment, these acceptance criteria should be justified and consistent across all parallel experiments.

iv. Skin from different donors should be chosen.

Test, comparator and negative control formulations should be tested using the same donor skin, ideally from adjacent sites, per replicate.

v. The number of skin donors should not be less than 12, with at least 2 replicates per donor.

vi. The apparatus should ensure consistent temperature control throughout the duration of the experiment. The skin surface temperature should be stable at 32±1°C.

b. Choice of receptor medium:

i. Sink conditions should be confirmed as described with IVRT (Annex 1).

ii. The receptor medium should be aqueous buffer, unless otherwise justified. Evidence should be provided that the chosen receptor medium does not compromise the skin barrier integrity throughout the test.

iii. The inclusion of an anti-microbial agent in the receptor medium, to mitigate potential bacterial decomposition of the skin membrane, is acceptable, but it should not interfere with the properties of the skin or the assay.

c. 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 thereafter, with more frequent sampling during the period of greatest change. 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.

d. The recommended dosing amount should be in the rage of 2-15mg/cm^2, based on SmPC posology, unless otherwise justified. Dose application should be validated to ensure reproducibility (±5 %) and homogeneous spreading of the formulation over the skin membrane. The donor compartment should be un-occluded unless otherwise specified in the SmPC.

e. To identify potential contamination and/or interferences, pre-dose samples collected from each diffusion cell and a parallel non-dosed blank control skin experiment are recommended.

f. A detailed description of the blinding procedure should be provided in the study protocol and final report. The packaging of the test, comparator and negative control products should be similar in appearance to maintain adequate blinding. The method of randomization should be described in the protocol and the randomization schedule provided.

g. For low strength drug product, the analytical methods should be sensitive enough to quantify the amount of drug in the receptor solution at various time points and be appropriately validated.

h. The stability of the active substance in the receptor solution over the duration of IVPT study, and sample storage prior to analysis, should be confirmed.

3. Method validation

The Marketing Authorisation Application should include documented evidence that the IVPT has been validated and are suitable for drug product comparison.

The suitability of the test conditions should be demonstrated using batches with different quality attributes (a 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.

To achieve this, batches with meaningful changes compared to the applied finished product should be manufactured. Such changes may relate to the quantitative formulation, critical quality attributes and/or using slightly modified process parameters. Current knowledge of the characteristics derived from the active substance and the finished product formulation must be considered when choosing the quality attributes to change. The complete omission of one or more specific excipients from the formulation (e.g., penetration enhancer, preservatives) is not supported.

4. Presentation of data

IVPT data should be provided in tabular and graphical formats. All individual data and parameters should be listed by formulation together with summary statistics. Both the plots of the cumulative amounts permeated per unit area (mass unit/cm^2) as function of time and the plot of the rate of absorption (mass unit/cm^2/hr) as a function of time should be provided to characterise the release profile.

Relevant permeation parameters, e.g., the maximal rate of absorption (J_{max}) and total amount permeated at the end of experiment (A_{total}) should be determined and compared.

In the case of a replicate design, results obtained in the duplicate sites from the same donor should be averaged (geometric mean) prior to further analysis.

The acceptance criteria for equivalence parameters (J_{max}) and (A_{total}) are:

- 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%, unless justified.
- Wider 90% confidence interval limits, to a maximum of 69.84 – 143.19, may be accepted in the case of high variability observed with low strength and limited diffusion drug products, and if clinically justified. The procedure in the Guideline on Investigation of Bioequivalence, "Section 4.1.10 Highly variable drugs or drug products" should be followed.

In addition, for the test to be valid:

The acceptance criteria for equivalence parameters (J_{max}) and (A_{total})

- The 90% confidence interval for the ratio of means of the test and *negative control* products should be entirely outside the interval of 80.00- 125.00%.
- The 90% confidence interval for the ratio of means of the comparator and *negative control* products should be entirely outside the interval of 80.00- 125.00%.

