EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

23 October 2014
EMA/CHMP/QWP/608923/2014
Committee for Medicinal Products for Human Use (CHMP)

Overview of comments received on 'Guideline on quality of transdermal patches' (EMA/CHMP/QWP/911254/2011)

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

Stakeholder no.	Name of organisation or individual
1	3M Drug Delivery Systems, 3M Health Care
2	Association of Clinical Research Professionals (ACRP)
3	AESGP
4	AMW GmbH, Dr. Wilfried Fischer
5	European Generic medicines Association (EGA)
6	Eli Lilly and Company
7	IFAPP (International Federation of Associations of Pharmaceutical Physicians)
8	Hexal AG
9	JnJ
10	LTS Lohmann Therapie-Systeme AG
11	Dr. Michael Horstmann, Neuwied, Germany
12	Merck Sharp & Dohme (MSD)
13	Andre Haeusermann, Novartis Group Quality – Quality Systems ad Standards
14	PIERRE FABRE MEDICAMENT - France
15	Paul Lehman, M.Sc. and Sam Raney, Ph.D. (PRACS Institute, Fargo, North Dakota, U.S.A.)
16	Dr. Steven W. Sanders, Pharm.D.
17	Skin Forum
18	UCB BioSciences GmbH
19	Medicines Evaluation Board, Netherlands

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1. General comments – overview

Stakeholder no.	General comment (if any)	Outcome (if applicable)
1	3M Drug Delivery Systems is a leading global supplier of transdermal components for use in pharmaceutical products, manufacturing a wide variety of backings, release liners, overlays and rate-controlling membranes for use in finished transdermal products. Currently, a majority of transdermal pharmaceutical products contain at least one component manufactured by 3M Drug Delivery Systems. In today's global economy, most customers opt to market their pharmaceutical product in multiple countries; as such it is imperative that global regulations be aligned, with similar regulations applying to a material regardless of country. In the case of transdermal components, these materials have long been considered to be parts of the container closure system for the drug product and not excipients. This view has historically been held by the U.S. Food and Drug Administration (FDA) Center for Drug Evaluation and Research (CDER), Health Canada and the European Medicines Agency (EMA), based on published guidances, regulatory experience and multiple product approvals. In the FDA CDER guidance document published in May 1999, "Container Closure Systems for Packaging Human Drugs and Biologics", the FDA specifically states the following: "Drug delivery refers to the ability of the packaging system to deliver the dosage form in the amount or at the rate described in the package insert. Some examples of a packaging system for which drug delivery	This is acknowledged. This is not accepted. See specific comments below.

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	aspects are relevant are... a transdermal patch...” (section III.B.1.d.ii). In the same guidance document (section III.F), the FDA states that “the presence of a liquid phase implies a significant potential for the transfer of materials from a packaging component into the dosage form. The higher viscosity of semisolid dosage forms and transdermal systems may cause the rate of migration of leachable substances into these dosage forms to be slower than for aqueous solutions”. Finally, in section III.A of the guidance document, Table 1 outlines examples of packaging concerns for common classes of drug products. This table specifies that there is a high likelihood of packaging component – dosage form interaction for transdermal patches. In each of these statements, the FDA is clearly referring to the backing and the release liner as packaging components of the transdermal patch. Furthermore, for the past 35+ years, the FDA has accepted and reviewed Type III Packaging Material Drug Master Files describing the manufacture of transdermal components in support of IND, NDA and ANDA submissions. It is clear that the U.S. FDA has a long-standing position of considering transdermal backings and release liners to be components of the container closure system. Health Canada also has a 20+ year history of accepting and reviewing Type II Packaging Material Drug Master Files for transdermal components. The EMA guidance document CPMP/QWP/4359/03, “Guideline on Plastic Immediate Packaging Materials”, effective December 2005, also indicates that transdermal backings and release liners are considered packaging materials. In section 4 of the guidance	

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	document, it is stated: “The aim of extraction studies is to determine those additives of the material that might be extracted by the preparation or the active substance in contact with the material. Extraction studies are considered to be necessary for plastic material used for container closure systems of non-solid active substances and non-solid dosage forms for oral and topical use... The studies typically involve exposing a sample of the material to an appropriate solvent system under stress conditions to increase the rate of extraction... the preferred solvent would be the medicinal product or placebo vehicle”. As with the FDA guidance document, it is clear that the EMA is referring to the transdermal patch backing and release liner as plastic immediate packaging materials. As such, 3M Drug Delivery Systems suggests that the definition of transdermal components (backings, release liners, overlays and rate-controlling membranes) as parts of the container closure system be accepted and integrated globally in order to facilitate and simplify the registration and approval of new transdermal products worldwide. This is in contradiction to the draft EMA guidance document, “Guideline on quality of transdermal patches”, currently being considered, which states that the transdermal backing should not be considered part of the container closure system (see below for details). Classification of these materials as excipients represents a paradigm shift that will significantly impact product development, including potential new testing requirements and ultimately the cost of these products. 3M Drug Delivery System requests that the EMA amend this position to include transdermal backings, along with release liners, overlays and	

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	rate-controlling membranes, as plastic immediate packaging materials. 3M Drug Delivery Systems further suggests that the EMA establish clear definitions of excipients and packaging components for transdermal drug products and their associated requirements.	
2	We appreciate the opportunity to comment on this revised draft Guideline on the quality of transdermal patches. The guideline states that it is for new applications. However consideration should be given to well-established transdermal patch products that have been in use for many years – some over 20 years. It would therefore be more appropriate for this guideline to be for new transdermal patch products rather than for new applications of these well-established products in new markets.	It is hoped that the scope of the guideline is clear – the guideline applies to new applications for both novel and existing drug substances.
3	We appreciate the opportunity to comment on this revised draft Guideline on the quality of transdermal patches. We consider this guideline extremely useful as it correlates well the various parameters linked to the formulation, the development, manufacture, control and stability of patches with respect to their impact of efficacy and safety. The guideline states that it is for new applications. However consideration should be given to well-established transdermal patch products that have been in use for many years – some over 20 years. It would therefore be more appropriate for this guideline to be for new transdermal patch products rather than for new applications of these well-established products in new markets.	See above.

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	This guideline is complex as it includes a lot of parameters to be assessed during the development of transdermal delivery systems, some of these parameters being linked to non-clinical and clinical evaluations.	
	It is our opinion it would have been easier for the reading to present the guideline in a similar way as the one on excipients (CHMP/QWP/296951/06) to bring more clarity on what has to be introduced in each relevant part of the dossier.	The guideline reflects the CTD format.
	In addition some information such as the ones for administration, SmPC should not be part of the guideline which should remain focused on the quality aspect.	This is not accepted. The ability of the product to be administered and used satisfactorily is considered to be within the scope of the quality dossier.
	Amount of residual drug substance - While it is desirable to minimise the amount of residual drug substance in the patch, this should be consistent with the mode of delivery.	
	The naming of excipients not described in a Pharmacopoeia – it would be more appropriate to define the critical functional characteristics relevant to the medicinal product performance in the (registered) specification rather than registering the Brand name from a specific supplier.	See discussion below.
	Methods for testing transdermal patches – Whilst the methods described in Ph. Eur. monograph should be generally followed, the use of another internationally accepted pharmacopoeial monograph, e.g. USP for Transdermal Patches, should be also be acceptable, where such methods do not exist in the Ph. Eur.	The possibility of using other techniques is not precluded. A better definition has been given.

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	The guideline should define precisely the size of a pilot batch, giving more information of the minimal batch size valid for development and stability in the submission dossier. Release and shelf life limits should be the same specifications – The concept of different acceptance criteria for release versus shelf-life specifications, where justified, is well established in Europe. Bioequivalence and *in vivo* skin adhesion equivalence studies – The use of *in vitro in vivo* studies can be justified and should be considered as suitable alternatives.	This issue relates particularly to performance tests.
3	Limits of in vitro drug release should be aligned with those for modified release oral dosage forms as far as possible.	This is accepted.
3	TTS-Manufacture as non-standard process (Line 489/490) is not necessarily a non-standard process for manufacturers with sound experience.	This is accepted.
3	Annex II (line 872 ff): The topics between quality aspects of TDDS (to be discussed in the present guideline) and safety aspects (to be discussed in the clinical guideline to be published) cannot easily be differentiated. EMA is requested to place the detailed guidance on clinical performance in the clinical guideline, where we feel it might be more appropriately discussed.	Annex II has been transferred to the clinical guideline.
3	Please hyperlink all guidance documents.	

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4	The author explicitly appreciates the well compiled and science-based draft guideline. Nevertheless, there is room for discussion from the view of a formulation scientist.	
5	The European Generic medicines Association (EGA) welcomes the opportunity to comment on the draft EMA guideline on the quality of transdermal patches.	
7	The guideline is well written, with several examples and suggestions: we have no comments and we consider it a good guideline.	
8	The guideline doesn't state any transitional rule. It is proposed that a transitional rule should be in place. The requirements of the guideline should be effective for Marketing Authorization applications submitted after the final guideline is in force. For Repeat Use Procedures (RUPs) the guidelines effective at the time of initial submission should remain valid. Requirements regarding in vivo adhesion studies and the corresponding study design should only be valid for studies which start after the effective date of the final guideline.	The guideline reflects current regulatory science, so a transition period may not be appropriate. Exceptions may be considered on a case by case basis.
10	Limits of in vitro drug release should be aligned with those for modified release oral dosage forms.	See above.
10	TTS-Manufacture as non-standard process (Line 489/490) is not necessarily a non-standard process for manufacturers with sound experience.	See above.
10	Annex II (line 872 ff): The topics between quality aspects of TDDS (to be discussed in the present guideline) and safety aspects (to be discussed in the clinical	See above.

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	guideline to be published) cannot easily be differentiated. EMA is requested to place the detailed guidance on clinical performance in the clinical guideline, where we feel it might be more appropriately discussed.	
10	Please hyperlink all guidance documents	
12	It is not expected that the in vitro drug release / dissolution correlates to the in vivo drug delivery especially when permeation enhancers are used in the formulation. The guidance should include language on the requirement levels once an appropriate correlation between in vitro and in vivo are established in clinical trials. If a correlation can be established, reduced in vivo studies may be applicable in later trials.	It is acknowledged that in vitro performance and in vivo PK are linked but not readily correlated. This may be possible on a case by case basis.
13	The draft presents in-depth data requirements for the development of transdermals, which in general are seen as appropriate and helpful. However although not strictly laid out under CTD headers, the implication is that the outlined data are expected under the Module 3 dossier sections stated in the guideline sub-headings. This raises a number of issues. Of particular concern is the extensive information newly listed under “Description and Composition”, implying that all the data outlined are expected to be provided in P1 of the dossier. This is in excess of the data expectations for P1 outlined in CTD and other established guidelines, much of the information belonging elsewhere in the dossier, e.g. under pharmaceutical development (P2).	The detail is considered necessary to fully describe what the transdermal patch is. P1 is considered a good place for this.

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	Duplication into P1 is not of value. More importantly, in light of the designation of P1 as a “Can Be Released” document under the new EU transparency paradigm, the proposed approach is unacceptable, as much of the information is commercially confidential (contrary to the suggestion under section 4.1, not all of the detail outlined appears in the labelling) and there is no guarantee that Health Authority redaction prior to release will address all confidential aspects. P1 should be restricted to the data requirements of CTD, i.e. a description of the dosage form in terms related to its galenic form and appearance and the delivered dose, composition table(s) with function and standards of components where there is an expectation that redaction will be performed prior to public release such that only qualitative composition remains, and a brief description of the container/closure (i.e. primary pack). Of secondary concern is listing of data in sections of the dossier where this is not in agreement with established CTD expectations. In a few instances this involves clinical aspects which would normally not be found in Module 3. Mostly it is transposition between different sites within Mod. 3. Either more attention needs to be given to precision on siting, or the guidance should take a clear position that the headers used are chosen only to focus guidance on the topic under discussion and are not intended to imply inclusion under the corresponding header in the dossier, advising that data should be presented in the regulatory	P1 provides the full qualitative and quantitative composition – it is understood that this remains confidential. The guideline reflects what quality aspects should be discussed in M3.

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	application in accordance with established CTD guidances. The latter would be the preferred strategy, in order to maintain the cohesion of the guidance. Many of the "data siting" comments in the line listings would not apply if such a strategy were followed. Some, however, such as those on content of the P1 document Description and Composition, would remain relevant as the text here too clearly implies inclusion in this document.	
13	Annex 1 is a valuable, in-depth guidance on expectations for performance of *in vitro* permeation studies and for content of study reports. A clear differentiation is however needed between what is expected to be considered in the development, performance and raw-data reporting of studies, and what is expected to be documented and submitted in the regulatory dossier (and for the latter, where and in what format). P2 would normally summarise the methodology and results of such studies where they contributed to product development; is it expected that full study reports are annexed?	The dossier should include sufficient information to allow critical appraisal. Summary information may be sufficient.
13	Annex 2 adresses *in vivo* adhesion studies. Here too it should be made clear what is expected where in the dossier – presumably the study reports (free-standing or incorporated into pharmacokinetic or efficacy studies) in Mod. 5, discussion of relevant results in P2 of Mod 3?	Annex 2 has been transferred to the clinical guideline.
15	The draft Guideline is clearly well-considered. Some clarification may be provided regarding the applicability of the Guideline specifications on *in vitro* skin permeation testing to studies conducted early in development, where the experimental procedures may not yet have been validated, and the numbers of donors or replicates may not be consistent with the Guidance.	

