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Guideline on quality of transdermal patches

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This guideline together with the new Guideline on Quality of Oral Modified Release Products replaces the “Note for Guidance on Modified Release products: A: Oral dosage Forms B: Transdermal Dosage Forms. Part I (Quality)” (CPMP/QWP/604/96).

Keywords	*Transdermal patch, adhesives, dissolution, skin permeation*

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Guideline on quality of transdermal patches

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Executive summary

This guideline addresses new marketing authorisation applications (including generic or abridged applications) and subsequent variation submissions for transdermal patches for systemic delivery.

Guidance is provided on the quality requirements for the description, development, manufacture, characterisation of excipients, control of drug product, packaging and stability of transdermal patches. In particular, *in vitro* performance testing with respect to drug release, adhesion and skin permeation is discussed, together with its relation to clinical and *in vivo* performance.

It should be read in conjunction with the Guideline on the Pharmacokinetic and clinical evaluation of modified-release dosage forms.

Transdermal patches are designed to provide a controlled delivery of the active substance(s) through the skin, principally by diffusion, resulting in a defined rate and extent of systemic delivery of active substance.

1. Introduction (background)

An important function of the skin is to protect the body from the external environment, and it is normally a very effective barrier to the permeation of active substances. However, for certain active substances, depending on their physicochemical properties, passive diffusion is possible to achieve a therapeutic effect.
Otherwise, this may be achieved by permeation enhancement, which involves the manipulation of the formulation by either:

- Increasing the thermodynamic activity of the active substance in formulation (e.g., by supersaturation)
- Passive penetration enhancement (e.g., solvents can act as a carrier of the active, prodrugs, nanocarriers, microemulsions, liposomes)

Permeation enhancement may also be achieved by physical technologies such as iontophoresis, microporation, sonophoresis and microdermabrasion, which could be characterised as active enhancement strategies.

A transdermal patch, which may also be considered a Transdermal Drug Delivery System (TDDS), is defined as a flexible, multi-layered, pharmaceutical single dose preparation of varying size containing one or more active substances to be applied to the intact skin for systemic absorption. This is normally formulated with pressure-sensitive adhesives that assure the adhesion of the preparation to the skin. A transdermal patch includes a backing sheet, impermeable to the active substance and normally impermeable to water. The releasing surface of the patch is covered by a protective liner to be removed before applying the patch to the skin.

Transdermal patches are designed to slowly deliver the active substance(s) through the intact skin, resulting in a prolonged and adequately constant systemic absorption rate. The rate limiting step for systemic absorption of the active substance is usually the absorption through the skin. Alternatively, absorption may be limited by incorporating or dissolving the active substance in a (semi solid) reservoir, with a membrane to control the release and the diffusion of the active substance(s) from the patch. The transdermal patch can also be formulated combining both drug delivery principles as the means of controlling drug delivery to the surface of the skin (see also Definitions).

The degree to which formulation and product design may influence active substance permeation through the skin may be characterised by means of performance testing (a) dissolution, (b) drug release using a synthetic membrane and (c) skin permeation testing. Each has advantages and disadvantages.

The results of dissolution and skin permeation can together inform about the contribution of the patch and the skin in controlling absorption.

To ensure the safe and effective use of transdermal patches, the active substance(s) should be delivered through the skin at an adequate rate that is maintained for an appropriate time during patch application and should not irritate or sensitise the skin. The excipients should not have an adverse effect on the skin or exacerbate the adverse effects of the active substance. Skin enhancers should have a reversible impact on the skin barrier. The solvents used should not interact with the components of the patch system.

Transdermal patches usually contain an excess of active substance than that delivered to the patient during use. This excess is necessary to maintain a clinically effective rate of delivery over time and allow the minimum patch surface area. Because the concentration of the active substance can be near to its saturation limit, there is a risk of crystallisation on storage with potential adverse effects on the quality and efficacy of the product. Furthermore, the residual active substance left in the patch after administration can pose a safety risk to the patients, others and the environment. There is also a risk of misuse of discarded transdermal patches e.g., those containing narcotic drugs.

It is acknowledged that transdermal patches can differ in drug content and surface area but still deliver the same amount of drug over the same period of time. It is desirable to minimise the amount of residual active substance in the patch as much as possible.

2. Scope

This guideline considers the general requirements concerning the development and quality of a transdermal patch for all new marketing authorisation applications and variations. In addition, specific guidance is provided concerning the data requirements to support generic or abridged applications.

Cutaneous patches (where the active substance is not intended to be systemically absorbed) are out of the scope of this guideline. However, some of the quality aspects of transdermal patches may be relevant and applicable, e.g., Sections 4.2 Pharmaceutical Development, 4.3 Manufacture and 4.5 Drug Product Specifications.

Annex 1 provides supplementary information with respect to *in vitro* skin permeation studies.

3. Legal basis

This guideline should be read in conjunction with Directive 2001/82/EC as amended, Directive 2001/83/EC as amended and relevant Pharmacopoeial monographs and ICH, CHMP/CVMP guidelines including:

- Ph. Eur. Monograph 1011 Transdermal Patches;
- Pharmaceutical Development, ICH Q8 (R2), EMEA/CHMP/167068/2004;
- Manufacture of the Finished Dosage Form, CPMP/QWP/486/95 and Annex: Start of Shelf-Life of the Finished Dosage Form CPMP/QWP/072/96;

- 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;
- Inclusion of Antioxidants and Antimicrobial Preservatives in Medicinal Products CPMP/CVMP/QWP/115/95;
- Q 6A Specifications: Test Procedures and Acceptance Criteria for New Drug 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 Drug Substances and Drug Products (ICH Q1A (R2)), CPMP/ICH/2736/99-ICH Q1A (R2);
- Stability Testing: Requirements for New Dosage Forms (ICH Q1C), CPMP/ICH/280/95-ICH Q1C;
- Stability Testing of Existing Active Ingredients and Related Finished Products, CPMP/QWP/122/02 Rev. 1 corr.;
- Guidelines of 16.05.2013 on the details of the various categories of variations, on the operation of the procedures laid down in Chapters II, IIa, III and IV of Commission Regulation (EC) No 1234/2008 of 24 November 2008 concerning the examination of variations to the terms of marketing authorisations for medicinal products for human use and veterinary medicinal products and on the documentation to be submitted pursuant to those procedures (C (2013) 2804); and
- Guideline on the pharmacokinetic and clinical evaluation of modified release dosage forms (EMA/CPMP/EWP/280/96 Corr1).