Additional permeation parameters, such as the time of maximal rate of absorption (t_{max}) and lag-times, should also be reported. The lag-times between the test and comparator products should be the same (i.e. within ± 10%) if present. Any differences in the permeation parameters should be appropriately discussed with respect to equivalence.

The mass balance should be determined. 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.

The amount of active substance retained in different skin layers (such as the stratum corneum and epidermis) may be analysed separately to understand the active substance distribution in human skin.

Annex III Stratum Corneum (S.C.) Sampling (Tape Stripping)

1. Introduction

This annex provides information for an *in vivo* stratum corneum sampling (or tape stripping (TS)) study for semi-solid formulations as a permeation kinetic method to show equivalence, *in lieu* of a therapeutic equivalence study.

The S.C. sampling study is a minimally invasive technique that involves sequential removal of the outermost skin layer (i.e., the stratum corneum (S.C.)) using adhesive tapes after application of a drug-containing formulation. The amount of drug in the S.C. depends on three main processes: drug partitioning from the formulation into the SC, drug diffusion across the S.C., and drug partitioning out of the S.C. into the viable tissues. A major advantage of TS is that the experiment is conducted *in vivo* with a fully functioning cutaneous microcirculation so that drug clearance from the skin is unimpeded.

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., TS data may provide a suitable surrogate to characterise the rate and extent of drug absorption to the underlying tissues.

In vivo TS studies are only applicable for products where drug diffusion into and through the SC takes place. Thus, TS should not be used for testing of drug products to be applied on significantly damaged skin (e.g. open wounds, burns) or skin of premature new-born. In addition, any products that contain volatile drugs or target primarily the cutaneous appendages (e.g. hair follicles, sebaceous glands) are also not suitable.

2. Method development and optimisation

A TS study is not an automated process and careful consideration of the experimental design is vital. The experimental conditions of the pivotal study should be assessed individually for the concerned products and should be established by performing a pilot TS study. A summary of the development and optimisation of the TS method should be provided.

The following experimental conditions should be established and verified during the pilot study:

- TS study should be conducted on healthy, normal forearm (volar) skin areas with adequate skin barrier function. The inclusion/exclusion criteria for skin conditions should be defined. Skin with tattoos, any signs of dermatological abnormality or exhibiting a significant density of terminal hair should be excluded. The preparation and cleaning procedures prior to the experiment should be established and further, that the treatment sites are not damaged by these processes.
- Skin integrity should be determined before and after the experiment. This is normally performed by the measurement of Transepidermal Water Loss (TEWL), although other techniques may be applicable if appropriate. The acceptance criteria should be fully discussed and justified.
- Due to inter-subject variability, the products to be compared should be applied on the same subject. Additionally, a negative control that is non-equivalent to the comparator product should also be included to demonstrate the discriminatory power of the method. It is