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	Clarification may be of value regarding the requirements for inclusion in the registration package of any *in vitro* release or permeation tests performed during development that may not have complied with the Guidance recommendations.	Non-compliance should be explained and justified.
17	Skin Forum is very pleased to be allowed to comment on the draft EMEA guidelines. The Skin Forum committee draws on expertise from the academic and industrial sectors and all the comments raised by committee are herewith listed. It may be useful to refer to OECD test Guideline 428 and Guidance Document 28 and SCCS guidelines as all of these items are already discussed and are working in practice for GLP work; there are noted claims of GLP compliance required in Line 850.	The guideline includes relevant references.
18	The executive summary states that this guideline addresses new marketing authorisation applications (including generic applications) and subsequent variation submissions for transdermal patches for systemic delivery. In paragraph 4 NEW APPLICATIONS it is specified that the data requirements are relevant to new applications for the first use of the drug substance…..and new generic applications. To our understanding this excludes variations to currently approved transdermal patches from the scope of this guideline. However, it should be clarified whether line extensions of a marketing authorisation are as well exempt from the scope of this guideline.	A line extension should be considered a new application.
19	Setting up a stand alone guideline for quality of transdermal patches is highly appreciated. The guideline is clearly organized with separate subsections on new, generic, and variation applications.	

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	Compared with the existing guideline the (quality) criteria for transdermal patches and their implications for in vivo release, efficacy, safety & effective use of the product are more thoroughly founded. Main new development & control testing aspects discussed are: 1. Bridging data to be presented in the Pharmaceutical Development part of the Module 3: In-vitro release/In-vitro permeation/In-vivo release. 2. Patch load vs. drug released & implications for safety. 3. Skin adhesion. 4. Patch size and its implications in skin adhesion. 5. Validation of the manufacturing process. 6. Dissolution methods and in vivo/in vitro correlation. 7. Additional release and shelf life specification testing parameters compared to the existing guideline: Cold flow, crystallisation, peel force, adhesion force. 8. For generic transdermal patches: patch area activity (% release/cm²). Several of these topics are (partially)clinical(/PK) and/or non-clinical areas; see e.g. the underlined texts at points 1-8 above: in-vitro permeation studies=non-clinical, in vivo skin adhesion tests=clinical, etc. This is confusing as the guideline is currently presented as quality guideline issued by the QWP. (Non-)clinical assessors will not be aware of this guidance unless clear cross-references to the current guideline are included in the clinical counterpart guideline or the	It should be acknowledged that some scientific areas are not exclusively either quality, non-clinical or clinical.

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	current guideline is classified as miscellaneous guideline and relevant (non-)clinical working parties are involved in the current guideline. It should be more clearly indicated in the current guideline which (non-)clinical aspects should be included in module 3 for information only (e.g. lines 189-195, section 4.2.6.2 and Annex 1 on in vitro skin permeation studies, section 4.2.6.3.2 and Annex 2 on in vivo adhesion studies, section 4.2.6.4 on pharmacokinetic studies, and section 5.3.2 on clinical aspect of generic applications) and that they will be assessed by (non-)clinical assessors. Apart from this general comment, some specific comments are made on the guideline text which may be considered by the drafting group.	

2. Specific comments on text

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
100-101	1	Comment: Patch design and materials of construction can also differ, yet result in equivalent drug delivery. Proposed change (if any): It is acknowledged that transdermal patches can differ in patch design, materials of construction, drug content and surface area but still deliver the same amount of drug over the same period of time.	Not accepted. The first sentence in line 100 is linked to the second one in line 101 both relating to minimising the amount of residual drug substance. Differences in drug content in relation to the surface area are because of patch design and materials of construction.
173	1	Comment: Some excipients may not have a brand name (and may not be listed in the pharmacopoeia).	Partly accepted. It is considered necessary to ensure suitable naming of non Ph excipients. Proposed change: *"The name 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."*
67-70	2	Comment: We suggest rephrasing this section and to delete "chemical", as the first example provided, supersaturation, is not strictly a "chemical" permeation enhancement. Furthermore we suggest adding bullet points.	Partly accepted. *"Otherwise, this may be achieved by permeation enhancement, which involves the manipulation of the formulation by either:* • *Increasing the thermodynamic activity of the drug substance in formulation (e.g. by super-saturation)* • *Passive penetration enhancement (e.g.*

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		Proposed change (if any): Otherwise, this may be achieved by permeation enhancement, which involves the design of the formulation by either: increasing the thermodynamic activity of the drug substance in formulation (e.g. by supersaturation) addition of solvents as e.g. carrier/solubilizer for the active pharmaceutical ingredient or skin penetration enhancers	*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, iontophoresis, sonsphoresis and microdermabrasion, which could be characterised as active enhancement strategies."* Rational: Passive penetration enhancement includes "chemical" enhancement as well. Rational: Microporation can be achieved by several technologies including microneedles, thermal ablation, radio-frequency ablation, or laser ablation.
73	2	Comment: We suggest aligning the definition with that of Ph.Eur. general chapter 1011, Transdermal Patches	Partly accepted. We have tried to align definitions.
84-87	2	Comment: In our view *in vitro* release is a tool for quality control, observing batch to batch variability, but there is no correlation to *in vivo* performance, as may be implied by the wording proposed. Proposed change (if any): The degree to which formulation and product design may influence drug substance permeation through the skin may be	Partly accepted. We agree with the comment that "in vitro" release is a tool for quality control. In addition in vitro permeation through skin on its own is a quality control tool, as well. The text is changed to: *"The degree to which formulation and product design may influence drug substance permeation through the*

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		characterized by the *in vitro* permeation through skin. *In vitro* release may serve as a quality control tool to control batch to batch variability.	*skin may be characterized 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."*
105	2	Comment: Please clarify the scope: New Applications and Variations of these products or New Applications and Variations of all currently marketed TDDS products? The latter would contradict line 139	The guideline is intended to provide advice for new applications and variations of authorised products. 'Subsequent' has been deleted from the sentence.
120	2	Comment: Please update reference, as new draft guideline on process validation has been published.	Accepted.
148-149	2	Comment: Please change order of lines 148 and 149, as 148 is more closely related to 150.	Accepted.
161-163	2	Comment: The wording suggested by EMA implies that the agency considers a laminate to be an excipient. Proposed change (if any): The composition of each laminate, including the function and grade of excipients, where grade has been identified during pharmaceutical development as a critical quality attribute for transdermal delivery, should be described.	Not accepted. The EMA defines the laminate as an excipient, as for historical reasons. Nevertheless, the use of the term "laminate" should be avoided and "layer" should be used instead. Anyhow, "to laminate" can be used to describe the manufacturing of a layer. "● *The form and function of each layer of the laminated product;"*

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			"● 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;"
169-170	2	Comment: Cutting (punching) of individual patches out of laminates is integral part of TDDS manufacturing. Proposed change (if any): Transdermal patch design should avoid cutting by patients or health care professionals - a smaller transdermal patch should be developed instead.	Accepted.
173	2	Comment: In many cases, a brand name refers to a broad range of products from a single supplier. The excipient should be well characterised and effectively controlled. The guideline should focus on the need to determine the critical functional characteristics of each excipient, and demonstrate that those critical factors do not negatively impact that functionality. There is no reason why an equivalent excipient from a different supplier with a different brand name should not be used as an alternative where it meets the currently approved specification. This is particularly important when companies merge or are taken over resulting in brand name changes. Likewise if for supply reasons an alternative supplier is sourced a variation should not be submitted for an equivalent material.	Partly accepted. See above.

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		Proposed change (if any): Excipients not described in a Pharmacopoeia should also be described with exemplary brand names.	
58	3	Comment: “Note for guidance” – please add reference to this guidance document in section 3, “legal basis”.	Accepted.
63ff	3	Comment: The paragraph ‘Introduction’ should refer to the definitions as per Ph. Eur. on “Transdermal patches” and “Medicated plasters”.	Previously addressed. See above.
67-68	3	Comment: Adapt terminology, as supersaturation is not strictly a "chemical" permeation enhancement; replace “manipulation” with “design”. Proposed change (if any): 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 permeation enhancement, which involves the design of the formulation by either:…	Previously addressed. See above.
69-70	3	Comment: Please change format and add bullet points.	Accepted.

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73	3	Comment: Please align this definition with that of Ph.Eur. general chapter 1011, Transdermal Patches.	Previously addressed. See above.
84-87	3	Comment: In vitro release is a tool for quality control, observing batch to batch variability, but there is no correlation to in vivo performance, as may be implied by the wording proposed by EMA. We kindly request to rephrase as proposed below. Proposed change (if any): The degree to which formulation and product design may influence drug substance permeation through the skin may be characterized by the in vitro permeation through skin. In contrast, in vitro release may serve as a quality control tool to control batch to batch variability.	Previously addressed. See above.
95-96	3	Comment: Consistency of argumentation can be increased: Replace “is” with “may be”. Proposed change (if any): Because the concentration of the drug substance can be near to its saturation limit, there may be a risk of crystallisation on storage…	Not accepted. The use of “risk” already defines a broad range.
	3	Comment:	The comment is acknowledged. In general the

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		Risks linked to overages of active substances are listed: does it means that these risks need to be assessed during the development of the product and discussed in the dossier: e.g. discussion on all development steps to justify the minimum amount of drug added to minimize the residual quantity.	introduction is used to provide general information – also about transdermal patch characteristics. Nevertheless, the discussion about the amount of the drug added to minimize the residual quantity should be given in section 3.2.P.2 of the dossier. Revision of the text is not considered necessary.
100-102	3	Comment: Transdermal products should be formulated in agreement with good pharmaceutical development practice, which aims to include only functional ingredients in the formulation, at the minimum effective concentration. In a passive diffusion type transdermal patch, the concentration of drug substance must be suitably high to maintain a differential osmotic gradient to adequately deliver the drug substance over the intended duration of administration. This is especially important in the case of a zero-order release transdermal product. Labelling requirements should ensure that the patch is safely disposed of. Proposed change (if any): It is desirable to minimise the amount of residual drug substance in the patch as much as possible, consistent with mode of delivery.	Not accepted. Consistency of mode of delivery is a prerequisite for marketing authorisation of transdermal patches. Nevertheless, also the authorisation of transdermal patches, emphasis should be put on the minimisation of residual drug substance after use, especially for generic drug products.

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105	3	Comment: The scope is not clear: Please confirm that “variations” only refers to variations to new applications. Please add "...thereof" at end of sentence in line 105. Proposed change (if any): … for all new marketing authorisation applications and subsequent variations thereof.	Previously addressed. See above.
108	3	Comment: Cutaneous patches are mentioned for local action, but it should be clarified how patches for a regional action (meaning absorption through the skin and then migration of the active substance in the subjacent tissues, or in a joint) are classified.	Not accepted. Currently, “patches for regional use” is not a recognised term and may be considered transdermal.
115	3	Comment: Please add reference to guideline on clinical aspects of TDDS (currently CPMP/EWP/280/96/ Corr*), cf. comment on line 58.	Previously addressed. See above.
120	3	Comment: Please update reference to Process Validation guideline.	Previously addressed. See above.
148	3	Comment: What is the pertinence of mentioning the amount of drug delivered by hour? It should be preferable to mention the dose delivered	Accepted.

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		during the expected whole duration of the application of the patch (e.g. per 24 hours).	
148-149	3	Comment: Please change order of lines 148 and 149, as 148 is more closely related to 150. The same holds true for lines 581 and 582.	Accepted.
149	3	Comment: The location of drug substance in the drug product: does it refer to the type of patch (reservoir, adhesive matrix)? If so, this is redundant with the description of the patch type at line 159.	Not accepted. Text is considered to be clear.
151-152	3	Comment: Are the “Drug substance utilization” and the “patch area activity” information to be part of this description as per Section 3.2.P.1?	Yes. P1 should be the place where a full description of the product is described. It does not imply that such information should be included in the SmPC.
153	3	Comment: It should be clarified if the title of this chapter refers to Module 3.2.P.1. If so, we consider that the information to be part of the SmPC and labels should not be mentioned in this section. This Section contains a lot of requested information that should be pertinent in Module 3.2.P.2 to justify the development of the transdermal system.	Previously addressed. See above.
153-155	3	Comment:	Previously addressed. See above.