4. New applications

The data requirements discussed below are relevant to new applications for the first use of the active substance for systemic delivery using a transdermal patch and new generic or abridged applications. Additional requirements for generic or abridged applications, in lieu of full clinical data, are given in Section 5 Requirements to support a generic or abridged application.

4.1. Description and composition of the drug product

The description should be in sufficient detail to fully characterise the drug product (all strengths) and inform the relevant quality sections of the SmPC and, as appropriate, the package leaflet and labelling.

The product description should include the following:

- Strength, as the mean dose delivered per unit time, normally mass delivered *in vivo* per 24 hours;
- *In vivo* release rate or strength per patch area (i.e. mass delivered *in vivo*/unit area/unit time);
- The content and location of active substance in the drug product;
- Active substance utilisation (% of total active substance absorbed per patient administration);
- Patch area activity (active substance utilisation/patch area);

- Residual (mass of active substance remaining in the drug product after completion of administration);
- Instructions for use, including the use of any overlay; and
- Patch period of use.

Unambiguous tabular formats, any necessary schematics (preferably supported by photographs) should be provided to describe the following:

- Patch type, with respect to the control of drug release (e.g., reservoir, drug in adhesive);
- The form and function of each layer of the laminated product;
- The composition of each layer, including the function and the grade of the excipient (the grade is normally considered to be a critical quality attribute for transdermal delivery). Backing layers and release liners should also be described;
- Overlay description (if applicable);
- Patch size, area and thickness (area weight may be considered if justified); and
- Appearance, including shape, colour and markings.

Drug product design aspects relating to patient administration and use throughout the period of use should also be described.

Transdermal patch design should avoid cutting by patients or health care professionals – a smaller transdermal patch should be developed instead.

However, in exceptional cases for good patient safety and efficacy reasons, cutting might be necessary. In such cases this should be described and supportive data should be given in 3.2.P.2 as well as in the clinical dossier.

The names of excipients not described in a Pharmacopoeia should be specific and distinct and should be supported by a brand name or name and address of manufacturer, if necessary.

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

Some elements of the description of the drug product such as product strength, active substance utilisation, residual and suitability of administration and use cannot be directly or indirectly (using surrogate markers) determined by quality tests. The determination and/or assessment of these quality elements can only be achieved by appropriate valid clinical studies. The description should therefore include cross references to other sections of the dossier that describe their determination and/or assessment, together with evidence of the validity of the clinical methods.

4.2. Pharmaceutical development

The pharmaceutical development component of the dossier should form a sound basis of the suitability of the transdermal patch for its intended use, provide a clear narrative of product development and include all relevant data.

4.2.1. Therapeutic objectives and principle of the delivery system

A summary of the therapeutic objectives and rationale for the choice of the transdermal route for the active substance, in terms of patient benefit / risk, should be provided.

Factors to be considered should include therapeutic use, local and systemic side effects associated with other routes, pharmacodynamics, pharmacokinetic properties of the active substance (e.g. t1/2, therapeutic index, first pass-effect).

Local tolerance, the means of administration (including occlusion, if relevant), administration site, posology, patient compliance in medication taking and the proportionality of different strengths should also be discussed.

Where appropriate, cross references to relevant clinical sections of the dossier should also be given.

The achievement of the therapeutic objectives by the design and function of the transdermal patch should be fully discussed and correlate with the Description and Composition of the Drug Product e.g., the identification and description of the type of transdermal patch (e.g. reservoir, drug in adhesive) and how drug release over the intended time of application is achieved.

4.2.2. Active substance

Active substance physicochemical and biological properties that determine the capability and / or influence the rate and extent of transdermal delivery and the manufacturability and stability of the drug product should be identified and discussed. Such properties include molecular weight, partition coefficient, melting point (boiling point if applicable), pKa, solubility and pH effects, as well as physical properties, such as particle size and polymorphism, if the active substance is present in the solid state in the drug product.

The target physical state of the drug substance, e.g. solute, suspension, and the degree of saturation or supersaturation are critical quality attributes and should be justified in terms of product efficacy and safety, supported by evidence of the means by which the target state is achieved during manufacture and its stability during storage.

The risks of precipitation / particle growth / change in crystal habit, or other active substance characteristics likely to affect the thermodynamic activity, arising from changes in temperature and on storage should be assessed and appropriate tests included in the stability studies.
These properties could be inter-related and might need to be considered in combination.

4.2.3. Excipients

The choice of excipients (including the adhesives, backing layer and release liners and rate control membrane), their concentration, and their characteristics that can influence the drug product performance should be discussed relative to their respective functions.

Detailed information on those materials which might have an influence on the adhesive properties and active substance transdermal permeation and bioavailability (e.g. solubiliser, penetration enhancer or retarder) should be provided, including their ability to provide their intended functionality and to perform throughout the intended drug product shelf life (see also the Note for Guidance “Excipients in the Dossier for Application for Marketing Authorisation of a Medicinal Product” CHMP/QWP/396951/06 Annex III).

For patches utilising a rate controlling membrane, the suitability and performance of the rate controlling membrane should be fully discussed.

The relevant characteristics of the layers (backing layer, the release liner, rate controlling membranes and adhesive liner), such as appearance, flexibility, tensile strength, porosity, occlusion and chemical inertness, and the other excipients should be discussed. This information can be used, as appropriate, to justify the choice and quality attributes of the excipients, their specification and safety (3.2.P.4.4 and 3.2.P4.6) and to support the drug product specification (3.2.P.5.6).

The composition and relevant characteristics of excipient mixes, e.g. adhesive solutions or suspensions, should be provided and characterised, including viscoelastic properties, if appropriate. Processing aids, including temporary lamination layers and solvents employed during manufacture, which are subsequently removed, should be identified and described.

4.2.4. Formulation development

A summary describing the development of the drug product should be provided. This should clearly and critically describe the means by which each of the defined quality product elements, given in 3.2.P.1 (see Section 4.1 above), were determined and achieved.

The development of the drug product should be described with respect to the defined quality target product profile, employing suitable tests to characterise and control the critical quality attributes, including adhesion properties, factors affecting ease of administration and duration of use, and product performance (dissolution, *in vitro* drug release, *in vitro* skin permeation).