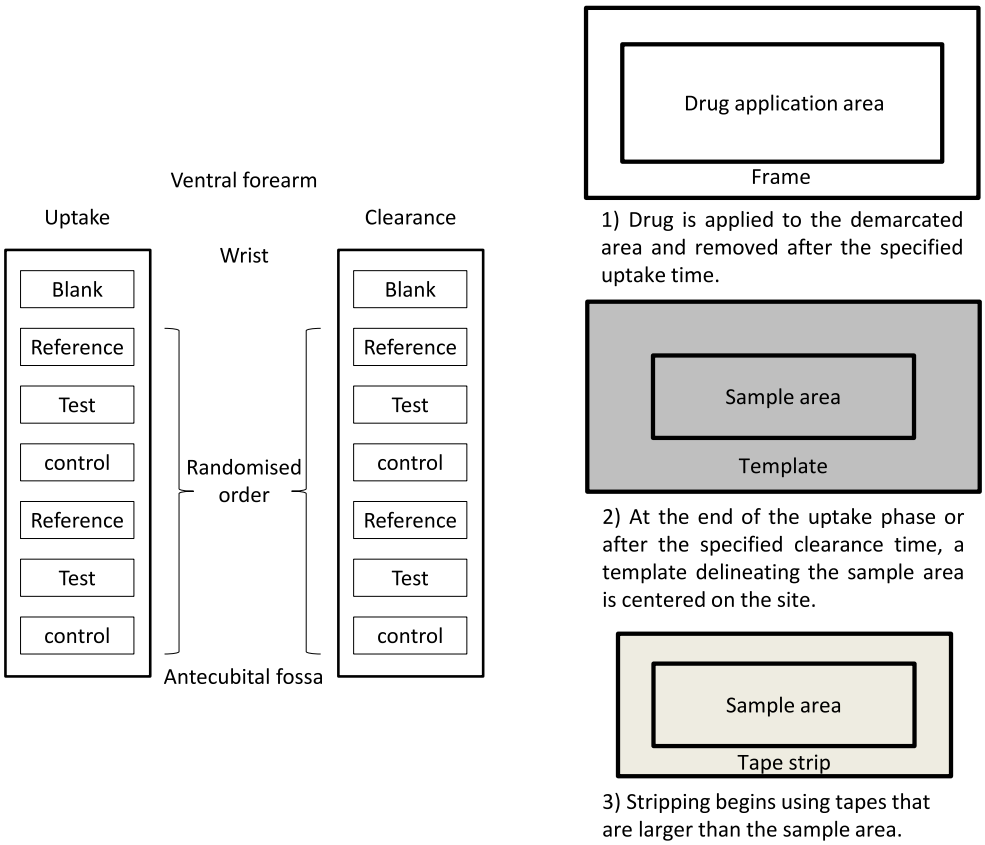
recommended to blind the investigator responsible for formulation application and tape stripping to minimise risk of bias.

- The dosing amount should be determined based on the SmPC. During the pilot study, the dosage and area of dose application should be verified to achieve a quantifiable mass of active substance in the SC. The dosing technique, blinding and randomisation procedures should also be established.
- A single dose approach should be followed, i.e. skin stripping is performed after a single application of the test and comparator products.
- It is necessary that the products are compared at two time points (one uptake, one clearance) for each subject. The optimal uptake and clearance times depend on the characteristics of the drugs and products and should be determined during the pilot study. Ideally and when relevant, the uptake time should be sufficiently long for the drug to have attained the diffusional steady-state. This can be established by testing at multiple uptake times and from which time the mass of drug recovered from the SC remains constant. The clearance time should be long enough to allow measurable transfer of drug from the SC into the viable skin (and beyond) but should not exceed 48 hours to avoid any skin desquamation effect. The clearance time providing at least a 25% decrease in the mass of drug recovered from the SC with respect to that at the uptake phase is preferred. In all cases, the sampling times should be carefully considered and justified.
- The drug product should be removed from the skin surface after the specified uptake time. The cleaning procedure should be established to ensure that the residual formulation is efficiently removed from the treatment sites before stripping.
- The adhesive tape chosen should meet the following requirements: a) does not lose mass when applied and rubbed against the skin surface; b) minimal weight loss and gain during storage; c) the drug is readily extracted from the SC adhered to the tape; d) the adhesive or other components of the tape do not interfere with the analytical quantification of the drug; and e) the adhesive power should be such that the majority of the SC is removed with a sufficiently low number of tapes (e.g. not more than 30 tapes).
- The TS procedure followed must ensure that most of the SC (≥75%) is sampled for each skin site. The minimum and maximum number of tapes should be established based on the TEWL (or other relevant) criteria, e.g. eight-fold increment over baseline value, safety stop value.
- Most commonly, the drug is first extracted from the tapes then quantified in the extraction solvent(s). Alternative methods of extraction/quantification may be used if justified. Satisfactory efficiency should be demonstrated for the proposed extraction method.