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		It is our understanding that this information is preferably for the SmPC.	
161-162	3	Comment: The wording suggested by EMA implies that the agency considers a laminate to be an excipient. “Laminates” may also refer to the coated intermediate products. Proposed change (if any): The composition of each laminate, including the function and grade of excipients, where grade has been identified during pharmaceutical development as a critical quality attribute for transdermal delivery, should be described.	Previously addressed. See above.
169	3	Comment: Cutting (punching) of individual patches out of laminates is integral part of TDDS manufacturing. Therefore, we kindly request to rephrase as suggested below. Proposed change (if any): Transdermal patch design should avoid cutting by patients or health care professionals.	Accepted.
171-172	3	Comment: Please rephrase. Proposed change (if any):	Accepted.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		However, in exceptional cases for good patient safety and efficacy reasons, cutting might be necessary. Then this should be described and supportive data given in 3.2.P.2 as well as in the clinical dossier.	
173	3	Comment: In many cases, a brand name refers to a broad range of products from a single supplier. The excipient should be well characterised and effectively controlled. The guideline should focus on the need to determine the critical functional characteristics of each excipient, and demonstrate that those critical factors do not negatively impact that functionality. There is no reason why an equivalent excipient from a different supplier with a different brand name should not be used as an alternative where it meets the currently approved specification. This is particularly important when companies merge or are taken over resulting in brand name changes. Likewise if for supply reasons an alternative supplier is sourced a variation should not be submitted for an equivalent material. Proposed change (if any): For excipients not described in a Pharmacopoeia it may be necessary to define the critical functional characteristics relevant to the medicinal product performance in the specification through registering an appropriate specification for the excipient.	Previously addressed. See above.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
174	3	Comment 1: While it is appreciated that details of the primary pack e.g. specification of the primary pack be detailed in the application the equivalent level of detail for the secondary packaging is not required unless it is a stability requirement. Proposed change (if any): The primary packaging should be described and, if necessary, any other materials or components or secondary packaging required for reasons of stability. Comment 2: Providing description of secondary packaging is not in line with NtA for presentation and content of the dossier. Provided it has no impact on the quality and stability of the drug product, what is the purpose of adding this type of information?	Accepted.
156	4	Comment: what is meant: Period of use of one patch or period of use of the product?	Acknowledged. Text amended to: Patch period of use.
160	4	Comment: … of the product laminates. In general, several films and layers build up one laminate, from which the patches are cut. Proposed change (if any): … of the product layers (films, matrices)	Previously addressed. See above.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
167, 168	4	Comment: this requirement is unclear. Should it be shapes or application aids, flexibility etc.?	Not accepted. The text is considered adequately clear. Patch design should address patient administration.
173	4	Comment: manufacturer of adhesives sometimes change brand names, keeping the composition and specifications. Is change of brand name a variation?	It is not possible to be definitive. A variation may be required, on a case by case basis, depending on the use of the name in the dossier.
73-76	5	Comment: The proposed definition for transdermal patches slightly differs from that provided by Ph. Eur. Proposed change (if any): We recommend aligning the EMA definition on that already present in the European Pharmacopoeia.	Previously addressed. See above.
86	5	Comment : Characterisation of in vitro skin permeation performance may also be carried out using alternative skin models derived from animals. These skin models (e.g. excised hairless model, porcine ear skin, reconstructed human skin tissue) are widely described and well accepted in scientific literature. Therefore, depending on the specific question or requirement, the use of alternative skin model shall be justified. Proposed change (if any):	Previously addressed. See above.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		The final wording of the guideline should clearly reflect the possibility of using alternative skin models.	
152 (see also 585 & 635-645)	5	Comment : The proposed definition for Patch area activity does not appear to provide any relevant information. Proposed change (if any): Please refer to comment for line 635-645 and proposal to amend the definition.	Not accepted. The term is considered to be of value in the characterisation of the patch.
160	5	Comment : The term 'laminate' usually refers to a multi-layered composition. It therefore appears to be more adequate to use the term layer within this context. Proposed change (if any): 1) Amend line 160 as follows "The form and function of each of the product **layers**" 2) Define the terms "laminate" and "layer" under section Definitions, if both terms are to be used within the scope of this guideline	Previously addressed. See above.
165 (See also 260/433/492)	5	Comment : Patch size, area and thickness are mentioned to be determined. It is pointed out that area weight which may be considered to correlate with thickness can be determined more precisely. Proposed change (if any): Amend line 165 as follows: "Patch size, **thickness and/or area weight**	Partly accepted but patch thickness is considered a CQA. Text changed to: *"Patch size, area and thickness (area weight may be considered if justified)."*

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		”	
173	5	Comment : The guideline requests that non-pharmacopoeial excipients are described with brand name. This is neither a relevant nor justified requirement provided all relevant quality attributes of the excipient that may influence the drug product quality are evaluated and specified. The reference to brand names appears superfluous. Proposed change (if any): Please delete line 173: “~~**Excipients not described in a Pharmacopeia should also be brand named**~~.”	Previously addressed. See above.
174-175	5	Comment : During transdermal patch development the secondary packaging is usually not specifically defined unless it exerts a barrier function to protect the drug product, in addition to primary container. Proposed change (if any): Please amend lines 174-175 as follows: “The primary and secondary packaging **(e.g., when exerting a barrier function) as well as any other materials or components required should be described, where relevant, for reasons of stability.**	Previously addressed. See above.
140	8	**Comment:** Please provide a definition/specification for “**new**	The wording is clear. No amendment to the text is necessary.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		generic applications".	
Line 78	9	Proposed change (if any): change from "The rate limiting step for…" to "For non-rate limiting transdermals (low degree of system control), the rate limiting step for…"	Partly accepted. The text is amended to: *"The rate limiting step for systemic absorption of the drug substance is usually the absorption through the skin. Alternatively, absorption may 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."*
Line 81	9	Proposed change (if any): change from "…drug substance(s) from the patch" to "…drug substance(s) from the patch or by dissolving the drug substance(s) directly into the adhesive matrix".	Not accepted. The text is considered clear.
Line 86	9	Comment: In Annex 1 in vitro permeation in other than human skin is also acknowledged.	Previously addressed. See above.
Line 89	9	Comment: rate of delivery will not be constant over the entire duration of patch application. Proposed change (if any): ... delivered at an adequate rate through the skin that is maintained for an appropriate time during patch application and should not...	Accepted. *"To ensure the safe and effective use of transdermal patches, the drug substance should be delivered at an adequate rate through the skin that is maintained for an appropriate time during patch application and should not irritate or sensitize the skin."*
Line 90	9	Comment: Are there any PE recognize as safe (see FDA GRAS). How should a reversible impact on the skin barrier be	This specific question should be addressed through scientific advice.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		demonstrated? Can animal experiments suffice?	
Line 148	9	Comment: Mean dose delivered per unit time: could you clarify if this based on the residual content after patch application, or based on systemic input obtained from deconvolution of exposure data.	See Guideline on the Pharmacokinetic and clinical evaluation of modified-release dosage forms.
58	10	Comment: “Note for guidance” – please add reference to this guidance document in section 3, “legal basis”.	Previously addressed. See above.
67/68	10	Comment: Adapt terminology, as supersaturation is not strictly a "chemical" permeation enhancement; replace “manipulation” with “design”. Proposed change (if any): 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 permeation enhancement, which involves the design of the formulation by either:…	Previously addressed. See above.
69/70	10	Comment: Please change format and add bullet points	Previously addressed. See above.
73	10	Comment: Please align this definition with that of Ph.Eur. general chapter 1011, Transdermal Patches	Previously addressed. See above.
84-87	10	Comment: In vitro release is a tool for quality control, observing batch to batch variability, but there is no correlation to in vivo performance, as may be implied	Previously addressed. See above.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		by the wording proposed by EMA. We kindly request to rephrase as proposed below. Proposed change (if any): The degree to which formulation and product design may influence drug substance permeation through the skin may be characterized by the in vitro permeation through skin. In vitro release may serve as a quality control tool to control batch to batch variability	
95/96	10	Comment: Consistency of argumentation can be increased: Replace “is” with “may be” Proposed change (if any): Because the concentration of the drug substance can be near to its saturation limit, there may be a risk of crystallisation on storage…	Previously addressed. See above.
105	10	Comment: Scope is not clear: Please confirm that “variations” only refers to variations to new applications. Please add "...thereof" at end of sentence in line 105. Proposed change (if any): … for all new marketing authorisation applications and subsequent variations thereof.	Previously addressed. See above.
115	10	Comment: Please add reference to guideline on clinical aspects of TDDS (currently CPMP/EWP/280/96/ Corr*), cf. comment on line 58.	Previously addressed. See above.
120	10	Comment: Please update reference to Process	Previously addressed. See above.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Validation guideline	
148/149	10	Comment: Please change order of lines 148 and 149, as 148 is more closely related to 150. The same holds true for lines 581 and 582	Previously addressed. See above.
161/162	10	Comment: The wording suggested by EMA implies that the agency considers a laminate to be an excipient. To us, “laminates” refers to the coated intermediate products. Proposed change (if any): The composition of each laminate, including the function and grade of excipients, where grade has been identified during pharmaceutical development as a critical quality attribute for transdermal delivery, should be described.	Previously addressed. See above.
169	10	Comment: Cutting (punching) of individual patches out of laminates is integral part of TDDS manufacturing. Therefore, we kindly request to rephrase as suggested below. Proposed change (if any): Transdermal patch design should avoid cutting by patients or health care professionals.	Previously addressed. See above.
171/172	10	Comment: Please rephrase, as a part of the wording	Previously addressed. See above.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		seems to be missing. Proposed change (if any): However, in exceptional cases for good patient safety and efficacy reasons, cutting might be necessary. Then this should be described and supportive data given in 3.2.P.2 as well as in the clinical dossier.	
173	10	Comment: Inclusion of brand names for excipients not described in Pharmacopeia may give rise to numerous variations due to name changes of excipients by suppliers. This might be particularly relevant for liners. Proposed change (if any): Excipients not described in a Pharmacopoeia should also be described with exemplary brand names.	Previously addressed. See above.
Lines 71-72	11	Comment: Physical enhancement methodology meanwhile has extended beyond the described techniques and should be addressed. Proposed change ("track changes"): (Permeation enhancement may also be achieved by physical technologies such as iontophoresis, ultrasound and electroporation.) "Furthermore, micromechanic, laser or thermal partial reduction or removal of stratum corneum is regarded to act in the same sense (e.g. microneedles)."	Previously addressed. See above.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
Lines 84-87	11	Comment: Skin permeation is a variable and not even a bias-free supplement for absorption in vivo. It is strongly recommended that the "thermodynamic force" of patches is tested instead on a clearly defined technical membrane (as it is conceded in line 301) to achieve sufficiently narrow variability and repeatability. Proposed change ("track changes"): (... by the *in vitro* release of the drug in a dissolution medium and by the *in vitro* permeation through human skin...) "or preferably an artificial test membrane, comparable to in vivo skin control."	Previously addressed. See above.
96	12	Comment: The impact of freezing of the finished units is higher with transdermal patches due to potential crystallisation or the development of 'channels' in the adhesive/API matrix, increasing the release rate. Proposed change (if any): …there is a risk of crystallisation on storage or freezing with potential adverse effects…	Not accepted. The general term storage should be taken to include storage conditions.
151 – 154	13	Comment: Information belongs in P2, not P1. Proposed change : Remove from P1.	Previously addressed. See above.
155	13	Comment:	Previously addressed. See above.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Detailed instructions for use do not belong in P1. Proposed change : Means of application (e.g. for application to unbroken skin), including the use of any overlay.	
167 - 172	13	Comment: Information does not belong in P1. The Mod 3 location for the points mentioned would be P2.	Previously addressed. See above.
174	13	Comment: Secondary packaging does not need to be addressed in P1; CTD requirement is for the immediate container/closure where this packaging step is an integral part of the primary manufacturing process of the product (e.g. vials, ampoules, tubes for semi-solids, bottles for liquids, pouches for transdermals). Proposed change : Remove.	Previously addressed. See above.
176 - 181	13	Comment: Belongs under P2. Even for a parameter such as product strength, assuming that label claim for delivered dose is meant, it is not established practice to cross-refer P1 to other dossier sections; it is known that P1 is an overview, and that all the detail supporting the information given is to be found under the appropriate CTD sections (quality standards for	Previously addressed. See above.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		components, removal of solvents during manufacture, etc). Proposed change: Remove from this section.	
Lines 71-72	14	Comment: add microneedles as a way to enhance drug permeation. Proposed change: “Permeation enhancement may also be achieved by physical technologies such as microneedles, iontophoresis, ultrasound and electroporation.”	Previously addressed. See above.
Lines 88-90	14	Comment: give more details on the situation described when excipients should exacerbate the adverse effects of the drug substance; is this requirement specific for generic applications?	Not accepted. The text is applicable to all transdermal patch.
Lines 153-154	14	Comment: the residual mass of drug substance remaining at the end of the administration is usually measured by “patch return analysis”. What kind of methodology should be recommended?	The comment is acknowledged. No amendment to the text is required. It is up to the Applicant to justify the methodology used.
84 -87	17	Comment: The statements here are vague and not necessarily true.	Previously addressed. See above
100-102	17	Comment: It is desirable to have as low a dose of the	Previously addressed. See above.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		active as follow not necessarily to minimise the amount of residual drug in the patch.	
58-59	18	Comment: Please add Note for Guidance relating to clinical aspects of transdermal patches (Note for guidance on modified release oral and transdermal dosage forms: Section II (Pharmacokinetic and clinical evaluation, CPMP/EWP/96/Corr*) under paragraph 3. Legal basis.	Previously addressed. See above.
73-76	18	Comment: Definition of "Transdermal Drug Delivery System" should be aligned to the general chapter 1011 of Ph.Eur. for transdermal patches.	Previously addressed. See above.
162	18	**Comment:** Use "Backing foil" or "Backing film" instead of "Backing layer" **Proposed change (if any): "**Backing ~~layers~~ **foils/films** and release liners…."	Not accepted. Layer is a more general term to describe sometimes a complex last layer of a transdermal patch. Therefore line 377 is also affected and is changed.
169-170	18	**Comment**: The text "Transdermal patch design should avoid cutting – a smaller transdermal patch should be developed instead." is ambiguous. Cutting of an intermediate laminate produced during manufacture into single patches (punching) cannot be avoided/is essential. **Proposed change (if any):** "Transdermal ~~patch design should avoid cutting~~ **patches should not be**	Previously addressed. See above.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		cut by patients or caregivers – a smaller transdermal patch should be developed instead".	
173	18	**Comment:** Description of excipients with brand names is unusual and would be affected by changes in brand names by a supplier. In exceptional cases it might be appropriate to provide an exemplary brand name. **Proposed change (if any):** Excipients not described in a Pharmacopoeia ~~should also be brand named~~ **might be further described by an exemplary brand name**.	Previously addressed. See above.
113-137	19	Comment: The new guideline on modified release products is missing here. This is almost out for consultation. Proposed change (if any): Make a reference to this guideline.	Previously addressed. See above.
Lines 213-215	1	Comment: Laminates and rate-control membranes should not be considered excipients. Proposed change (if any): "The choice of adhesives and excipients in the drug product, their concentration, and their characteristics that can influence the drug product performance should be discussed relative to their respective functions."	Previously addressed. See above.
Lines 224-	1	Comment: Laminates should not be considered	Previously addressed. See above.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
225		excipients. Proposed change (if any): “The relevant characteristics of the excipients should be discussed.”	
Lines 282-283	1	Comment: As indicated elsewhere within the proposed guideline, there is a large amount of variability associated with skin permeation testing and as such its usefulness in stability testing (which is intended to identify small changes in the product) is highly questionable. Proposed change (if any): “This should include performance tests with respect to *in vitro* drug release and adhesion.”	Not accepted. Skin permeation testing is appropriate for transdermal products. It is acknowledged that dissolution, drug release using a synthetic membrane and skin permeation, as performance tests, have different advantages and disadvantages. Nevertheless, each can contribute to the assessment of stability of the drug product.
Lines 344-348	1	Comment: A specification of +/-10% is excessively tight for release rate testing that does not model *in vivo* performance. Content specifications are often +/-10%, so setting the release rate specifications at +/-10% does not make allowance for any method variability in the release rate at all. Proposed change (if any): 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 ± 15% 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	The limits have been aligned to the modified release guideline.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		be 85-115µg.	
Line 448	1	Comment: The primary package would consist of the backing layer and the release liner. Proposed change (if any): “Each pouch should normally contain only a single transdermal patch.”	Previously addressed. See above.
Line 449	1	Comment: The backing layer should be considered a part of the container closure system. Proposed change (if any): “The backing layer should be considered a part of the container closure system.”	Previously addressed. See above.
213-215	2	Comment: We suggest replacing "laminates" with "intermediate products" to broaden the scope. Proposed change (if any): The choice of adhesives, excipients, intermediate products, 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.	Previously addressed. See above.
224-225	2	Comment: This wording implies that the agency considers laminates to be excipients. Proposed change (if any): The relevant characteristics of the laminates, such as appearance, flexibility, tensile strength, porosity, occlusion and chemical inertness, and of relevant excipients should be discussed.	Previously addressed. See above.
228	2	Comment: We suggest clarification which parameters should be provided. The term "fully" is apodictic and	Accepted. *“The composition and relevant characteristics of*