Satisfactory evidence of the suitability of the methods employed should be provided (see also Section 4.2.6 In Vitro and *in vivo* Drug Product Performance and Annex 1 *In vitro* Permeation Studies).

Satisfactory evidence of compliance with Ph Eur requirements for transdermal patches should be demonstrated.

The relationship between the product quality profile, critical quality attributes and the Finished Product Specification should be fully discussed. Product development should include appropriate feasibility studies taking into account physicochemical and solubility properties of the active substance in the formulation, stability, drug release and rate and extent of drug permeation.

When the formulation composition is decided, up-scaling of the manufacturing process will start and the critical process parameters will 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, these adjustments may have an effect on *in vitro* release / dissolution, *in vitro* skin permeation and adhesion properties of the drug product and therefore should be assessed.

The clinical trial formulation and the batches used in the pharmacokinetic studies need to be described in detail. Any differences in formulation and manufacturing processes between clinical batches and the product to be marketed should be justified. Results from comparative *in vitro* studies (e.g., drug release / dissolution, skin permeation, adhesion) or comparative *in vivo* studies (e.g., bioequivalence) should be provided.

The critical formulation and manufacturing elements that influence the adhesive properties of the drug product should be understood and may support minor changes in adhesive composition.

In terms of quality in relation to efficacy:
The active substance content, formulation, patch size and thickness should be justified by a sound rationale, *in vitro* quality testing and clinical evidence, described by a clear narrative of product development.

In terms of quality in relation to safety:
Those quality elements that may influence the safety of the drug product such as material specifications, qualification, identification and control of residual solvents and impurities should be discussed. The risks of dose dumping, leakage from reservoir, residuals and product residues should be discussed. Cross reference to relevant non-clinical or clinical data should be given.

In terms of quality with respect to the administration and use:
The adhesive properties of the drug product should be fully discussed and characterised, by both *in vitro* and *in vivo* testing.

The adhesion / cohesion balance should be considered, with respect to minimisation of cold flow (formation of a “dark ring” around the transdermal patch in use), satisfactory elasticity and the avoidance of detachment, or edge lifting throughout use and skin damage following removal.

Ph. Eur. adhesion requirements should be met. When removed (whatever the ways and directions it can be removed), the protective liner does not detach the preparation (matrix or reservoir) or the adhesive from the patch.

The transdermal patch should adhere firmly to the skin by gentle pressure of the hand or the fingers and can be peeled off without causing appreciable injury to the skin or detachment of the preparation from the outer covering.

The design elements of the drug product to ensure satisfactory practical administration should be discussed.

Cross reference to the verification of the suitability of the adhesive properties of the drug product and the product design by clinical studies should be given.

4.2.5. Stability programme development

The proposed stability programme (3.2.P.8) should take into account the product understanding gained during pharmaceutical development. This should include performance tests with respect to (a) dissolution, (b) drug release using a synthetic membrane and (c) skin permeation testing, as appropriate, and adhesion.

The risk factors to product stability should also be fully discussed and a satisfactory drug product stability protocol should be developed.

The stability programme should ensure that the drug product is subject to appropriate stressed and real time storage conditions (including temperature cycling), representative of the proposed marketing of the product.

The requirements for special storage warnings e.g., do not refrigerate, should be addressed.

With respect to physical stability, factors should include formulation changes arising from active substance and / or excipient evaporation or migration, active substance crystallisation or other change in its thermodynamic activity, changes in the state of excipients. Changes in adhesion properties under different storage conditions should be assessed.

To support (any) proposed holding times and storage conditions, the stability of intermediate products, including laminated rolls should also be subject to a stability programme.

4.2.6. *In vitro* and *in vivo* drug product performance

4.2.6.1. In vitro drug release / dissolution

An *in vitro* release test evaluates the rate and extent of release of an active substance from a transdermal patch. Although the test may not model *in vivo* performance, it is a critical quality attribute to be specified in the finished product release and shelf life specification.

The methods described in Ph. Eur. monograph for Transdermal Patches should be followed i.e. a dissolution test or a release test using an appropriate, non rate-limiting membrane. If appropriate, alternative methods, with improved discriminative power compared to the compendial methods, may be employed.

The test itself and / or sample preparation should not damage or otherwise alter the performance of the transdermal patch. Any special requirements for sample preparation should be discussed. It may be possible to test only a defined sample area of patch which is applicable to all strengths, if it is shown that sample preparation has no impact on drug release / dissolution. If the size of the patch is too large to be inserted into standard dissolution testing apparatus or if sink conditions cannot be achieved using entire patches, suitability of testing specimens might be inferred from dose proportionality studies for samples of different size.

The *in vitro* drug release / dissolution profile of the active substance from the drug product should be characterised and established from clinical batches for which satisfactory efficacy has been demonstrated. These should be used to support the *in vitro* drug release / dissolution limits in the drug product specification (3.2.P.5.6), and so provide an assurance that future production batches are of similar quality to the pivotal clinical batches.

Satisfactory evidence of discrimination should be provided, with respect to:

- Critical manufacturing variables;
- Excipient and active substance critical quality attributes; and
- The stability indicating power of the method.

A summary of the development of the dissolution test should be provided, where the transdermal patch is tested under various conditions (media, pH, apparatus, agitation, etc.). Testing conditions providing the most suitable discrimination should be chosen. In case of media with a low buffering capacity, the pH should be controlled during the dissolution test to avoid influence of the dissolved active ingredient and/or excipients on the dissolution conditions during the test period.

The test period should be sufficient to achieve complete drug release, unless justified.

For the release / dissolution profile, the number of sampling time points should be sufficient to obtain meaningful profiles, with more frequent sampling during the period of greatest change.

At least 3 sampling time points are recommended to give a sharper and more differentiated profile.

An early time point to exclude dose dumping and/or to characterise a loading/initial dose (typically 20 to 30% dissolved), at least one point to ensure compliance with the shape of the dissolution profile (around 50% dissolved) and one to ensure that the majority of the active substance has been released (generally more than 85% dissolved i.e. Q=80%).

For most matrix type patches earlier sampling times (between 0 to 1 hour) were found to be more discriminative, i.e. quality indicating than later time points, when already up to 50% of active substance is released from the patch. Changes in formulation or manufacturing parameters are more likely to be detected within the first hour of *in vitro* dissolution testing if the specification ranges are set in accordance to the requirements listed below.