3. Study design

Detailed standard operating procedures should be prepared for the conduct of TS studies to ensure precise control of dosing, cleaning, stripping, extraction, quantification and other study variables or potential sources of experimental bias. The inclusion/exclusion criteria should be pre-defined and clearly stated in the protocol.

The following study design is recommended for TS studies. The final protocol developed for each specific case should be justified.



- Subjects – TS studies should be performed in healthy volunteers. The subjects should be screened for suitability in line with the principles of bioequivalence studies.
- Treatment area –healthy skin of the volar forearm areas sufficient to accommodate at least six application sites per forearm. Skin integrity should be verified e.g. by TEWL measurement. The same number of application sites should be assigned to each forearm;
- Number of subjects – the choice of the number of subjects should be justified based on the variability estimated from the pilot studies and demonstrated to be statistically relevant. A minimum of 12 subjects should be used to demonstrate equivalence;
- Number of replicates – at least two application sites per product (test, comparator and a negative control) per forearm. One forearm should be used for uptake samples and the other for clearance;
- The products should be applied at pre-determined doses (±5%) and spread evenly over the entire demarcated application sites. Blank samples should be collected from the adjacent areas to verify the absence of background levels of drug or other compounds that may interfere with the quantification of drug in the treated SC;
- The application sites should be randomised to avoid bias. The application time should be staggered to allow time for S.C. sampling;
- Un-occluded conditions, unless occlusion is recommended in the product information, or otherwise justified e.g. to prevent inadvertent removal of formulation.

- The formulation should be removed from all treatment sites (uptake and clearance) at the end of the uptake phase. The total cleaning time should be minimised to avoid any artefacts due to further drug diffusion. Skin integrity of the treated area should be checked before stripping;
- The 'uptake' sites should be tape-stripped immediately after formulation removal. The 'clearance' sites should be tape-stripped at the pre-defined clearance times;
- The exact number of tapes required should be determined based on TEWL measurements of the stripped area and the stopping criteria established from the pilot study;
- The mass of SC removed per tape should be determined using a gravimetric method by weighing the tapes strips before and after stripping. Alternative methods of quantification of the SC can be used if suitably described and justified;
- All stripped tapes collected from each treatment site should be analysed. The first two tapes should be analysed separately from the remaining tapes, so their contribution to the total amount of drug recovered can be evaluated. To enhance analytical detectability, the subsequent tapes can be combined in groups (e.g. each group containing the required minimum content of SC) for extraction. The total mass of drug in the SC should be calculated as the sum extracted from all tape strip samples. The mass balance, including the drug content removed from the surface by cleaning should be determined for each treatment site. The overall recovery of 90-110% would be acceptable without justification; larger variation should be fully explained.

4. Method validation

Cleaning the skin surface at the end of the application period prior to tape-stripping is important and must be capable of removing excess formulation (i.e. unabsorbed drug) efficiently without inadvertently 'driving' the drug into the barrier. The cleaning procedure usually involves quickly and gently wiping the skin with dry/wet tissue, cotton swabs and/or fresh alcohol wipes. The cleaning components should be known not to influence drug diffusion into and through the SC. A careful evaluation and validation of an efficient skin cleaning procedure should be performed prior to the pivotal study, e.g. by demonstrating satisfactory recovery (>90%) of the drug formulation removed from the skin surface and the negligible drug content (<10%) recovered by stripping the cleaned skin immediately after application. Other ways of validation may be used if suitably justified.

The bioanalytical method employed for drug quantification in the tape strips should be validated. The efficiency of the extraction procedures (including extraction of tape strips in groups) should be established and demonstrated as consistent prior to the pivotal study.

The discriminatory power of the TS method should be demonstrated for batches with different quality attributes (a 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 analytical methods for determining the content of active substance in the tape-stripped SC should be validated according to the Guideline on Bioanalytical Method Validation.