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		unclear from our view; for most polymers, no state of the art technique will be able to allow a "full" description of their properties.	*excipient mixes, e.g. adhesive solutions or suspensions, should be provided and characterised, including viscoelastic properties, if appropriate."*
235-237	2	Comment: Not all parameters listed will be critical quality attributes for all formulations, as might be implied from the proposed wording. *In vitro* drug release should be deleted from this listing, as it is a quality control parameter with no correlation to *in vivo* performance of the drug. Wording as given might imply that formulation development should be optimized to *in vitro* rather than to clinical performance. Proposed change (if any): The development should be described with respect to those attributes demonstrated to be critical quality attributes during pharmaceutical development, e.g., in vitro skin permeation, adhesion/cohesion and viscoelastic properties and those factors affecting ease of administration and duration of use.	Partly accepted. It is acknowledged that dissolution is a QC test. BUT: *In vitro* drug release is a required monograph test and fulfils the criterion of a CQA, as described in ICH Q8. For other territories, USP states: *The dissolution test is a powerful in vitro physiochemical test that measures drug product quality and performance for a variety of dosage forms, such as solid oral dosage forms, transdermal dosage forms.* *The text has been amended to:* *"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)."*
253	2	Comment: Please correct typo "needs".	Accepted.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Proposed change (if any): The clinical trial formulation and the batches used in the pharmacokinetic studies **need** to be...	
282-283	2	Comment: The period of use for frozen skin is limited and will not span an entire stability programme. As a consequence, skins from different donors will have to be used for different time points. This inter-individual variation, together with the inherent large variability of biological samples, would lead to a vast margin of error for the experiments, heavily limiting any relevant scientific information to be gained from these studies. Proposed change (if any): This should include quality performance tests with respect to content (drug, solubilizer, penetration enhancer, retarder), *in vitro* drug release and adhesion. Skin permeation test should only be done if the content of solubilizer, penetration enhancer or retarder significantly changes during stability programme.	Not accepted. Skin permeation testing is appropriate for transdermal products. It is acknowledged that dissolution, drug release using a synthetic membrane and skin permeation, as performance tests, have different advantages and disadvantages. Nevertheless, each can contribute to the assessment of stability of the drug product.
300-301	2	Comment: In our view non-rate controlling membranes are appropriate, only. Proposed change (if any): 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 membrane.	Accepted. Text has been amended to: *"or a release test using an appropriate, non rate-limiting membrane."*
303-306	2	Comment: Under certain circumstances, it might be difficult or even impossible to demonstrate for large patches (section 4.2 does apply to topical patches)	Accepted.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		that sample preparation for a defined small sample area has no impact on drug release / dissolution. There is no other way of testing patches with sizes that cannot be inserted into drug release apparatus than analysing smaller samples. Proposed change (if any): 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.	
324	2	Comment: We suggest alignment with the draft guideline on modified release oral dosage forms (EMA/492713/2012). Proposed change (if any): At least 3 sampling times are recommended to give a sharper and more differentiated profile.	Accepted.
325-329	2	Comment: We suggest alignment with the wording of the draft guideline on quality of oral modified release dosage forms. (EMA/492713/2012), lines 245ff:" ...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 %).	Previously addressed. See above.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
344-348	2	Comment: We would strongly suggest not to set too strict limits and to align this section with the wording in the oral modified release draft guideline (EMA/492713/2012, lines 259-262) to allow +/-10 % relative, not absolute.	Previously addressed. See above.
361-363	2	Comment: We suggest deletion of the requirement to include in vitro skin permeation studies into the stability programme. (See comments to lines 282-283).	Previously addressed. See above.
404-405	2	Comment: t_{max} is missing in the listing.	Accepted.
452-455	2	Comment: We suggest providing a definite list of classes of drugs requiring child resistant packaging.	Not accepted. Risk assessment by applicants required.
212	3	Comment: Due to their role and impact on the quality and efficacy of the transdermal patches, we recommend that more importance should be given to the permeation enhancers in this section. The permeation enhancer(s) allow(s) reducing amounts of drug substances and in consequence of residual drug substance in the patch after use.	Not accepted. Although it is acknowledged that permeation enhancers should be important to product performance, it is considered simplistic to focus on one type of excipient used in these complex formulations.
213	3	Comment: Please clarify: Is "liners" meant instead of "laminates"?	Previously addressed. See above.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		To us, laminates refers to the coated intermediate products. Proposed change (if any): The choice of adhesives, excipients, laminates, liners, and rate control membrane…	
218	3	Comment: We suggest performing quantification of relevant excipients in lieu of performance testing. cf. line 283.	Previously addressed. See above.
225	3	Comment: cf. comment on line 213.	Previously addressed. See above.
228	3	Comment: We kindly request the EMA to clarify which parameters should be provided. The term "fully" is apodictic and unclear; for most polymers, no state of the art technique will be able to allow a "full" description of their properties. Excipient mixes, e.g. adhesive solutions or suspensions, should be identified and described according to their functional attributes.	Previously addressed. See above.
235-236	3	Comment: Not all parameters listed will be critical quality attributes for all formulations, as might be implied from the agency's proposed wording. In vitro drug release is suggested to be deleted from	Previously addressed. See above.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		this listing, as it is a quality control parameter which may have no correlation to in vivo performance of the drug. Wording as given by the agency might imply that formulation development should be optimized to in vitro rather than to clinical performance. cf. line 283. Proposed change (if any): The development should be described with respect to those attributes demonstrated to be critical quality attributes during pharmaceutical development, e.g.critical quality attributes such as in vitro drug release, in vitro skin permeation,…	
253	3	Comment: Typo. Proposed change (if any): …need to be…	Previously addressed. See above.
266-267	3	Comment: Typo. Proposed change (if any): The risks of dose dumping, leakage from reservoir, residuals and product residues should be discussed.	Accepted.
280	3	Comment: The definition of the pilot batch size should be provided in particular when considering the batches to be placed under stability. Is it correct to define that	Accepted.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		the pilot batch size should at least be equivalent to one jumbo roll having the same size as for the industrial /commercial size batch?	
282	3	Comment: As stability tests should include performance tests with respect to skin permeation and adhesion, the frequency test approach should be acceptable as a general principle for such parameters for a transdermal system (as per lines 361-362). This means that we recommend that skin permeation and adhesion tests should be performed at start and at the end of stability testing, assuming that the MAH will inform immediately HAs in case of change or trend observed that might impact the quality and efficacy of the transdermal delivery system.	Previously addressed. See above.
282-283	3	Comment: Cf. comment on lines 361-363. Proposed change (if any): This should include quality performance tests with respect to content (drug, solubilizer, penetration enhancer, retarder), in vitro drug release and adhesion. Skin permeation test should only be done if the content or performance of solubilizer, penetration enhancer or retarder significantly changes during stability programme.	Previously addressed. See above.
292-293	3	Comment:	Accepted.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Typo. Proposed change (if any): Changes in adhesion properties under different storage conditions should be assessed.	
294	3	Comment: We consider that the stability of the “jumbo rolls” should be understood as the stability of the intermediate: it should be useful to give more information on what is considered a prolonged storage for the jumbo roles, what we have to justify for their container system to protect them during the bulk storage.	Partly accepted. Text amended: *“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.”*
300-301	3	Comment: Transdermal products originating in non-EU countries may have established monographs in local compendia, e.g., USP, JP or other, that describe appropriate methods for testing those products. In addition, it would not be appropriate to use rate-controlling membranes for this test. Proposed change (if any): The methods described in Ph Eur monograph or another internationally accepted well-accepted reference e.g. USP for Transdermal Patches should be followed i.e. a dissolution test or a release test using an appropriate membrane.	Previously addressed. See above.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
306	3	Comment: In certain circumstances, it might be hard or even impossible to demonstrate for large patches (section 4.2 does apply to topical patches!) that sample preparation for a defined small sample area has no impact on drug release / dissolution. There is no other way of testing patches with sizes that cannot be inserted into drug release apparatus than analyzing smaller samples. Therefore, we request to add the following wording after line 306: Proposed change (if any): 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.	Previously addressed. See above.
308	3	Comment: We kindly request to consider rephrasing, as in practice, the dissolution profile will be established from all relevant batches. It has to correspond to the profile of clinical batches.	Not accepted. Comment unclear – as to term “all relevant batched”.
321	3	Comment: We kindly request to abolish the requirement for complete release and replace it with the requirement	Not accepted – the general position should be for complete release, unless justified.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		to demonstrate release of not less than 85 % of the dose, unless otherwise justified. Reason: It is empirically known, that due the system design needed to achieve the desired release characteristic some API-substances will not be released quantitatively from patches, even under harsh conditions. Proposed change (if any): The test period should be justified, and be sufficient to achieve at least 85 % drug release.	Proposed rewording: *"The test period should be sufficient to achieve complete drug release, unless justified."*
324	3	Comment: It is common practice for dissolution profiles to be shown with a minimum of 3 time points. Please align with the draft guideline on modified release oral dosage forms (EMA/492713/2012) and replace "More than" with "At least". Proposed change (if any): At least 3 sampling times are recommended to give a sharper and more differentiated profile.	Previously addressed. See above.
325-329	3	Comment: Please align with wording in draft guideline on quality of oral modified release dosage forms. (EMA/492713/2012, lines 245ff:" ...an early time point to exclude dose dumping and/or to characterise a loading/initial dose (typically 20 to 30% released), at	Previously addressed. See above.