For the dissolution profiles, the value to be reported at each time point should be the quantity of active substance released in mass units (mg or µg) per surface area. The quantity of active substance should also be reported as a % of the total.

In addition, the first derivative of this profile should also be reported, to allow assessment of the change in the rate of release over time i.e. the value to be reported at each time point should be the quantity of active substance released per surface area, per time.

For transdermal patch products showing an *in vitro* zero order release (e.g., which may be seen in those patches with a rate-controlling membrane) a specification of the dissolution rate at a given time point may be more appropriate than the cumulative amount dissolved at a given time point.

The number of samples used to characterise the dissolution profiles should normally be a minimum of 12 units per batch (for routine release, a minimum of 6 units would be accepted).

Dissolution profile data should be provided in tabular and graphical formats, with a measure of variability between units e.g., 95 % confidence interval, range, or other justified statistical approach.

The dissolution profiles should be discussed taking into account the type of transdermal patch.

Dissolution limits should be data driven and fully justified. They should be characteristic of production capability and in line with clinical batches for which satisfactory efficacy has been demonstrated.

Normally, the permitted range in mean release at any given time point should not exceed a total numerical difference of ±10% of the labelled content of active substance (i.e. a total variability of 20%: a requirement of 50±10% thus means an acceptable range from 40-60%), unless a wider range is supported by a bioequivalence study.

Wider limits may be accepted only if satisfactorily explained and justified on quality grounds and supported by a bioequivalence study.

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. Tighter limits at release should be set to ensure that the product will remain within the shelf life specification.

4.2.6.2. In vitro skin permeation studies

In vitro permeation studies are not normally expected to correlate to *in vivo* release, but may be considered a valuable measure of product quality, reflecting the thermodynamic activity of the active substance in the product.

In-vitro skin permeation studies should be principally used to direct and assess development and optimisation of the drug product formulation and are not currently suitable for routine batch control testing. However, permeation studies could be included in the stability study protocol, albeit at a reduced frequency, to provide supportive stability data of product performance on storage.

In vitro skin permeation should be consistent throughout the shelf life of the drug product.

Establishing the characteristic permeation profile of the drug product, using a discriminative *in vitro* skin permeation method, can be of value in change control during life cycle management (see Section 6 Variation Applications).

Advice on the conduct of and requirements for *in vitro* skin permeation studies is given in Annex 1.

4.2.6.3. Adhesive properties

4.2.6.3.1. In vitro adhesion tests

In vitro adhesive tests should characterise the adhesion/cohesive properties of the transdermal patch. Although these tests may not model *in vivo* adhesion, they are critical quality attributes to be specified in the finished product release and shelf life specification.

Tests to characterise adhesive properties may comprise tests such as peel force tests (force required to remove the patch from the release liner), adhesive strength tests (force required to remove the patch from a defined surface) and tack tests (maximum force required to break a bond formed under low pressure between the adhesive layer of the patch and a stainless steel probe).

Residue remaining on the release liner after peeling from the patch and skin residues, following transdermal patch removal, should also be addressed.

The range and sufficiency of the *in vitro* tests used to characterise the adhesive properties of the drug product should be justified. A summary of their development should be provided to support any justification, if necessary.

The suitability and discriminatory power of the test methods employed to characterise the adhesive properties of the drug product need to be proven during product development, in particular with respect to:

- Critical manufacturing variables;
- Excipient and/or active substance critical quality attributes; and
- Stability indicating power of the method.

The *in vitro* adhesive properties of the drug product should thus be characterised, with the specifications limits for the specified tests in accordance with the results obtained on clinical batches for which satisfactory *in vivo* adhesive properties under product use have been demonstrated and used to support their justification of the drug product specification (3.2.P.5.6) (see also Section 4.2.9 Administration).

Release and shelf life limits should be the same, unless justified by reference to clinical batches.

4.2.6.3.2. In vivo adhesion studies

Studies to investigate and establish the satisfactory *in vivo* adhesive performance of the drug product should be undertaken.

Since an *in vivo* adhesion study is pivotal for approval, a feasibility or pilot study could be helpful in ensuring the methods can be satisfactorily undertaken, producing result from which valid conclusions can be made.

The assessment should be undertaken throughout the proposed period of use of the patch. This is because satisfactory adhesion performance of the clinical batches used would be a requirement for any clinical conclusions to be valid (see also Guideline on the Pharmacokinetic and clinical evaluation of modified-release dosage forms).

The clinical batches should be representative of the product to be marketed (see Section 4.2.6.5 Product Batches used in Clinical Studies).

Reference to the *in vivo* adhesion studies described in the clinical dossier should be provided.

4.2.6.4. Pharmacokinetic studies

A summary of all the bioavailability and pharmacokinetic studies should be given.

The data should include information on pharmacokinetics, e.g., $AUC_{(0-t)}$, t_{max}, $AUC_{0-\infty}$, C_{max}, and other relevant parameters.

Cross references to details of the bioanalytical methods and their validation should be provided.

The pivotal studies used to determine drug product strength, dose proportionality between strengths (if necessary) and the residual active substance content should be clearly identified.

Full details of the determination of drug product strength, dose proportionality and drug residual should be provided and linked to the data in the clinical dossier.

The clinical batches should be representative of the product to be marketed (see Section 4.2.6.5 Product Batches used in Clinical Studies).

4.2.6.5. Product batches used in clinical studies

Data should be provided for all clinical batches to demonstrate that they are representative of the product to be marketed (including sites, scales and dates of manufacture and certificates of analysis).

To be representative, both the scale of manufacture of the liquid coating mass containing the active substance and the scale of manufacture of the final transdermal patches should be considered.

Studies should be performed with batches representative of the product to be marketed manufactured using industrial scale equipment and conditions, e.g., full scale manufacture for the production of the laminate rolls and for roll conversion to transdermal patches, or at least 10% of full production.

Bioavailability studies may be performed with batches of a smaller scale, if these batches have been produced in a manner representative of the full scale manufacturing process and supported by other clinical batches of at least 10% scale.

4.2.7. Manufacturing process development

The steps in the process should be identified and their purpose described.

A risk assessment should be undertaken of the manufacturing process and the critical process parameters identified by the extent to which their variation can have impact on the quality of the drug product.

The selection and optimisation of the manufacturing process described in 3.2.P.3.3, in particular its critical aspects, should be explained.

