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4 Guideline on quality of transdermal patches

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7 This guideline together with the new Guideline on Quality of Oral Modified Release Products replaces
8 the Note for Guidance on Modified Release products: A: Oral dosage Forms B: Transdermal Dosage
9 Forms. Part I (Quality).

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

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Guideline on quality of transdermal patches

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Executive summary

This guideline addresses new marketing authorisations applications (including generic 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 Note for Guidance relating to clinical aspects of transdermal patches.

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

1. Introduction (background)

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

increasing the thermodynamic activity of the drug substance in formulation (e.g. by supersaturation)

chemical enhancement (e.g. solvents can act as a carrier of the active, skin penetration enhancers).

Permeation enhancement may also be achieved by physical technologies such as iontophoresis, ultrasound and electroporation.

A Transdermal Drug Delivery System (TDDS) or transdermal patch is defined as a flexible, multi-laminated, pharmaceutical preparation of varying size containing one or more drug 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.

Transdermal patches are designed to slowly deliver the drug 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 drug substance is usually the absorption through the skin. Absorption may also be limited by incorporating or dissolving the drug substance in a (semi solid) reservoir, with a membrane to control the release and the diffusion of the drug 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 drug substance permeation through the skin may be characterized by the *in vitro* release of the drug in a dissolution medium and by the *in vitro* permeation through human skin. The results of these two experiments 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 drug substance should be delivered at an adequate rate through the skin and should not irritate or sensitize the skin. The excipients should not have an adverse effect on the skin or exacerbate the adverse effects of the drug 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 drug 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 drug 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 drug 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 drug 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 subsequent variations. In addition, specific guidance is provided concerning the data requirements to support generic applications.

Cutaneous patches (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.

Annex 2 provides supplementary information with respect to *in vivo* skin adhesion studies.

3. Legal basis

This guideline should be read in conjunction with Directive 2001/82/EC, as amended and Directive 2001/83/EC, as amended and relevant Pharmacopoeial monographs and Notes for Guidance, 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;
- Process Validation CPMP/QWP/848/96 and Annex II: Process Validation - Non-Standard Processes CPMP/QWP/2054/03;
- 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.;
- Guideline on the details of the various categories of variations to the terms of marketing authorisations for medicinal products for human use and veterinary medicinal products Communication from the Commission (2010/C 17/01).

4. New applications

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

The product description should include the following:

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

- 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 – a smaller transdermal patch should be developed instead.

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

Excipients not described in a Pharmacopoeia should also be brand named.

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

The description is the achieved quality product profile. Some elements such as product strength, drug 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, which 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 drug 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 drug 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. Drug substance

Drug 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, pKa, solubility and pH effects, as well as solid state characteristics such as particle size and polymorphism.

The solution state and solubility of the drug substance in the drug product should be determined and discussed. When possible the thermodynamic activity of the drug substance should be determined.

The risks of precipitation / particle growth / change in crystal habit / changes in 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 adhesives, excipients, laminates, and rate control membrane in the drug product, 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 drug 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 reservoir type transdermal patch, the suitability and performance of the rate controlling membrane should be fully discussed.

The relevant characteristics of the laminates, 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).

Excipient mixes, e.g. adhesive solutions or suspensions should be identified and fully described.

Processing aids, including temporary laminates, 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 should be described with respect to critical quality attributes such as *in vitro* drug release, *in vitro* skin permeation, adhesion/cohesion and viscoelastic properties and those factors affecting ease of administration and duration of use. 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 drug substance in the formulation, stability, drug release and rate and extent of drug permeation.

When the formulation composition is decided, gradual up-scaling of the manufacturing process will start and the critical process parameters 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 most 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 needs to be described in detail. Any differences between clinical formulations and the formulation 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.

Information on placebo patches may be helpful in developing product understanding with respect to its adhesive properties and may support minor changes in adhesive composition.

In terms of quality in relation to efficacy:

The drug substance content, formulation, patch size and thickness should be justified by a sound rationale and *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, and 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 and viscoelastic 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 of skin damage following removal. Residue formation following release liner removal and following transdermal patch removal should also be addressed.

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 *in vitro* drug release, skin permeation and adhesion.

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

The stability programme should ensure that the drug product is subject to appropriate stressed and real time storage conditions (including consideration of 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 drug substance and / or excipient evaporation or migration, drug substance crystallisation or other change in its thermodynamic activity, changes in excipient habit. Changes in adhesion properties on under different storage conditions should be assessed.