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		least one point to ensure compliance with the shape of the dissolution profile (around 50% released) and one to ensure that the majority of the active substance has been released (generally more than 85% released)." Proposed change (if any): For most matrix type patches, an early time point should be included to exclude dose dumping and/or to characterise a loading/initial dose (typically 20 to 30% released), at least one point to ensure compliance with the shape of the dissolution profile (around 50% released) and one to ensure that the majority of the active substance has been released (generally more than 85% released).	
339	3	Comment: Please clarify whether this applies to all development batches or only to those use during BA/BE studies. Proposed change (if any): …should be a minimum of 6 units…	Not accepted: During development 12 patches should be used.
344-348	3	Comment: We kindly request not to set such extremely strict limits and to align with wording in oral modified release draft guideline (EMA/492713/2012, lines 259-262) to allow +/-10 % relative, not absolute.	Previously addressed. See above.
354 and 389	3	Comment: The concept of different acceptance criteria for release	Partly accepted.

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		versus shelf-life specifications, where justified, is well established in Europe. ICH Q6A Specifications: Test Procedures and Acceptance Criteria for New Drug Substances andNew Drug Products: Chemical Substances clearly states the regulatory expectations on this. Tighter limits at the time of release may be needed to provide increased assurance that the product will remain within the regulatory acceptance criterion throughout its shelf-life. Proposed change (if any): Tighter limits at the time of release may be needed to provide increased assurance that the product will remain within the shelf life specification up to the expiry date.	Proposed change: *"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."*
361-363	3	Comment: We request to drop this requirement. The period of use for frozen skin is limited and will not span an entire stability programme. As a consequence, skins from different donors will have to be used for different time points. This interindividual variation, together with the inherent large variability of biological samples, would lead to a vast margin of error for the experiments, heavily limiting any relevant scientific information to be gained from these studies.	Previously addressed. See above.
414	3	Comment:	This is correct.

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		Please clarify: Will "all clinical studies" include phase I studies?	
416-419	3	Comment: Please rephrase sentence in lines 416 to 419, as the meaning is not clear due to disturbance in syntax.	Previously addressed. See above.
416-419	3	Comment: Please clarify whether the 100,000 unit rule derived from the BE guideline (CPMP/EWP/QWP/1401/98.Rev.1/Corr) will be applicable. Please also clarify on how the manufacturing scale should be defined: Based on mass, based on patches punched out of laminate etc.	Previously addressed. See above.
423-424	3	Comment: Please rephrase to clarify. Proposed change (if any): Hold times should be stated and validated for all intermediate products, where no immediate processing is intended.	Accepted.
445-447	3	Comment: Typo. Proposed change (if any): 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 and light, drug product compatibility and safety.	Accepted.

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448	3	Comment: As section 4.2 does also apply to topical patches, it is not out of the normal for topical patches to provide more than one patch per primary package. Therefore, please reconsider wording.	Not accepted, since the guideline is for transdermal patches and 1 patch/pouch is considered best practice. Other situations can only be considered on a case-by-case basis.
449	3	Comment: Please provide a corresponding statement on release liners.	Accepted. Proposed *"The backing layer and release liner should not be considered a part of the container closure system."*
452	3	Comment: A provision of a definite list of classes of drugs requiring child resistant packaging by the agency would be appreciated.	Previously addressed. See above.
456-457	3	Comment: As per EMA Q&A part 2, 2012, the suitability of the packaging for intermediates, bulk storage, and transportation (shipping) should be justified and discussed in Module 3.2.P.3.4 in manufacturing section and not as part of the container-closure system that should refer to the finished drug product.	Accepted. Text to be transferred to Section 4.2.7.
460-462	3	Comment: Typo. Proposed change (if any): Consideration should be	Accepted

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		given to the safety of medical personnel and patients after the use of the product, especially for controlled drugs (e.g. opioids).	
481	3	Comment: Please replace line 481 with the following wording, as this section does also apply to topical patches, where cutting might be explicitly intended: Proposed change (if any): Restrictions and limitations to cutting of the patch	Not accepted since the guideline is for transdermal patches and these should preferably not be cut. Other situations can only be considered on a case-by-case basis.
205	4	Comment: in the majority of patches, the drug is completely dissolved in the matrix or in solution of enhancers or the like. Thus, no crystal specific properties occur. The polymorphism of the drug substance is only of importance in the rare cases of suspension systems. Proposed change (if any): polymorphism in cases of suspension type systems.	Accepted. Proposed change: *"as well as physical properties, such as particle size and polymorphism, if the drug substance is present in the solid state in the drug product."*
207	4	An absolute measurement of thermodynamic activity is not possible, due to the fact that currently there is no analytical method available to determine the required solubility (at saturation) of drugs in complex polymer mixtures, like PSAs. All methods, like crystallisation measurements, thermoanalytic methods, the membrane permeation method (involves additional phase distribution steps,	Accepted. Proposal change *"The target physical state of the drug substance, e.g. solute, suspension, and the degree of saturation or super-saturation are critical quality attributes and should be justified in terms of product efficacy and safety, supported by evidence of the means by which*

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		including uptake of water, that changes the solubility in adhesives) lead to different results.	*the target state is achieved during manufacture and its stability during storage."*
236 - 238	4	Comment: cited from literature ref 1. P. Minghetti et al. "There is a lack of evidence for a relationship between the results obtained in *in vitro* adhesion tests and the *in vivo* adhesion performance of TDSs. Therefore, an analysis of the percentage of TDSs that lifted and/or detached during pharmacokinetic and clinical studies should be performed during development studies." In this light the measurement and justification of the applied method for the determination of viscoelastic properties of patches not possible, as values for elastic and viscous moduli are without any correlation to in vivo skin adhesion properties. The measurements of cohesion and adhesion are more appropriate. Proposed change (if any): omit measurement of viscoelastic properties.	Previously addressed. See above.
257	4	Comment: Use of placebo patches is often very critical, as most drugs alter the adhesion properties of the adhesive masses, see: Ho KY, Dodou K. Int J Pharm. 2007 Mar 21;333(1-2):24-33. Epub 2006 Sep 29. who state, that inclusion of any drug in silicone PSA increase the cohesive strength (thus reducing the adhesive strength)	Partly accepted. Proposed change: *"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."*

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		To our experience liquid drugs like nitroglycerine, rivastigmine change the adhesion forces completely to the opposite of the corresponding placebo.	
269	4	Comment: to my knowledge there is no method to determine the elastic or viscous moduli in invivo conditions. Proposed change (if any): omit viscolelastic properties.	Accepted.
274	4	Comment: unclear: what should be determined, the residues of the release liner on the patch and residues of the patch on skin?? Proposed change (if any): the residues of the adhesive matrix on the release liner after removal of the release liner should be addressed.	Accepted. This text essentially relates to Ph Eur requirements for Transdermal patches. Proposed amendment: *"Ph. Eur. adhesion requirements should be met. When removed, the protective liner does not detach the preparation (matrix or reservoir) or the adhesive from the patch.* *The transdermal patch adheres 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."*
283	4	Comment: as the skin permeation test is no precise analytical method, use in stability testing is not appropriate (lack of iviv correlation, variation of skin	Previously addressed. See above.

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		properties, age, origin etc). It may be used as a supplementary test, but cannot decide the instability of a patch.	
294	4	Comment: is there a minimum storage time required?	Previously addressed. See above.
301	4	Comment: the dissolution test is only applicable in the case of soluble adhesive matrices, like acrylic/succinic acid adhesives. The normal patch consists of non-soluble adhesives. For these patches the drug release test works without an additional membrane.	Not accepted. All approved transdermal patches include a dissolution test.
321	4	Comment: unlike with many oral controlled release formulation with patches in general, it is not possible to achieve complete release, at least in aqueous media. Lipid/water partition coefficients of transdermal drugs are in the range of 10^1 to 10^3 or 10^4. Thus, it will not be possible to extract 100% of the drug with one extraction step, as it is required in drug release tests Proposed change (if any): replace by meaningful drug release,	Not accepted since there are many oral drug products with drug substances that are practically insoluble in water.
349	4	Comment: this requirement will work only with mean values being patch mass normed. In praxi these tight limits, when taken as absolute values will not reflect the drug release mechanism in vivo.	Previously addressed. See above.

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		In vivo the difference of thermodynamic activities between patch and skin determine the rate of absorption, not the absolute amount of drug. For a given system the activity may be acceptably replaced by the concentration in the patch, thus the influence of the absolute amount of drug can be eliminated by norming as mentioned above. Unavoidable mass variations between that lead to meaningless drug release results are eliminated.	
356, 357	4	Comment: when in vitro skin permeation is not regarded as a predictive model for in vivo behaviour, skin should be replaced by synthetic membranes for the purposes of measuring product quality. For quality testing it is required to set up a drug release model with discriminatory power. Detection of changes in chemical potential is also possible in such a model with high precision, without introduction of high variances by using skin, and using only very small fractions of a patch, usually between 0,5 and 1 cm^2 . Skin permeation studies should be used throughout the development phase to assess the risks for initial application to man and to check the right concept for generic products. Recommendation of J. Schomakers, Forum Seminar 1209274, Update Transdermaly Systeme, September 2012, D-Bonn to use skin permeation during development only because of high variation of natural	Previously addressed. See above.

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		skin, depending on preparation and provenance.	
363	4	Comment: what is meant by “in vitro skin permeation should be consistent ...” Taking into consideration the variation of easily up to ± 20% at a given time point, it will be even higher at different time points, because of differences in age, provenance etc. of skin samples throughout a stability study of up to 3 years. Proposed change (if any): use of skin permeation should be limited to development phase to demonstrate the suitability of the product for the intended use. For stability reasons, a well-designed in vitro release test should be sufficient.	Previously addressed. See above.
370 385-389	4	Comment: in vitro adhesive tests as described in the current ASTM, FINAT etc., norms characterise the adhesion/cohesion properties only indirect as the result of peel force vs way. The adhesion/cohesion properties are described more appropriately by creep and shear resistance tests, cohesion failure tests etc. The current adhesion tests cannot describe viscoelastic properties, like elastic or viscous moduli, though these properties (among others) lead to adhesion. For this reason probe-tack testing would be one suitable method. It is agreed that the aforementioned parameters are crucial for sufficient adhesion to skin, in addition to van der Waals forces, ionic, hydrogen, dipole bonds etc. Thus, measurement should be performed during	Partly accepted. Reference to viscoelastic properties should be deleted. Release liner peel test is not considered sufficient to monitor adhesive properties on storage. It is acknowledged that there is no correlation between the quality tests and in vivo – but the limits of the quality tests may be qualified by clinical testing.

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		development phase. The use in stability tests should be limited to peel tests from e.g. release liner in order to detect blocking etc. As there is no correlation to in vivo adhesion values, it will not be possible to set thoroughly justified in vitro limits.	
393	4	Comment: as the measurement of adhesion properties is not product dependent, conduction of a pilot study not necessary in most cases.	Partly accepted. Proposed rewording: *"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."*
207 (as well as 208 and 605)	5	Comment : Line 207 acknowledges the difficulty to determine thermodynamic activity by direct means. Generally the drug concentration is related to the thermodynamic activity (well-known and accepted simplified model). It is therefore proposed to add this information. Proposed change (if any): Amend line 207 as follows "**Where appropriate,** the thermodynamic activity **or** drug substance **concentration** should be determined".	Partly accepted. It is understood that performance is dependent upon the thermodynamic active of the drug substance – but this cannot be directly determined. Text has been amended to: *"The risks of precipitation / particle growth / change in crystal habit, or other drug 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."*
208 (as well	5	Comment :	Previously addressed. See above.

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as 207 and 605)		Line 207 acknowledges the difficulty to determine thermodynamic activity by direct means. Line 208, however, seems to make the assessment of changes in the thermodynamic activity at different temperatures a requirement. Proposed change (if any): Amend line 208 as follows “The risks of precipitation / particle growth / change in crystal habit / changes in thermodynamic activity **(where possible) or** drug substance **concentration** arising from changes in temperature and on storage should be assessed and appropriate test included within drug product development programme”.	
213-215	5	Comment : The term “laminates” seems inappropriate in this context and should be replaced by “films and foils”. The parameter ‘concentration’ may be deleted within this context for lack of relevance. Proposed change (if any): 1) Please amend paragraph as follows: “The choice of adhesives, excipients, **film and foils** and rate control membrane in the drug product**~~, their concentration,~~** and their **respective** characteristics that can influence the drug product performance should be discussed relative to their respective functions”. 2) Define the terms “film & foil”, “laminate” and	Previously addressed. See above.

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		"layer" under section Definitions, if both terms are to be used within the scope of this guideline (see also comment to line 160).	
224	5	Comment: The term "laminates" seems inappropriate in this context and should be replaced by "films and foils". Proposed change (if any): 1) Amend paragraph as follows: "The relevant characteristics of the **films and foils**, such as […]" 2) Define the terms "film & foil", "laminate" and "layer" under section Definitions, if both terms are to be used within the scope of this guideline (see also comment to line 160 & 213-215).	Previously addressed. See above.
229	5	Comment: The term "laminates" seems inappropriate in this context and should be replaced by "films and foils". Proposed change (if any): 1) Amend paragraph as follows: "Processing aids, including temporary **films and foils**, and solvents […]" 2) Define the terms "film & foil", "laminate" and "layer" under section Definitions, if both terms are to be used within the scope of this guideline (see also comment to line 160 & 213-215 & 224).	Previously addressed. See above.