The following non exhaustive list should be discussed:

- The preparation and homogeneity of the bulk drug containing and if applicable the bulk non-drug containing adhesive masses;
- The coating process, including those parameters that control the layer thickness;
- Drying, curing and where applicable the removal of residual solvents, including water for aqueous based blends;
- Laminations steps;
- The storage and handling of intermediate rolls;
- Roll conversion to transdermal patches; and
- Primary packing.

The proven acceptable ranges of the process parameters should be described and justified.

Differences between the manufacturing process(es) used to produce pivotal clinical batches and the process described in 3.2.P.3.3 should be avoided, unless justified by data showing that there is no influence in the product performance and critical quality attributes (see also Section 4.3 and Section 4.2.6.4).

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

4.2.8. Container closure system

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, drug product compatibility and safety.

The primary package should normally contain only a single transdermal patch.

The backing layer and release liner should not be considered a part of the container closure system.

Appropriate tests should be included in the stability study protocol to ensure that the suitability of the container closure system is satisfactorily assessed throughout shelf-life.

For certain classes of drugs presenting a serious risk of harm to children, e.g., controlled drugs, it will be necessary to provide evidence of container closure child resistance according to EN 14375:2003/AC:2006 (Child-resistant non-reclosable packaging for pharmaceutical products - Requirements and testing).

4.2.9. Administration

The SmPC, package leaflet and labelling should fully address the correct administration of the transdermal patch and include any necessary warnings for the safe use of the drug product. Consideration should be given to the safety of medical personnel and patients after the use of the product, especially for controlled drugs (e.g., opioids).

The Development Pharmaceutics package should include the data to support this information or else include cross reference to other parts of the dossier, including the efficacy, pharmacokinetic and *in vivo* adhesion studies.

The suitability of the transdermal patch in use should be fully discussed. The following should be considered:

- The identification, markings, appearance and visibility of the transdermal patch;

  Accidental dosing due to lack of visibility should be addressed.

- Site of administration, and change in site per dose;
- The necessity to avoid damaged skin;
- The requirements for skin pre-treatment;
- The administration and securing the transdermal patch, including if applicable the use of an overlay;
- Effect of exposure to environmental extremes of heat and cold;
- Effect of normal human behaviour such as washing, showers, sleeping, use of sun screens and moisturisers;
- Action to take in the event of adhesion failure, patch displacement or detachment, cold flow;
- Accidental transfer of patches to the skin of a non-patch wearer (particularly a child);
- Any necessary restrictions e.g., metallised backing and Magnetic Resonance Imaging, avoidance of occlusion;
- The practical suitability of any special storage conditions;
- Avoiding appeal to and inadvertent use by children;
- Avoidance of cutting of the transdermal patches; and
- Special precautions for disposal e.g., used patches should be folded so that the adhesive side of the patch adheres to itself and they should be safely discarded and unused patches should be returned to the pharmacy.

4.3. Manufacture

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 (see also Section 4.2.7 Manufacturing Process Development).

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

Transdermal patches are considered complex dosage forms manufactured by non-standard manufacturing processes. The scale of manufacture should be supported by manufacturing batch data at the proposed production scale. Exemption may be accepted if adequately justified by the transdermal patch manufacturer, on a case-by-case basis, as described in the guideline on process validation (EMA/CHMP/CVMP/QWP/BWP/70278/2012-Rev1).

In particular, the control of homogeneity and the thickness (area weight may be considered if justified) of the drug release and other layers, if present, together with the removal of residual solvents should be fully validated.

4.4. Control of excipients, including layers and liners

If the material(s) is new or has not been previously authorised for cutaneous and/or transdermal use, then full quality details should be provided according to the active substance format.

Critical quality attributes of the materials should be controlled in their specifications and their limits fully justified. The safety of the materials should be addressed, which should include consideration of leachables, solvents and monomers. The safety of these materials may be supported by suppliers' certificates of compliance to relevant EU Directives, if applicable e.g., the Plastics Directive.

For adhesive materials, the molecular weight and adhesion /cohesion properties should be characterised and satisfactorily controlled.

For adhesive mixes, the composition should be provided. The quality standard of each component should be discussed and justified.

4.5. Drug product specifications

The scope of the specification should comply with Pharmacopoeial and relevant ICH guideline requirements, and should include appropriate performance tests with respect to *in vitro* release / dissolution and adhesion (see Section 4.2.6.1 *In vitro* drug release / dissolution and Section 4.2.6.3.1 Adhesive Properties *in vitro* tests). The appearance of the transdermal patch should also be fully specified.

The limits should be in line with representative batch and stability data, unless suitably qualified by non clinical, clinical or other data.

Limits for performance tests 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.

Crystal formation is a quality deficiency likely to adversely influence the *in vivo* performance of the patch.

With the exception of suspension patches where the active substance is intentionally dispersed within the matrix, at release a transdermal patch should show no signs of crystallisation.

Exceptionally, the occurrence of crystals during shelf life is sometimes unavoidable. In these cases, a satisfactory description and explanation should be included in SmPC and package leaflet.

Any shelf life specification for the presence of crystals in the drug product would need to be fully justified by relevant *in vitro* drug release / dissolution and permeation data, and, as necessary, clinical studies.

For better quantification, microscopic and photometric methods are preferred rather than a simple visual count.

Since residual solvents may affect adhesion and permeation enhancement, it may be necessary to apply stricter limits than those in ICH Q3C. Reference to the batch data of clinical batches for which satisfactory efficacy has been demonstrated should also be made.

With respect to other impurities i.e. degradation products of the active substance or reaction products of the active substance with an excipient and/or immediate container closure system, the specified limits should comply with ICH Q3B, Impurities in New Drug Products, and qualified by reference to the maximum daily systemic dose of the active substance (i.e., nominal release rate per day), the relative

skin penetration of the impurities to that of the active substance, and clinical skin irritation safety studies.

4.6. Control strategy

Other regulatory guidance (including ICH Q8, Q9 and Q10) on the establishment and justification of a control strategy for the drug product is given in other relevant guidelines. Particular attention should however be paid to the *in vitro* drug release / dissolution, *in vitro* skin permeation and skin adhesion of transdermal patches.

Pharmaceutical development should establish the links between the pharmacokinetic drug product properties and clinical efficacy (including *in vivo* skin adhesion) to *in vitro* dissolution rate, *in vitro* skin permeation and *in vitro* adhesion studies, if possible.