The stability of the intermediate laminate 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 a drug 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 release and shelf life finished product specification.

The methods described in Ph Eur monograph for Transdermal Patches should be followed i.e. a dissolution test or a release test using a 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 is no impact on drug release / dissolution.

The *in vitro* drug release / dissolution profile of the drug substance from the drug product should be characterised and established from clinical batches for which satisfactory efficacy has been demonstrated and 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 drug substance critical quality attributes;
- 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 dissolved active ingredient and/or excipients on the dissolution conditions during the test period.

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

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.

More than 3 sampling times are recommended to give a sharper and more differentiated profile.

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 drug 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 drug substance released in mass units (mg or µg) per surface area. The quantity of drug substance may 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 drug 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 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.

In the case where the amount of drug substance released per surface area is specified, the permitted variability in release at any given time point should not exceed a total numerical difference of ± 10% of the cumulative amount of drug substance in mass units (mg or µg), unless a wider range is supported by bioequivalence or other clinical studies. e.g. if the expected amount released at a given time is 100µg, then the permitted limits would be 90-110µg.

If reporting limits as a % of total, and the total amount was 500µg, then in the above case, the limits would be 18% - 22%.

In the case where the quantity of drug substance released per surface area and time is specified, the permitted variability in release at any given time point should not exceed a total numerical difference of ± 10% of the mean set value, unless justified by bioequivalence or other clinical data.

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

4.2.6.2. In vitro skin permeation studies

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

In-vitro skin permeation studies should be principally used to direct and assess development and optimization 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 and viscoelastic properties of the transdermal patch. Although these tests may not model *in vivo* adhesion, they are critical quality attributes to be specified in the release and shelf life finished product specification.

Tests should address the removal of the release liner, the adhesion of the drug product to a suitable surface e.g. tack, and the removal of adhered drug product from a suitable surface e.g. peel adhesion and shear adhesion.

Residue formation following release liner removal and transdermal patch removal should be addressed and the anchorage / detachment of the formulation to the backing foil 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.

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

- critical manufacturing variables;
- excipient and/or drug substance critical quality attributes;
- stability indicating power of the method.

The *in vitro* adhesive properties of the drug product should thus be characterised, with the limits for the specified test established and qualified from 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.

A feasibility or pilot study should be considered to establish that the study methods and assessments can be carried out satisfactorily.

The assessment should be undertaken throughout the proposed period of use. This is because satisfactory adhesion performance of the clinical batches used would be a requirement for any clinical conclusions to be valid and to achieve a representative number of subjects (both volunteers and patients).

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

Advice on the conduct of such studies is given in Annex 2.

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, i.e., AUC0 - t(last), AUC0 - ∞, Cmax, 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 drug 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 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 to show that the batches used in all clinical studies are representative of the product to be marketed (including site, scale and date of manufacture and certificate of analysis).

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, at least 10% of full production scale and, unless pivotal clinical studies have been performed with batches of smaller size. In this case, bioavailability studies performed with batches of a smaller scale may be sufficient if these batches have been produced in a manner representative of the full scale manufacturing process.

4.2.7. Manufacturing process development

The steps in the process should be identified and their purpose described. Hold times should be stated and validated including any holding times for coating solutions.

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 the removal of residual solvents;
- Laminations steps;
- The storage and handling of intermediate rolls;
- Roll conversion to transdermal patches;
- 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).

4.2.8. Container closure system

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

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

The backing layer 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).

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

4.2.9. Administration

The SmPC and product information 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) should be discussed.

The Development Pharmaceutics package should include the data to support this information or else include cross reference to other parts of the dossier.

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;
- 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;
- 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;

- Transfer to others;
- 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;
- Special precautions for disposal of a used transdermal patch.

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 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.

In particular, the control of homogeneity and the thickness 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, laminates and liners

If the material(s) is new or has not been previously authorised or for transdermal use, then full quality details should be provided according to the drug 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, viscoelastic 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.

In general, at release a transdermal patch should show no signs of crystallization.

The occurrence of crystals throughout in a transdermal patch is unwanted but sometimes unavoidable since the drug in adhesive or reservoir is incorporated close to or even at its saturation limit.

Crystal formation is a visible quality deficiency which may not have an influence on the *in vivo* performance of the patch.

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 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 drug substance or reaction products of the drug 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 drug substance, the relative skin penetration of the impurities to that of the drug 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 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, and 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.