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260 (See also 165/433/492)	5	Comment : Patch size, area and thickness are mentioned to be determined. It is pointed out, that area weight which may be considered to correlate with thickness can be determined more precisely. Proposed change (if any): Amend line 260 as follows: “The drug substance content, formulation, patch size, **thickness and/or area weight** should be justified by a sound rationale and in vitro quality testing and clinical evidence, described by a narrative of product development”.	Previously addressed. See above.
283/361-363	5	Comment : In vitro skin permeation tests results are highly variable and cannot be included within a product specification, which is usually required for tests conducted within the stability studies as presented within Module 3.2.P.8. However, it is acknowledged that skin permeation performance shall not be significantly altered during shelf-life, as requested in line 363. Skin permeation should principally be addressed under 3.2.P.2 and only where relevant in the context of stability data in 3.2.P.8. Proposed change (if any): Please amend line 282-283 as follows: “This should include performance tests with respect to	Previously addressed. See above.

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		in vitro drug release, skin permeation and adhesion**, as relevant based on product characteristics determined during pharmaceutical development.**" Please amend lines 361-363 as follows: "However, skin permeation studies could**, where relevant based on product characteristics determined during pharmaceutical development,** be included **within stability studies**, albeit at a reduced frequency, to provide supportive stability data on product performance on storage. **Where relevant**, in vitro skin permeation should be consistent throughout the shelf life of the drug product."	
294	5	Comment: Short-term stability studies to determine the holding time of intermediates should not be limited to laminate rolls. Other relevant intermediates (e.g. coating masses) also need to be evaluated. Proposed change (if any): Please amend line 294 as follows: "The stability of the **relevant** intermediate **products which are subject for holding time periods** should also be **covered by a** stability programme."	Previously addressed. See above.
321	5	Comment: Depending on the polymers, complete drug release cannot always or systematically be achieved by using an aqueous media (as requested in literature, e.g. USP <711>).	Previously addressed. See above.

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		Additionally, one should avoid the use of organic solvents to achieve complete drug release, since this may significantly reduce the discriminatory power of the dissolution test. The guideline should therefore encourage the development and validation of a suitable and discriminating method, without imposing a strict requirement for complete drug release. Proposed change (if any): Please amend line 321 as follows: "**The dissolution method should be validated to be suitable and discriminative so that** the test period is justified, and **a sufficient and significant level of** drug release is achieved".	
330-332	5	Comment: The guideline requests that dissolution data is expressed in mg or µg per surface area. This does not reflect the current requirements of the Ph. Eur., which asks for mg or µg per surface area and unit time (release rate). In addition, we note important divergences in approaches between the EU (present draft guideline and European Pharmacopoeia) as well as USP. For example, USP asks for percentage released to be reported (see e.g. Chapter <724>: …requirements are met if the quantities of active ingredient released from the system conform to …, also: Monographs on Estradiol Transdermal System or Nicotine Transdermal System, only Monograph for Clonidine Transdermal	Accepted.

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		System asks for release rates), . In addition USP provides clear quality requirements with the acceptance table under chapter <724>. Furthermore it clearly allows for stage testing, equivalent to controlled release oral dosage forms (Ph. Eur. 2.9.3, USP <711>) Given the global nature of pharmaceutical product development, we strongly encourage that convergent approaches to reporting and specification of dissolution data for transdermal patches is promoted in order to avoid unnecessary regulatory hurdles. Proposed change (if any): We recommend that the final EMA guideline does not introduce a 3rd way of reporting to the existing USP and EP ways. We encourage the EMA to foster, through the finalisation of this guideline, a convergence of the approaches to transdermal patches in dialogue with the EDQM and USP. Also, it is encouraged that stage testing is clearly spelled out as allowed for transdermal dosage forms.	
344-353	5	Comment: The draft guideline proposed approach as presented in lines 344-353 is not acceptable; for the proposed limits are too tight and therefore not realistic in practice. The limits are solely to be referred to the labelled claim, expressed in %. E.g. allowance for variability range of +/-10% for each test time point should refer to the labelled content of	Previously addressed. See above.

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		the active substance, as outlined e.g. in CPMP/QWP/604/96 (in cases where no IVIVC could be demonstrated). The proposal in the draft guideline can lead to acceptance ranges that cannot be fulfilled, since the usual precision and accuracy of the analytical method as well as slight variation in drug content (as allowed by uniformity of dosage units) can easily, by chance, lead to results outside the range. This cannot be the scope of specification establishment. Proposed change (if any): This section should be completely rewritten so that the following important aspects are taken into consideration: - Acceptance ranges should be defined as +/- 10% for each time point based on the labelled drug content. - Dissolution data shall be reported as percentage released - Stage testing shall be allowed to also harmonize with USP requirements and Ph. Eur. requirements for prolonged/extended release oral forms **“Providing that drug release is specified in % of the total, the permitted variability in release at any given time point should not exceed a total numerical difference of ±10% of the labelled**	

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		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 bioequivalence or other clinical studies. As for other controlled release dosage forms, a stage testing may be allowed according to the following table:	

Level	Number tested	Acceptance criteria
L_1	6	No individual value lies outside the stated range.
L_2	6	The average value of the 12 units (L_1 + L_2) lies within the stated range. No individual value is outside the stated range by more than 10% of the average of the stated range.
L_3	12	The average value of the 24 units (L_1 + L_2 + L_3) lies within the stated range. Not more than 2 of the 24 units are outside the stated range by more than 10% of the average of the stated range; and none of the

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		units is outside the stated range by more than 20 % of the average of the stated range."	
373-375	5	Comment : This section is unclear and would benefit from rewording. Proposed change (if any): Please amend lines 373-375 as follows: "**Tests to characterize 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)**."	Accepted.
393-394	5	Comment : This sentence does not seem applicable for generic transdermal formulation developments and submissions Proposed change (if any): Please amend as follows: "**For the development of new transdermal patches,** a feasibility or pilot study […]"	Previously addressed. See above.
416-421	5	Comment :	Accepted that clarification is required.

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		This passage appears to be confusing and clarification is needed. Proposed change (if any): This paragraph should be re-written. The definition of 'full scale production batch' should be added in the definitions section. The following text is proposed: **Relevant clinical studies, as e.g. bioequivalent studies and / or Phase III pivotal studies, shall be performed with drug product batches representative for the product to be commercialised. Generally, the batch size for a transdermal product is considered as the amount of liquid coating mass containing the active pharmaceutical ingredient. It is encouraged, that those relevant clinical studies are conducted with batches derived from a batch size of not less than 10% of full production scale. As far as these batches have been produced in a manner representative of the full scale manufacturing process, the batch size may also be smaller than 10% of full production scale, if justified.**	Text amended as follows: *"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."*
433 (See also 165/260/492)	5	Comment : Patch size, area and thickness are mentioned to be determined. It is pointed out, that area weight which may be considered to correlate with thickness can be	Previously addressed. See above.

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		determined more precisely. Proposed change (if any): Amend line 433 as follows: "The coating process, including those parameters that control the layer **thickness and/or area weight**".	
269-270	8	**Comment:** According to the draft guideline "the adhesive and viscoelastic properties of the drug product should be (…) characterized, by both in vitro and in vivo testing". While the draft guideline gives more details about in vivo adhesiveness testing, it is not clear what is meant by the in vivo characterization of viscoelastic properties. **Proposed change:** Either "in vivo testing" should be deleted in this sentence or further clarification should be provided what sort of in vivo characterization of viscoelastic properties is expected.	Previously addressed. See above.
393-394	8	**Comment:** According to the draft guideline, "a feasibility or pilot study ***should*** be considered to establish that the study methods and assessments can be carried out satisfactorily". **Proposed change:**	Previously addressed. See above.

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		It is proposed to re-word the text to read: “A feasibility or pilot study ***could*** be considered to establish that the study methods and assessments can be carried out satisfactorily”. The applicant should be free to decide on the need of a pilot study. In particular, once more experience with the methodology of adhesiveness studies is available, it should not be necessary to carry out a pilot study for each specific product.	
397-398	8	**Comment:** The meaning of “and to achieve a representative number of subjects (both volunteers and patients)” is not clear. **Proposed change:** Please either clarify the meaning or delete.	Accepted.
404	8	**Comment:** The listed pharmacokinetic parameters are only for single dose studies. **Proposed change:** It is proposed to either write “e.g.” instead of “i.e.” or give the parameters for single dose and multiple dose studies separately or to delete the parameters here and refer to the respective guideline.	Accepted.

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407-410	8	**Comment:** The paragraph in lines 407-410 seems to refer rather to new than to generic applications, where only a single dose and a multiple dose study are required. However, according to lines 139-142, this seems to be applicable to both new and generic applications. **Proposed change:** It should be differentiated between the requirements for new and generic applications.	Not accepted. New applications refer to both new innovative as well as new generic applications. The text is considered a requirement for both new innovative and generic applications.
Line 222	9	Comment: Rate Controlling membranes may apply to other transdermal patch types, in addition to Reservoir type. Proposed change (if any): Suggest that a general statement of “For patches utilizing a rate controlling membrane, the suitability, performance, and critical attributes should be fully discussed.”	Accepted.
Line 246	9	Comment: Up-scaling of the process should be left to the manufacturer’s discretion based on the product and process knowledge. Proposed change (if any): Suggest removal of the word “gradual”.	Accepted.
Line 251	9	Comment: I think they overemphasize the impact of equipment scale up for transdermals. Proposed change (if any): suggest changing “In most	Accepted.

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		cases" to "In some cases".	
Line 257-258:	9	Comment: Information on placebo patches may be helpful in developing product understanding with respect to its adhesive properties and may support minor changes in adhesive component. Proposed change (if any): Delete statement since it is not true. The presence of the API has a large impact on adhesive properties of transdermal patches.	Previously addressed. See above.
Line 283	9	Current document suggests that skin permeation tests should be part of the stability programme. We suggest that skin permeation studies are not practical for marketed stability studies, but they should be utilized as part of product development, and may also be useful for qualification of a change in critical materials, process parameters, or equipment.	Previously addressed. See above.
Line 283:	9	Comment: See comments from 1st reviewer. I agree with their comments regarding skin permeation testing as part of the stability programme. Proposed change (if any): Delete skin permeation testing. For adhesion testing recommend peel force tests including removal of patch from surface, force required to remove protective liner from patch and probe tack test.	Previously addressed. See above.
Line 292:	9	Comment: Please clarify what is "... changes in excipient habit. "	Accepted. Proposed rewording:

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			"With respect to physical stability, factors should include formulation changes arising from drug 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 on under different storage conditions should be assessed."
Line 294:	9	Comment: Hold time for intermediate laminate rolls has been established. Stability of the intermediate laminate rolls should not also be subject to a stability programme. Proposed change (if any): Hold time for intermediate laminate rolls should be established under development.	Previously addressed. See above.
Line 321:	9	Comment: "... be sufficient to achieve complete drug release." With some formulations complete drug release may not be possible within a set time point.	Previously addressed. See above.
Line 337	9	Proposed change (if any): with a rate controlling membrane **or those with unit activity maintained**.	Not accepted, since "rate controlling membrane" is an example only.
Line 354:	9	Comment: ICH allows for differences in release and shelf life limits. Proposed change (if any): Delete line 354.	Previously addressed. See above.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
Line 356	9	Comment: “not expected to correlate to in vivo release” is a strong statement. I would think there is a correlation, though it may not be linear. Does this close the door for any IVIVC efforts?	Accepted. Proposed: *“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.”*
Lines 359-362	9	Comment: Similar to Line 283, in vitro skin permeation studies are not practical for annual stability studies, but may be a useful tool for assessing a change in a critical raw material, process parameter, or equipment. Due to inconsistencies in skin samples, and limited physical size of a skin sample, it may not be possible to compare studies that are done at different times or with different samples.	Previously addressed. See above.
Lines 359-362:	9	Comment: See 1st reviewer’s comments regarding skin permeation studies performed as part of stability programme. Proposed change (if any): Delete lines 361 and 362.	Previously addressed. See above.
Line: 363	9	Comment: In vitro skin permeation studies should not be part of routine stability programme due to the variability of in vitro test caused by different controlled skin samples used. Results of test are very dependent on control skin sample preparation and from the region of the body from which the controlled skin sample is taken. In vitro skin permeation studies are a useful development tool, but not useful as a routine quality	Previously addressed. See above.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		control test. Further to annex 1, pages 22-26: Performing in vitro permeation studies on fresh human skin and even animal presents a major safety risk to the analysts performing the testing. In addition is there sufficient supply of fresh human skin from breast or abdomen available to routine for every transdermal product manufacturer to routine perform this test on stability? Proposed change (if any): Delete lines 363 regarding results should be consistent throughout the shelf life of the drug product.	
Line 364	9	Comment: a discriminative in vitro skin permeation method can be of value but there is great within and between skin permeation variability thru human skin in vitro.	Previously addressed. See above.
Line 375	9	Comment: Removal of liner, adhesion to a surface, and tack should be suitable to characterize adhesives. Proposed change (if any): Recommend stating “peel adhesion and/or shear adhesion” rather than peel adhesion and shear adhesion”.	Previously addressed. See above.
Line 417	9	Comment: Clarification on full scale vs. Full scale equipment. Proposed change (if any): “full scale manufacture” should state “full scale manufacturing equipment”. (Later in the sentence it states “at least 10% of full production scale”.)	Previously addressed. See above.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
Lines 419 - 421	9	Comment: Not very clear regarding batch size and equipment requirements for pivotal clinical studies. Proposed change (if any):	Previously addressed. See above.
Line 445	9	remove “for” after (described in 3.2.P.7)	Accepted.
213	10	Comment: Please clarify: Is "liners" meant instead of "laminates"? To us, laminates refers to the coated intermediate products. Proposed change (if any): The choice of adhesives, excipients, liners, and rate control membrane…	Previously addressed. See above.
218	10	Comment: We suggest performing quantification of relevant excipients in lieu of performance testing. cf. line 283.	Previously addressed. See above.
225	10	Comment: cf. comment on line 213.	Previously addressed. See above.
228	10	Comment: We kindly request EMA to clarify which parameters should be provided. The term "fully" is apodictic and unclear; for most polymers, no state of the art technique will be able to allow a "full" description of their properties.	Previously addressed. See above.
235/236	10	Comment: Not all parameters listed will be critical	Previously addressed. See above.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		quality attributes for all formulations, as might be implied from the agency's proposed wording. In vitro drug release is suggested to be deleted from this listing, as it is a quality control parameter with no correlation to in vivo performance of the drug. Wording as given by the agency might imply that formulation development should be optimized to in vitro rather than to clinical performance. cf. line 283. Proposed change (if any): The development should be described with respect to those attributes demonstrated to be critical quality attributes during pharmaceutical development, e.g., in vitro skin permeation,…	
253	10	Comment: Typo. Proposed change (if any): …need to be…	
266/267	10	Comment: Typo. Proposed change (if any): The risks of dose dumping, leakage from reservoir, residuals and product residues should be discussed.	Previously addressed. See above.
282/283	10	Comment: cf comment on lines 361-363. Proposed change (if any): This should include quality performance tests with respect to content (drug, solubilizer, penetration enhancer, retarder), in vitro	Previously addressed. See above.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		drug release and adhesion. Skin permeation test should only be done if the content of solubilizer, penetration enhancer or retarder significantly changes during stability programme.	
292/293	10	Comment: Typo. Proposed change (if any): Changes in adhesion properties under different storage conditions should be assessed.	Accepted.
301	10	Comment: It would not be appropriate to use rate-controlling membranes for this test. Proposed change (if any): …dissolution test or a release test using an appropriate membrane.	Previously addressed. See above.
306	10	Comment: In certain circumstances, it might be hard or even impossible to demonstrate for large patches (section 4.2 does apply to topical patches!) that sample preparation for a defined small sample area has no impact on drug release / dissolution. There is no other way of testing patches with sizes that cannot be inserted into drug release apparatus than analysing smaller samples. Therefore, we request to add the following wording after line 306. Proposed change (if any): 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	Previously addressed. See above.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		might be inferred from dose proportionality studies for samples of different size.	
308	10	Comment: We kindly request to consider rephrasing, as in practice, the dissolution profile will be established from all relevant batches. It has to correspond to the profile of clinical batches.	Previously addressed. See above.
321	10	Comment: We kindly request to abolish the requirement for complete release and replace it with the requirement to demonstrate release of not less than 85 % of the dose, unless otherwise justified. Reason: It is empirically known, that due the system design needed to achieve the desired release characteristic some API-substances will not be released quantitatively from patches, even under harsh conditions. Proposed change (if any): The test period should be justified, and be sufficient to achieve at least 85 % drug release.	Previously addressed. See above.
324	10	Comment: Please align with the draft guideline on modified release oral dosage forms (EMA/492713/2012) and replace "More than" with "At least". Proposed change (if any): At least 3 sampling times are recommended…	Previously addressed. See above.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
325-329	10	Comment: Please align with wording in draft guideline on quality of oral modified release dosage forms. (EMA/492713/2012, lines 245ff:" ...an early time point to exclude dose dumping and/or to characterise a loading/initial dose (typically 20 to 30% released), at least one point to ensure compliance with the shape of the dissolution profile (around 50% released) and one to ensure that the majority of the active substance has been released (generally more than 85% released)." Proposed change (if any): For most matrix type patches, an early time point should be included to exclude dose dumping and/or to characterise a loading/initial dose (typically 20 to 30% released), at least one point to ensure compliance with the shape of the dissolution profile (around 50% released) and one to ensure that the majority of the active substance has been released (generally more than 85% released).	Partially accepted. The text has been amended as follows: *"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 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."*
339	10	Comment: Please clarify whether this applies to all development batches or only to those use during BA/BE studies. Proposed change (if any): …should be a minimum of 6 units…	Not accepted. It is considered prudent and for the information to be useful that during the development the number of batches should normally be 12.
344-348	10	Comment: We kindly request not to set such	Previously addressed. See above.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		extremely strict limits and to align with wording in oral modified release draft guideline (EMA/492713/2012, lines 259-262) to allow +/-10 % relative, not absolute.	
361-363		Comment: We request to drop this requirement. The period of use for frozen skin is limited and will not span an entire stability programme. As a consequence, skins from different donors will have to be used for different time points. This interindividual variation, together with the inherent large variability of biological samples, would lead to a vast margin of error for the experiments, heavily limiting any relevant scientific information to be gained from these studies.	Previously addressed. See above.
414	10	Comment: Please clarify: Will "all clinical studies" include phase I studies?	Previously addressed. See above.
416-419	10	Comment: Please rephrase sentence in lines 416 to 419, as the meaning is not clear due to disturbance in syntax. Please also clarify whether the 100,000 unit rule derived from the BE guideline (CPMP/EWP/QWP/1401/98 Rev. 1/ Corr) will be applicable. Please also clarify on how the manufacturing scale should be defined: Based on mass, based on patches	Previously addressed. See above.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		punched out of laminate etc. Proposed change (if any): Studies should be performed with batches representative of the product to be marketed manufactured using industrial scale equipment and conditions, e.g., at least 10% of full scale manufacture for the production of the laminate rolls and for roll conversion to transdermal patches, at least 10% of full production scale or 100,000 patch units, whichever is the larger ~~and~~, unless pivotal clinical studies have been performed with batches of smaller size.	
423/424	10	Comment: Please rephrase to clarify. Proposed change (if any): Hold times should be stated and validated for all intermediate products, where no immediate processing is intended.	Previously addressed. See above.
445-447	10	Comment: Typo. Proposed change (if any): 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 and light, drug product compatibility and safety.	Accepted.
448	10	Comment: As section 4.2 does also apply to topical patches, it is not out of the normal for topical patches to provide more than one patch per primary package.	Not accepted. The text refers to transdermal patches. Proposal for cutaneous patches can only be accepted on a case-by-case basis.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Therefore, please reconsider wording.	
449	10	Comment: Please provide a corresponding statement on release liners.	Previously addressed. See above.
452	10	Comment: A provision of a definite list of classes of drugs requiring child resistant packaging by the agency would be appreciated.	Previously addressed. See above.
460-462	10	Comment: Typo. Proposed change (if any): 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).	Accepted.
481	10	Comment: Please replace line 481 with the following wording, as this section does also apply to topical patches, where cutting might be explicitly intended: Proposed change (if any): Restrictions and limitations to cutting of the patch.	Not accepted. The text refers to transdermal patches. Proposal for cutaneous patches can only be accepted on a case-by-case basis.
Lines 336-338	11	Comment: Some historic patch formulae, despite being nominally membrane controlled, carry a considerable burst amount of drug substance in the adhesive, which	Not accepted. This issue can only be addressed on a case-by-case basis.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		may lead to overdosage. Proposed change ("track changes"): (... dissolution rate at a given time point may be more appropriate than the cumulative amount dissolved at a given time point.) "Deduction and explanation of any burst effect of drug substance should be addressed and explained in pharmacokinetic results."	
Lines 344-348	11	Comment: Variability or trends in in vitro release may have serious as well as negligible reasons. Critical may be e.g. the diffusion to "deep compartments" of the patch or impaired solubility. Much less meaningful are for example variations of the diffusibility of the adhesive. As a proposal, the 10% limit may be addressed as a challenging reason for the applicant to analyse and explain the background e.g. of changes during stability testing. Proposed change ("track changes"): (...e.g. if the expected amount released at a given time is 100µg, then the permitted limits would be 90-110µg.) "Applicants may further analyse reasons for deviations and may give evidence for changes to be relevant or not relevant for bio-performance."	Not accepted. The guideline requires that the limits are fully justified.
Lines 395-398	11	Comment: Adhesion studies in humans are essential to give proof of performance of the adhesive system part. One should be aware however that variability is mainly	Comment acknowledged. Text has been amended and simplified with reference to clinical guideline.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		caused by functional differences in skin stratum of volunteers and patients. Long term adhesion is more dependent on adhesion inbetween corneocytes than to skin's surface. This fact is frequently overlooked when failure or variability of adhesion is criticized. There are both "good and bad performers" (there exist people from which repeatedly loosen any patches) as well as "preferers" of certain groups of adhesives. In absence of benchmarking to comparable formulation, any adhesion study is questionable. Age-related differences in the adhesive behaviour of patches are quite rare and not easy to detect in the background framework of in vivo variability. Proposed change ("track changes"): "The assessment should ~~be undertaken~~ include patches 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).~~ Adhesion performance should be studied in connection to the individual clinical-pharmacokinetic performance."	
204	12	Comment: Consideration for API that is a liquid at room temperature. Proposed change (if any): …coefficient, melting point, boiling point, pKa, solubility and pH effects…	Accepted.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
224-225	12	Comment: Extractable/leachable of laminates of release liners should be included in the characteristics of Excipients. Proposed change (if any): …appearance, tensile strength, porosity, extractable/leachables, occlusion and chemical inertness…	Previously addressed. See above.
370-389	12	Comment: Tack, peel and sheer resistance specifications will be dependent on the surface area of the units. If different strengths of the product are made by only varying the surface area of the patch, different specifications may be needed. A test method that cuts all strengths to a uniform surface area for adhesion tests may be employed to have a uniform tack, peel or sheer resistance specification.	Noted, but no amendment of the text is considered necessary.
424	12	Comment: Hold Times should be established for in-process intermediate laminates. Proposed change (if any): … including holding times for coating solutions and in-process intermediate laminates.	Previously addressed. See above.
434	12	Comment: Some coating solutions are aqueous and residual solvents may not be applicable.	Accepted.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Proposed change (if any): … and the removal of residual solvents where applicable. Or … and the removal of residual solvents when solvents are used.	
430-438	12	Comment: Add bullet point to non-exhaustive list or amend line 434 to include moisture levels for aqueous based blends Proposed change (if any): Add: ● Moisture levels in dried laminates for aqueous based blends. Or Edit Line 434 … and the removal of residual solvents when solvents are used or moisture levels in dried laminates for aqueous based blends.	Accepted.
446	12	Comment: Container closure system needs to also protect from oxygen. Proposed change (if any): … include the choice of materials, protection from moisture' oxygen and light…	Accepted
641	12	Comment: The '2' in 15 cm^2 is not superscripted.	Accepted.
242 - 243	13	Comment: Discussions on the relationship between specification and product quality profile/CQAs belong primarily in	Not accepted. It is appropriate that control strategy is discussed throughout product development.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		P5, Justification of Specs. The paragraph starting line 235 addresses P2 content on this aspect adequately. Proposed change: Transfer to Control section.	
274	13	Comment: Is what is meant, residue on release liner after removal? Proposed change: Residue remaining on the release liner after peeling from the patch and skin residues following transdermal patch removal….	Previously addressed. See above.
280 - 294	13	Comment: The comments relating to generation of stability protocols are relevant. However, discussions on a stability protocol would not be a routine topic for P2. Proposed change: Reduce the text in 4.2 to advice to consider providing justification for excluding any critical quality attributes which could be considered to be subject to change from proposed stability protocols. If desired to maintain the guidance in full, create a free-standing section not appearing under "Pharmaceutical Development". In this can be	Previously addressed. See above.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		mentioned that non-inclusion of testing on critical parameters would be expected to be justified in the dossier.	
351 - 353	13	Comment: Is this not repetitive of the preceding two paragraphs?	Previously addressed. See above.
361	13	Comment: Inclusion of skin permeation studies in stability protocols should not be represented as a standard expectation throughout life-cycle, but should be restricted to consideration for the development phase of the original dosage form, or for changes which may reasonably be expected to influence *in-vivo* performance.	Previously addressed. See above.
376	13	Comment: Same comment as to 274. Proposed change: Residue remaining on the release liner after peeling from the patch and skin residues following transdermal patch removal…	Accepted.
379	13	Comment: To what extent is a summary of the development of all tests necessary? Important is that the tests yield relevant information. Proposed change: A brief summary of their development may be	Accepted.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		provided if helpful to justifying decisions.	
380 - 384	13	Comment: Demonstration of “discriminatory power” for the physical tests related to adhesivity should be limited to relationship with parameters and attributes *related* to adhesion.	Accepted.
390 - 401	13	Comment: It should be made clear that P2 is only expected to reference the *in vivo* adhesion studies in relation to formulation development; the studies themselves will be sited in the clinical section of the dossier. Furthermore, the message of lines 395 – 398 is not fully clear.	Accepted.
402 - 412	13	Comment: Not all studies mentioned need have all the data mentioned provided – for examples, studies on formulations which were not pursued. The Quality section of the dossier need only summarise relevant findings of pharmacokinetic studies. Information on bioanalytical methods and validation is to be found in Mod 5 of the CTD and need not be referenced out of Mod 3.	Not accepted. The requirement in the guideline relate only to including a reference to the clinical and bio-analytical methods in the clinical dossier.
409 - 410	13	Comment: Could be more clearly phrased, as it is not obvious what is meant by details of determination of drug product strength – presumably, in vivo release rate?	Not accepted. Strength is described in section 4.1 of the guideline.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
413 - 421	13	Comment: Much of this section is open to misinterpretation. There may be clinical studies discussed where the batches may not necessarily be representative of commercial product (e.g. early in development). The requirements in brackets in line 415 (site, scale, date of manufacture and CoA) are presumably meant as information to be *provided* for clinical batches, but it could easily be misunderstood that all clinical batches must be at same site/scale as for commercial. The sentence 416 – 419 is challenging to interpret. Fact is that many operations in transdermals production are continuous and therefore less sensitive to scale effect. Important is that any equipment/scale differences between pivotal clinical batches and commercial production are addressed and justified. The whole section should be reworked to indicate unambiguously what is required from a scientific perspective.	Acknowledged. The text has been amended to improve clarity.
423	13	Comment: The need for definition and validation of hold-times for intermediates is acknowledged – suggest though that this should be addressed in P3 rather than P2.	Accepted.
431 - 439	13	Comment: Taken literally, for a primarily mechanical, automated process as is used for transdermals manufacture, a	Not accepted. A description of the development of the manufacturing process is considered necessary.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		discussion of all the points listed, with proven acceptable ranges for all parameters, would involve addressing selection of machine settings. It is suggested that these belong in the GMP area and the text should be modified to indicate that this level of detail is not required.	
458 - 482	13	Comment: Whereas it is acknowledged that the list of “points to consider” is of relevance to the overall development and commercialisation of the product, P2 of the CTD does not foresee a section titled “Administration”. Furthermore, some of the points listed are clinical in nature and do not fit well in the dossier in Pharmaceutical Development or even, in a guidance titled “Quality of transdermal patches” – e.g. selection of sites of administration, avoidance of damaged skin, human behavioural aspects not directly related to formulation development decisions and not needing supporting pharmaceutical data, transfer to others… Proposed change : Suggest transferring those features driving pharmaceutical development decisions or needing supporting physicochemical data and thus warranting discussion in the Quality Module of the dossier to the existing header Formulation Development. Application to unbroken skin can be a simple statement in P1 as part of the description of the dosage form. The	Not accepted. Administration has previously been neglected and it is known that poor design and product development may lead to failures in administration.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		remainder should be deleted, or, if a wish remains to address them somehow in this guideline, consideration could be given to including the desired points under the Introduction.	
Lines 304-306	14	Comment: / Proposed change: “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.”	Accepted.
Lines 351-353	14	Comment: could you confirm that “+/- 10% of the mean set value” is corresponding to +/- 10% of the final theoretical cumulative amount? (ie +/- 10% absolute)	Previously addressed. See above
Lines 356–367	14	Comment: for reservoir patches, how to perform skin permeation studies using Franz cell; usually, matrix patches are punched for.	Comment acknowledged. Alternative skin diffusion apparatus may be used.
Lines 373-375	14	Comment: it is not justified to ask 4 tests (release liner anti adherence, tack, peel and shear adhesion) to be considered as release tests. During the product development, these tests should be performed and only some of them could be retained finally. It is important to consider that (i) these tests are no longer described in any Pharmacopoeia and (ii) these tests have high inter-intra variability coming from its operating conditions (adhesion on a steel surface or	Comment acknowledged. Section 4.5 of the guideline states that only appropriate performance tests should be undertaken.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		not ; quality of the surface of the substrate ; cleanliness of the substrate …). By experience, we suggest to select both the release test and the tack test for routine controls.	
Lines 385-388	14	Comment: / Proposed change: "The *in vitro* adhesive properties of the drug product should thus be characterised, with the specifications 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).	Accepted.
Lines 445-446	14	Comment: / Proposed change: "The suitability of the container closure system (described in 3.2.P.7) should be discussed and justified."	Accepted
Lines 460-462	14	Comment: / Proposed change: "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)."	Accepted.
295-354	16	Comment: Reproducible *in vitro* dissolution methods for a given product may be developed, however, they will generally not have sufficient discriminatory power	Not accepted. No evidence to support this claim. It is important that dissolution methods are developed to be appropriately discriminating and so have value.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		to detect changes in CQA such as manufacturing controls or excipient characteristics.	
355-367	16	Comment: *In vitro* skin permeation studies provide relative permeation information which is valuable during product development. Significant skin to skin variability exists, precluding the use of this test as a stability indicating method.	Previously addressed. See above
369-389	16	Comment: *In vitro* tests of adhesion of patches to inanimate objects reflect the static condition of the adhesive system and will not be reflective of *in vivo* performance. The tests of adhesion to steel and probe tack lack discriminating power with respect to excipient and manufacturing control CQAs.	Previously addressed. See above
206-207	17	Comment: How will the thermodynamic activity of the drug substance be measured?	Previously addressed. See above
257-258	17	The presence of an active may influence adhesive properties we are not sure that the information on placebo patches is relevant.	Previously addressed. See above
307-308	17	The dissolution medium may transfer into the patch and statements need to be made about the influence of this on dissolution rates.	Comment acknowledged. No change in text proposed since satisfactory method development has been requested.
316-320	17	Again, it is important to note that the dissolution	Previously addressed. See above