5. Data analysis and metrics

Data from all subjects should be reported and the validity and variability of the results should be discussed. All treated subjects and application sites should be included in the statistical analysis. The

permitted reasons for exclusion must be pre-specified in the protocol. Data exclusion based on statistical analysis or for kinetic reasons alone is not acceptable.

For each product, the thickness of SC removed, the number of tapes used and final TEWL value measured at both uptake and clearance times should be reported. Any differences in these parameters between the test and comparator products should be discussed with respect to equivalence.

A plot of drug content profile in the SC should be presented for each application site, e.g. the drug content of each SC tape strip (single or grouped) versus SC depth.

The duplicated measurements for each product in each subject should be averaged (population geometric mean) prior to analysis.

For the comparison of products, the equivalence parameters: mass of drug recovered from the uptake (M_{uptake}) and clearance ($M_{clearance}$) sites, should be statistically compared, according to the Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/ Corr).

The acceptance criteria for equivalence parameters (M_{uptake}) and ($M_{clearance}$) are:

- 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%, unless justified.
- Wider 90% confidence interval limits, to a maximum of 69.84 – 143.19, may be accepted in the case of high variability observed with low strength and limited diffusion drug products, and if clinically justified. The procedure in the Guideline on Investigation of Bioequivalence, "Section 4.1.10 Highly variable drugs or drug products" should be followed.

In addition, for the test to be valid:

The acceptance criteria for equivalence parameters (M_{uptake}) and ($M_{clearance}$)

- The 90% confidence interval for the ratio of means of the test and *negative control* products should be entirely outside the interval of 80.00- 125.00%.
- The 90% confidence interval for the ratio of means of the comparator and *negative control* products should be entirely outside the interval of 80.00- 125.00%.
- The 90% confidence interval for the ratio of means of the *test product* clearance ($M_{clearance}$) and ($M_{uptake)}$ comparator products should be entirely below 1.0.
- The 90% confidence interval for the ratio of means of the comparator *product* clearance ($M_{clearance}$) and ($M_{uptake)}$ comparator products should be entirely below 1.0.

The overall conclusions of the study should be provided. This should be supported by a sound scientific discussion and interpretation of the TS data.

Annex IV Vasoconstriction assay for corticosteroids

A description of the protocol for the assay should be provided.

The following testing principles should be followed:

An *in vivo* pilot dose duration-response study should be undertaken to determine the study requirements for determining the equivalence parameters to be used in the pivotal equivalence study.

Relevant human volunteer inclusion and exclusion criteria should be stated and adhered to for both pilot and pivotal studies.

Healthy subject with an adequate vasoconstriction to topical corticosteroids must be included.

Test product, vehicle, comparator product, and untreated control should be randomly assigned to application sites on the ventral forearms.

The study should be appropriately blinded.

For the pivotal study, a minimum of 12 subjects should be included.

The vasoconstriction reaction should be determined at baseline (before drug application), time of drug product removal, and several times after drug product removal (e.g. 2, 4, 6, 19, 24 hours).

The time course of response should be followed until return to baseline to ensure that maximal pharmacodynamic response is observed. The assay must be optimised to ensure that the products are compared in the linear portion of the blanching curve. Several application times should be tested in pre-test. The lower limit of sensitivity should be determined.

The vasoconstriction reaction should be determined at several time points and AUC data should be generated. A single time point for estimation of the vasoconstriction reaction is not acceptable.

The measurement of the vasoconstriction reaction should be performed by using a chromameter, or other methods more sensitive than visual estimation, and by a secondary clinical assessment by an independent observer.

References:

1 FDA Guidance for Industry: Topical Dermatologic Corticosteroids: *in vivo* bioequivalence 2 June 1995.

2 "Quantification of corticosteroid-induced skin vasoconstriction", Dermatology, (2002), 205, 3-10.

3 "The skin-blanching assay", Journal of the European Academy of Dermatology and Venerology (2012), 26, 1197-1202.