Since drug release rate and skin adhesion may be susceptible to scale-up effects, it is particularly important that it is verified at the commercial scale.

5. Requirements to support a generic or abridged application

5.1. General remarks

The requirements to be considered for the development of an application for a generic transdermal patch are not significantly different from the development of the original reference product transdermal patch. The data requirements as described for New Applications should be met, supplemented by appropriate comparative quality and clinical data with respect to the reference product.

5.2. Development pharmaceutics

The data requirements are as described under New Applications.

The studies undertaken during pharmaceutical development to determine the *in vivo* release rate (mass delivered *in vivo*/unit area/unit time), active substance utilisation and residual should be fully described.

These elements have an important influence on the medication compliance (patient friendly to allow easy and correct use) as well as safety, including environmental safety.

Adhesion properties, skin tolerance, *in vitro* release and skin permeation, as well as patch size and ease of use should also be addressed and discussed in relation to the reference product.

Given that there is little or no IVIVC between quality attributes and clinical efficacy and safety, quality testing parameters need to be established based on the quality characteristics shown by the satisfactory clinical batches; these should also be representative of the product to be marketed.

Of special interest are those quality related issues that might directly or indirectly indicate the *in vivo* release characteristics of a transdermal patch e.g., *in vitro* drug release / dissolution, adhesion properties, amount of enhancer.

Generic patches should have preferably either the same or a higher patch area activity compared to the reference product. However, if justified that the benefit / risk has otherwise improved e.g., with respect to skin tolerability, adhesion properties, potential crystallisation, cold flow a larger patch can be accepted. Nevertheless, patch area activity comparison to the reference product should be a crucial aim of the pharmaceutical development.

With respect to the residual, it is acknowledged that an overload of active substance in some formulations may be unavoidable to ensure a sufficient thermodynamic activity. In the case of generic or hybrid applications, the amount of residual drug should not exceed that of the reference product, unless scientifically justified.

5.3. Comparative quality and clinical data requirements

5.3.1. Quality

With respect to drug product quality, the following elements (see Section 4.1 Description and Composition of the Drug Product) should be compared:

- Strength, as the mean dose delivered per unit time, normally mass delivered *in vivo* per hour;
- The content and location of active substance in the drug product;
- *In vivo* release rate or strength per patch area (i.e. mass delivered *in vivo*/unit area/unit time);
- Active substance utilisation (% of total active substance absorbed per patient administration);
- Patch area activity (active substance utilisation/patch area);
- Residual (mass of active substance remaining in the drug product after completion of administration);
- Instructions for use, including the use of any overlay; and
- Period of use.

With respect to *in vitro* performance:

Comparative drug release / dissolution, *in vitro* skin permeation and adhesion / cohesive properties should be investigated and the differences and similarities in *in vitro* performance between the generic and reference products should be discussed, supported by appropriate data.

For a generic or abridged application, the product strength must be the same as the reference product. The other quality elements, given above, should also be the same or similar, unless fully justified.

5.3.2. Clinical

To support a generic or abridged application, bioequivalence with the reference product and also non-inferiority (absence of statistically significant difference) with respect to *in vivo* skin adhesion should be demonstrated. Reference is made to Guideline on the pharmacokinetic and clinical evaluation of modified release dosage forms (EMA/CHMP/EWP/280/96 Rev. 1).

Non-inferiority regarding clinical safety and local tolerance of the generic product should also be demonstrated.

6. Variations applications

The manufacturing process for transdermal patches in general is considered complex, in respect to current variation guidance. Exemption may be accepted if adequately justified by the transdermal patch manufacturer, on a case-by-case basis, as described in the guideline on process validation (EMA/CHMP/CVMP/QWP/BWP/70278/2012-Rev1).

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

The following changes are considered to have a significant impact on the safety, quality or efficacy of the drug product:

- Change in the physicochemical state and / or thermodynamic activity of the active substance.
- Change in the qualitative and/or quantitative composition of excipients.
- Change in the manufacturing process:
    - Change in a single Critical Process Parameter; and
    - Changes in a number of non-critical process parameters.
- Any other change that affects the *in vitro* dissolution release, *in vitro* permeation or *in vitro* adhesion characteristics of the drug product.

In these cases, the change should be supported by appropriate and representative batch data of the original and proposed change, of all critical quality attributes, including adhesion properties, *in vitro* drug release/dissolution and *in vitro* permeation performance, as appropriate.

In addition, bioequivalence and *in vivo* skin adhesion equivalence studies may also be required, unless justified.

With respect to a change in adhesive, the respective characteristics should be compared to the whole set of information available for the former formulation, e.g., properties of the adhesive excipient and properties of the laminate with and without active substance.

Definitions

Cold flow:
Cold flow refers to the dimensional change/deformation of a patch polymeric matrix beyond the boundaries. Cold flow (or creep) is caused by an excess of adhesive over cohesive forces present in the adhesive matrix. The balance of adhesive and cohesive properties should be carefully adjusted to avoid cold flow emerging on storage and during use - as this may significantly increase the active substance releasing surface, affect handling of the patch by sticking to the sachet or leave a sticky residue around the patch.

In use, the appearance of cold flow is readily visible as the formation of a dark ring around the transdermal patch, patch movement or displacement, or patch wrinkling during use.

Cutaneous patch:
Flexible single-dose preparation intended to be applied to the unbroken skin to obtain a local effect by penetration of the active substance(s) into the skin.

Dosage strength:
Amount of active substance released *in vivo* per time unit.

Patch area activity:
Expressed in %/cm²; It is a measure of the formulation's intrinsic capability to release active substance from the patch *in vivo* and as such a surrogate measurement of thermodynamic activity.

Indirect tool to determine appropriateness of formulation development for a generic transdermal patch by putting two major product development parameters into relation: patch area and overall amount of active substance necessary to achieve bioequivalence to the reference product.

Example: transdermal patch dosage strength 25 µg/h, application time 72h, patch size 15cm^2, overall amount of active substance incorporated 4.8 mg:72 X 25µg = 1.8 mg;
1.8 mg corresponds to 37.5 % release related to 4.8 mg overall amount in the patch;
37.5% / 15 cm²=2.5%/cm² patch area activity.

Peel adhesion:
The force required to peel away a patch from a standardised surface like stainless steel.