A comparable transdermal patch design with respect to the following should be considered:

- Patch type, with respect to the control of drug release (e.g. reservoir, drug in adhesive);

- Overlay (if applicable);
- Patch size, area and thickness for each strength.

5.2. Development pharmaceutics

The data requirements are as described under New Applications.

The studies undertaken during pharmaceutical development to optimize the *in vivo* release rate (mass delivered *in vivo*/unit area/unit time), drug 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 drug 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 drug substance in the drug product;
- *In vivo* release rate or strength per patch area (i.e. mass delivered *in vivo*/unit area/unit time);
- Drug substance utilisation (% of total drug substance absorbed per patient administration);
- Patch area activity (drug substance utilisation/patch area);
- Residual (mass of drug substance remaining in the drug product after completion of administration);
- Instructions for use, including the use of any overlay;

- Period of use.

With respect to *in vitro* performance:

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

For a generic 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 application, bioequivalence with the reference product should be demonstrated (see clinical guideline) and also non-inferiority with respect to *in vivo* skin adhesion (see Annex II).

Satisfactory clinical safety and local tolerance of the generic product should also be demonstrated.

6. Variations applications

The manufacturing process for transdermal patches is normally considered complex, in respect to current variation guidance.

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 drug substance;
- Change in the qualitative and/or quantitative composition of excipients.
- Change in the manufacturing process:
    - Change in a single Critical Process Parameter;
    - 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.

In addition, bioequivalence and *in vivo* skin adhesion equivalence studies should also be required, unless extensively 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 drug substance.

Definitions

Cold flow:

The viscoelastic properties of a pressure sensitive adhesive, used in transdermal patches, are a balance between adhesive properties that allows good adhesion to the skin and resistance to peel or detachment and cohesive properties that are necessary to avoid creep or cold flow of the adhesive beyond the patch boundaries.

In use, the appearance of adhesive surrounding a transdermal patch due to cold flow is readily apparent as a the formation of a dark ring about 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 drug substance released *in vivo* per time unit (preferably per hour)

Patch area activity:

Expressed in %/cm²; It is a measure of the formulation's intrinsic capability to release drug 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 drug substance necessary to achieve bioequivalence to the originator's product.

Example: transdermal patch dosage strength 25 µg/h, application time 72h, patch size 15cm2, overall amount of drug 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 surface.

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 drug 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 drug substance(s) and normally impermeable to water.

In reservoir systems, the drug 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.

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 drug 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 dispersion of the drug 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.

References

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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);

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

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;
- 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 a drug 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 drug 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 waved. 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.

The chosen *in vitro* skin model should be as similar as possible to the in-use conditions, to better reflect skin penetration *in vivo* in man.

It is recommended to use fresh human skin from breast or abdomen. 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, 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. After the experiment, an assessment of skin integrity should also be undertaken and reported, unless otherwise justified.

A variety of integrity tests is currently available, e.g. measurement of Transepidermal Water Loss (TEWL), monitoring the permeation of triturated 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 cm2. Diffusion cells should be inert, robust and easy to handle. It is also important that the diffusion cell is maintainable at a constant temperature (32oC), 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 ensure 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 submitted to demonstrate that sink conditions can be maintained throughout the experiment.

The drug 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 drug substance is not limited by the receptor medium. An acceptable sink condition is one where the maximum concentration of the drug substance in the receptor solution achieved during the experiment does not exceed 10% 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 drug 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 for drug substance content or by any other suitably validated analytical technique.

At the end of the experiment, the mass balance should be determined by determining the total content of drug substance in each of the compartments of the experiment i.e. the receptor compartment, that remaining in the donor compartment and that present in the skin layers.

Mass balance should be satisfactory for the experiment to be valid.

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 validated;
- The preparation and treatment (thickness, separation) of the skin should be described and justified.

The integrity of the skin should be determined before and after 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, under unoccluded conditions, to mimic *in vivo* conditions.