Tack:
The property that enables an adhesive to form a bond with the surface of another material upon brief contact and under light pressure.

Shear adhesion:
The resistance of the matrix to flow (creep resistance or shear adhesion). Indication of the cohesion of a matrix.

Transdermal patch:
Flexible single-dose preparation intended to be applied to the unbroken skin to obtain a systemic delivery over an extended period of time. Transdermal patches consist of a backing sheet supporting a reservoir or a matrix containing the active substance(s) and on the top a pressure-sensitive adhesive, which assures the adhesion of the preparation to the skin.

The backing sheet is impermeable to the active substance(s) and normally impermeable to water.

In reservoir systems, the active substance may be dissolved or dispersed in a semi-solid basis or in a solid polymer matrix, which is separated from the skin by a rate-controlling membrane and a pressure sensitive adhesive.

The pressure-sensitive adhesive may, in this case, be applied to some or all parts of the membrane, or only around the border of the membrane and the backing sheet.

Matrix systems contain the active substance in a solid or semi-solid matrix, the properties of which control the diffusion pattern to the skin. The matrix system may also be a solution or solid dispersion of the active substance in the pressure-sensitive adhesive.

The releasing surface of the patch is covered by a protective liner to be removed before applying the patch to the skin.

Pilot batch:
Pilot batch size should at least be equivalent to one jumbo roll having the same size as for the industrial /commercial size batch.

Laminate:
A laminate is an intermediate product of the manufacturing of transdermal patches. It consists of different layers, e.g., backing film, adhesive layer and release liner. Also backing films consisting of different layers may be considered as laminate (multi-laminate backing film).

Layer:
A layer is a single coherent composite. More than one layer forms a laminate. Transdermal patches consist of several layers as e.g., release liner, drug-in-adhesive, drug-controlling membrane or backing film.

References

1. “Measuring Adhesive Performance in Transdermal Delivery systems”, P. Minghetti, F. Cilurzo and A. Casiraghi; Am J Drug Deliv 2 (3): 193-206, (2004);

2. “Modified Release Drug Delivery Technology”, Edited by M. J. Rathbone, J. Hadgraft, M. Roberts; Drugs and Pharmaceutical Sciences; volume 126; Marcel Deker, Inc. ;(2003);

3 “Transdermal and Topical Drug Delivery”, A.C. Williams, Pharmaceutical Press, (2003);

4 “Basic criteria for the *in vitro* assessment of dermal absorption of cosmetic ingredients”, Scientific Committee on Consumer Safety (SCCS), European Commission, Health & Consumers Directorate, (2010); and

5 “OECD Guideline for testing of chemicals - Guideline 428 : Skin absorption: *In vitro* method” Organization for Economic Cooperation and Development, Paris, (2004). Annex 1 (*In vitro* permeation studies).

Annex 1 (*In vitro* permeation studies)

1. Introduction

Percutaneous/dermal absorption describes the passage of compounds across the skin:

- Penetration which is the entry of a substance into a particular layer or structure such as the entrance of a compound into the stratum corneum; and
- Permeation which is the penetration through one layer into another, that is both functionally and structurally different from the first layer.

In vitro permeation studies are often used throughout pharmaceutical development to evaluate the permeation of an active substance from a transdermal patch. A major advantage of *in vitro* studies is the possibility for controlling the conditions of the experiment and therefore changes in permeation should only arise from changes in the transdermal patch and/or the membrane used.

In vitro permeation studies are not expected to correlate with *in vivo* release, but the characterisation of the permeation profile is considered a valuable measure of product quality and performance and may reflect the thermodynamic activity of the active substance in the product.

Establishing the characteristic permeation profile of the drug product, using a discriminative *in vitro* skin permeation method, can be of value in change control during life cycle management.

For the comparison of products, the need to perform bioequivalence studies may, in certain cases, potentially be waived. However, given that the product formulation may have a great impact on efficacy and modify skin permeation, the products to be compared should have the same or similar qualitative and quantitative excipient composition.

In line with the requirements for *in vitro* drug release / dissolution methods, satisfactory evidence of discrimination and a summary of the development of the permeation test should be provided.

It is recommended to use human skin from the torso (breast, abdomen or back) or relevant to the site of clinical application. However, if not possible, non-viable skin or skin from other species (such as pig, rodent, guinea pig) can be used. In some cases, artificial/synthetic membranes can be suitable. The choice of skin model used throughout the development should be justified.

In the case of a comparative test (development of a generic transdermal patch or formulation comparison), it is necessary that the products are compared with the same skin type.

The skin type, preparation and storage are elements that should be satisfactorily controlled, and that the skin samples for experiment are not damaged by these processes and are of suitable quality.

The integrity of the skin should be determined before the experiment and shown to be satisfactory for the experiment to be valid.

A variety of integrity tests is currently available, e.g., measurement of Transepidermal Water Loss (TEWL), monitoring the permeation of tritiated water or measurement of electrical resistance. The suitability of integrity test for the proposed experiment and criteria for acceptability should be fully discussed.

To address the variability of skin, preparation and skin integrity, a sufficient and justified number of replicates should be included in the experiment. Typically, six replicates may be used, or more for pivotal experiments.

In vitro permeation studies are usually performed using diffusion cells, with a skin diffusion area between 0.5-2 cm^2. Diffusion cells with larger skin diffusion areas should be used for transdermal patches that cannot be cut to size, e.g., reservoir type patches. Diffusion cells should be inert, robust and easy to handle. It is also important that the diffusion cell provides easy sampling and replenishment of the receptor phase and that it maintains the membrane integrity. The most common diffusion cells are Franz-type (static) cells, which consist of two chambers that can be side-by-side or upright separated by the skin. Flow through cells can also be used and are particularly useful to maintain skin viability.

The receptor solution used should mimic the *in vivo* conditions. One appropriate receptor medium for water soluble drugs is aqueous buffer. Solubilising agents e.g., surfactants or hydro-alcoholic media e.g., ethanol/water media, or protein e.g., bovine serum albumin can also be used in the case of drugs that are less soluble in water, if justified. The liquid in the receptor compartment has to be in contact with the skin, i.e., it should be ensured that there are no air bubbles under the skin.

The receptor solution should not affect skin integrity.

Permeation of solubilising agents from the receptor solution into the skin sample should be considered and avoided.

The composition of the receptor medium should be described and solubility studies to demonstrate that sink conditions can be maintained throughout the experiment should be submitted.

The active substance should be stable in the receptor solution for the duration of the test and subsequent analysis.

The receptor solution should provide solubility sink conditions throughout the experiment and ensure that the permeation of the active substance is not limited by the receptor medium. An acceptable sink condition is one where the maximum concentration of the active substance in the receptor solution achieved during the experiment does not exceed 10-30% of its maximum solubility in the receptor solution. Sink conditions can be maintained during the experiment in static cells by continuous replacement of the receptor phase or by using a flow through system.

For satisfactory permeation, satisfactory means should be in place to ensure that the receptor medium is fully in contact with all the exposed skin.

The diffusion of the active substance through the membrane is evaluated measuring the arrival of drug in the receptor compartment by assay of sequentially collected samples of the receptor fluid.

Aliquots of the receptor fluid can be analysed by a validated HPLC or LC-MS for active substance content or by any other suitably validated analytical technique.

It is acknowledged that the variability in results seen with *in vitro* skin permeation data is related to the variability in the skin used. In addition, if these methods are poorly developed, without satisfactory validation and / or poorly executed, then the results from permeation studies can only be difficult to interpret or without merit or meaning. Therefore, method development, optimisation and execution should comply with known best practice, be satisfactorily validated, and subject to appropriate data analysis and quality assurance principles.

2. Skin and sample preparation

The following should be described and their suitability discussed:

- The type of skin (origin, species, part of the body) should be stated;
- The storage and transport of the skin should be described and appropriately controlled; and
- The preparation and treatment (thickness, separation) of the skin should be described and justified.

The integrity of the skin should be determined before the experiment and shown to be satisfactory for the experiment to be valid.

Sample preparation of the drug product transdermal patch should be described and its suitability discussed. Normally, the patch is carefully cut to size and applied to the skin in the donor chamber. In case overlays are used, the effect of occlusion should be investigated.

The test itself and / or sample preparation should not damage or otherwise alter the performance of the transdermal patch.

3. Study design / study conditions

The following study design is recommended for permeation studies using *ex vivo* human skin. Any deviations from the proposed test protocol should be fully justified.

- Diffusion cell – Franz type or flow through;
- Receptor phase, to mimic *in vivo* conditions that also provides active substance sink conditions, degassed, e.g., in an ultrasound bath to prevent the build-up of air pockets;
- The medium may be aqueous buffer and include justified solubilising agents and / or protein;
- Receptor phase should be continuously agitated and remain in contact with the skin. The stirring speed should be justified;
- Temperature - the surface of the skin, in the diffusion cell, is maintainable at a temperature close to the physiological human skin temperature (32°C±1°C). The skin surface temperature may be suitably verified prior to dose application using an infrared thermometer;
- Humidity – Extremes of relative humidity in the laboratory should be avoided, i.e. above 70% RH and below 30% RH;
- Human skin integrity should be tested at the beginning of the experiment;
- The suitability of integrity test e.g., (TEWL), permeation of tritiated water, electrical resistance or visual inspection (but not accepted for pivotal studies) and criteria for acceptance should be fully discussed;
- Number of replicates – The choice of the number of samples should be justified with regard to the scope of the experiment and demonstrated to be statistically relevant;
- Number of skin donors – at least 2 different donors;
- Skin anatomical region –torso (breast, abdomen or back) or relevant to the site of clinical application;

- The number of time points should be sufficient to satisfactory characterise the permeation profile. Minimum of 5 suitably timed receptor sampling time points and an early time point, based on study requirements;
- Study duration should be justified in regards to the in-use administration. If the study duration is longer than 24 hours, it should also be shown that skin barrier function and integrity is adequately maintained; and
- Un-occluded conditions, in case overlays are used the effect of occlusion should be investigated.

4. Method development and validation

A summary of the method development and optimisation should be provided.

The most appropriate receptor medium for water soluble drugs is aqueous buffer. Hydro-alcoholic medium or indeed any other appropriate medium can be used in the case of drugs that are sparingly soluble in water, provided that it is justified. Testing conditions providing the most suitable discrimination should be selected. The composition of the receptor phase should not influence the permeation of drugs, should ensure sink conditions and should not alter the membrane.

The method should be suitably discriminating. The following should be considered:

- It is discriminating between batches with respect to critical manufacturing parameters that are known to have an impact on the bioavailability of the product.
- It is discriminating between products formulated at different concentrations, and altered formulations (e.g., drug content, permeation enhancer).
- The stability indicating power of the method should be assessed.

The analytical methods for determining the content of active substance in the receptor fluid and mass balance determinations should be provided and validated according to ICH Q2(R1).

The reference standards used during the validation and study sample analysis should be obtained from an authentic and traceable source.

The method validation should also address the variability of the method and the coefficient of variation established. For artificial membranes, the coefficient of variation should be less than 10%, for human skin a coefficient of variation greater than 10% can be accepted.

5. Data analysis

Data from all diffusion cells should be reported and the validity, variability and reproducibility of the results should be discussed. The results should be subject to an analysis of variance.

Outliers may be excluded from the statistical analysis, if satisfactorily explained and justified.

The plot of the cumulative amount of drug permeated per unit area (mass/cm^2) as function of time should be presented. The slope of the curve represents the permeation rate (flux) of the drug.

The permeation profile should be supported with tabulated data and statistical analysis. The permeation rate (flux) should be calculated for each diffusion cell and the mean flux reported together with the corresponding standard deviation (SD), coefficient of variation.

A discussion, interpretation and conclusions of the results of the experiment should be provided, supported, as necessary, by appropriate scientific rationale.

For the comparison of products, relevant permeation parameters, e.g., flux, should be statistically compared. The 90% confidence interval for the ratio of the two products should be determined and should be contained within the ratio of 0.8 to 1.25 to support a claim of equivalence, unless justified. The method should be based upon a null hypothesis of non equivalence.

6. Quality system and study report

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

This should include:

- A declaration of compliance with a suitable quality system, e.g., GMP (Directive 2003/94/EC);
- The technical ability of the performing laboratory and the validity of the method used should be assessed at regular intervals, at least twice per year, by using reference compounds like caffeine or benzoic acid. The recent results of such studies should be provided;
- The laboratory should be subject to external audit e.g., by the Marketing Authorisation Applicant or a suitable accreditation body; and
- Audits certificates, if available.