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 drug 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 diffusion cell is maintainable at a constant temperature close to the physiological human skin temperature (32°C±1°C);
- Humidity – 30-70%;
- Human skin integrity should be tested at the beginning of the experiment;
- The suitability of integrity test e.g. (TEWL), permeation of triturated water or electrical resistance and criteria for acceptance should be fully discussed;
- The integrity of the skin at the end of experiment should also be assessed and discussed;
- Number of replicates – The choice of the number of samples should be explained and demonstrated to be statistically significant;
- Number of skin donors – at least 2 different donors;

- Skin anatomical region – abdominal, breast or back;
- The number of time points should be sufficient to satisfactory characterise the permeation profile. Minimum of 5 receptor sampling time points and an early time point, e.g., 15 or 30 min;
- Study duration - the duration of the exposure should be justified in regards to the in-use administration. Nevertheless, it should not exceed 24 hours since skin integrity is likely to deteriorate after 24 hours. Longer periods should be justified in respect to *in vivo* use and satisfactory data to show that the integrity of the skin has not been compromised should be provided.
- Unoccluded conditions
    - The mass balance should be determined. The overall recovery of the drug substance of 90 -110% would be acceptable without justification, larger variation should be fully justified and explained.

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 drug 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/cm2) 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.

Mass balance and drug substance distribution in the various compartments (receptor solution, membrane, residual product remaining in the patch) should be reported and discussed.

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 interval of 80 - 125% to support a claim of equivalence, unless justified.

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 place1.

This should include:

- A declaration of compliance with the principles of Good Laboratory Practice1;
- 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;
- Audits certificates, if available, should be included in the report.

The study report should give the complete documentation of the experimental protocol, including skin and sample preparation, study design and conditions, method development and validation, data analysis and evaluation, together with quality system evidence and signed by the investigator.

Names and affiliations of the responsible investigator(s), the site of the study and the period of its execution should be stated.

Further information on quality systems and Principles of Good Laboratory Practice is given in the following:

- DIRECTIVE 2004/10/EC on the harmonisation of laws, regulations and administrative provisions relating to the application of the principles of good laboratory practice and the verification of their applications for tests on chemical substances
- The Rules Governing Medicinal Products in the European Union Volume 4 EU Guidelines to Good Manufacturing Practice Medicinal Products for Human and Veterinary Use Part I Chapter 6 Quality Control
- ICH Q10 “Pharmaceutical Quality Systems”.

Annex 2

In vivo skin adhesion

The investigation of *in vivo* adhesive performance may be included as a component part of human clinical pharmacokinetic and efficacy studies (both single dose and multi dose), or may be an independent study with either patients or volunteers.

For transdermal patches covering a range of different dosage strengths, as a minimum, the smallest and the largest patch sizes should be tested *in vivo*. For transdermal patches covering a range of different dosage strengths the smallest and the biggest patch sizes should be tested *in vivo*.

The elements of assessment should include:

- The sites of application;
- Transdermal patch application;
- Residue formation on release l liner removal and on transdermal patch removal;
- The percentage transdermal patch area adherence to the skin;
- Cold flow, such as the formation of a dark ring about the transdermal patch during use, patch movement or displacement, wrinkling;
- The robustness of the product to normal human behaviours e.g. moisture resistance to washing, showering, saunas, use of moisturisers, risk of removal during exercise and or sleeping, possible transfer to partners or family.

The results of the study should inform the SmPC and PI. See also section 4.2.9.

The transdermal patch should be used as proposed. Patch reinforcement such as over-taping is not allowed.

A satisfactory protocol, with justified visual or other scales of measurement should be provided.

The frequency of assessment should be stated and justified, and should include transdermal patch administration and removal time points.

Satisfactory and unsatisfactory performance should also be supported by photographs.

For the determination of the percentage transdermal patch area adherence, the following is recommended:

- The frequency of assessment should be more than daily;
- May be supported by analysis of photographs, to show validity of the method.

The scores for adhesion of transdermal patches should be scaled in 5 % increments as indicated below:

- more than 95 % of the patch area adheres;
- more than 90 % of the patch area adheres;
- more than 85 % of the patch area adheres ;
- more than 80 % of the patch area adheres ;
- more than 75 % of the patch area adheres ;

- more than 70 % of the patch area adheres.
- less than 70 % adheres or patch detachment is regarded as significant patch adhesion failure.

For patches that completely detach during the study the score should be carried forward in the adhesion analysis for all remaining observations in the application period.

In general, a mean adherence of greater than 90% should be expected and no instances of detachment should be seen. Poor adherence events should be investigated and possible causes and risk factors determined.

The results should be reported in explanatory tabular and graphical formats, including:

a. frequency table showing the number of patches with each adhesion score at each evaluation time point.

b. number of patches that are completely detached at each evaluation time

A critical assessment and statistical analysis should be provided.

For the other *in vivo* assessment elements as indicated above, similar reports, critical assessment and statistical analysis should be provided, as appropriate.