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		medium should not interact with the patch and affect its dissolution rate.	
331	17	Rather than “may” it should read “should”	Accepted.
404	17	**Tmax should be included**.	Previously addressed. See above
224-225	18	**Comment:** *“The relevant characteristics of the laminates, such as…….flexibility, tensile strength, porosity, occlusion… “* Especially these characteristics are sometimes difficult to determine or a determination is even impossible. **Proposed Change:** Delete these specific characteristics/part of development only.	Previously addressed. See above.
282-283	18	**Comment**: The stability programme should ensure that the performance of a patch does not change throughout the proposed shelf-life period. This should be confirmed by testing of the relevant quality determining parameters. Performance tests like skin permeation and adhesion should not be mandatory in the routine stability programme. **Proposed Change:** This should include performance tests with respect to *in vitro* drug release~~, skin permeation and adhesion. s~~. **S**kin permeation and adhesion **testing may be added to the stability programme.**	Previously addressed. See above
292-293	18	**Comment**: Typo.	Previously addressed. See above

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Proposed change (if any): Delete 'on': "Changes in adhesion properties ~~on~~ under different storage conditions should be assessed."	
300-301	18	**Comment**: Currently, only a paddle-over-disk dissolution test is performed on a routine basis and for batch release of commercial supply. Drug release testing using a membrane, e.g. EVA membrane tests, is only performed during development. **Proposed change (if any)**: The methods described in Ph Eur monograph for Transdermal Patches should be followed i.e. a dissolution test or **when relevant** a release test using a membrane.	Not accepted. The option to having a routine release test using a membrane should remain an unqualified possibility.
321	18	**Comment**: The requirement to achieve complete drug release may be difficult to fulfil depending on the patch design, or may lead to an unrealistically long dissolution time. A dissolution rate of not less than 85% should be considered instead. **Proposed change (if any)**: The test period should be justified, and be sufficient to achieve ~~complete~~ **not less than 85%** drug release.	Previously addressed. See above
324	18	**Comment**: For consistency with the draft guideline on quality of oral modified release products (EMA/492713/2012) replace "More than 3 sampling times are recommended…" by "In general, a minimum	Previously addressed. See above

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		of 3 points (sampling times) should be included…". **Proposed change (if any)**: "~~More than~~ **In general, a minimum of** 3 sampling times are recommended…"	
325-329	18	**Comment:** For consistency with the draft guideline on quality of oral modified release dosage forms. (EMA/492713/2012), lines 245ff we recommend to add similar wording to the draft guideline on quality of transdermal patches. **Proposed change (if any)**: Add text as follows **" …an early time point to exclude dose dumping and/or to characterise a loading/initial dose (typically 20 to 30% released), at least one point to ensure compliance with the shape of the dissolution profile (around 50% released) and one to ensure that the majority of the active substance has been released (generally more than 85% released)."**	Previously addressed. See above
339-340	18	**Comment**: It should be further clarified to which batches/under which circumstances the following requirement applies: "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)." Does this refer to those batches used in BA/BE studies only or to further batches in development?	Previously addressed. See above

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Proposed change (if any): "The number of samples used to characterise the dissolution profiles**, i.e. for batches used in BA/BE studies,** should be a minimum of 12 units per batch (for routine release, a minimum of 6 units would be accepted)."	
344-350	18	**Comment:** The requirement that: *" , 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%".* is unrealistic and not acceptable. In particular at early time points such tight acceptance criteria might be impossible to achieve, e.g. the results could be overly impacted by small temperature variations, within the permitted range, during in vitro testing (as an example: Considering an activation energy for drug diffusion in the range of about 25 to 70 kJ/mole variation of water bath temperature by ±0.5°C would already lead to a variation of release rate of up to about ± 2% (!). As such a numerical difference above	Previously addressed. See above

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		10% of the cumulative amount of drug substance in mass units is generally justified.) Please align the requirements with those defined for oral modified release products in Draft “Guideline on quality of oral modified release products” (EMA/492713/2012) where limits of ±10% of the nominal (labelled) content are requested. **Proposed change (if any):** “ , the permitted variability in release at any given time point should not exceed a total numerical difference of ± 10% of the ~~cumulative~~ **nominal (labelled)** amount of drug substance in mass units (mg or µg) **or as a % of total nominal (labelled) content**, 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%”.~~	
361-363	18	**Comment:** It is acknowledged that permeation studies included in the stability protocol, albeit at a reduced frequency, could be helpful to demonstrate consistent release performance of the product on storage. On the other hand, as the period of use of frozen skin is	Previously addressed. See above

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		limited, skins from different users need to be used. This has a high impact in terms of variability of test results and may contradict the requirement in line 363: "*In vitro* skin permeation should be consistent throughout the shelf life of the drug product." In addition, if the relationship between drug release and PK has been satisfactorily demonstrated during development, and if drug release/dissolution is part of release and stability testing, and if permeation is not stability-indicating, and if permeation/drug release correlation is not expected (says the guideline), then why add permeation as a stability test item? **Proposed change (if any):** "However, permeation studies ~~could~~ **may** be included in the stability study protocol…".	
395-398	18	**Comment:** Please confirm that the assumption is correct that 'period of use' in the sentence: "The assessment should be undertaken throughout the proposed period of use……." refers to the proposed application time of one single patch, e.g. 24h, 3 days etc. rather than to the overall treatment duration (weeks, months or even years). **Proposed change (if any):** The assessment should be undertaken throughout the proposed period of use, **ie application time of the patch**.	Previously addressed. See above

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414-415	18	**Comment:** Please clarify whether 'batches used in all clinical studies' include batches from phase I studies rather than BA/BE batches.	Previously addressed. See above
416-419	18	**Comment:** It is acknowledged that batches for clinical phase II and phase III studies should be manufactured using industrial scale equipment and should be representative of the product to be marketed. However, the requirement of full scale manufacture for the production of the laminate rolls and for roll conversion to transdermal patches is overly strict. It should be allowed to produce batches at industrial scale but not necessarily the full scale intended for commercial batches. For example, the requirement for primary (stability) batches which should also be representative of the product to be marketed, is "at least pilot scale" (corresponding to 10% of full commercial scale). Please clarify further whether the definition as for solid oral dosage forms: "A pilot scale is generally, at a minimum, one-tenth that of a full production scale or 100,000 tablets or capsules, whichever is the larger." (ref ICH Q1 A (R2) and CPMP/EWP/QWP/1401/98/98 Rev. 1/Corr.) can be translated to patches. **Proposed change (if any):** Studies should be performed with batches representative of the product	Previously addressed. See above

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		to be marketed manufactured using industrial scale equipment and conditions, e.g., **at least 10% of** full scale manufacture for the production of the laminate rolls and for roll conversion to transdermal patches, at least 10% of full production scale **or 100,000 patch units, whichever is the larger** ~~and~~, unless pivotal clinical studies have been performed with batches of smaller size.	
445-447	18	**Comment:** Typo **Proposed change (if any):** 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 **aspects** ~~should be discussed~~.	Previously addressed. See above
Lines 254-255	19	Comment: Besides formulation differences, differences in the manufacturing process should also be justified. Proposed change (if any): Add “and manufacturing process” after “clinical formulations”.	Accepted.
Lines 259-267	19	Comment: An overlay may have an effect on drug delivery / skin irritation. Proposed change (if any): Please add the requirement to discuss the effect of an overlay here or in section 4.2.9.	Accepted.

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Lines 263-267	19	Comment: The possibility of extraction of excess drug (e.g., opioids) from patches should be investigated / discussed. Proposed change (if any): Please add this requirement.	Not accepted. Already addressed in the introduction and administration.
Lines 268-279	19	Comment: The size of the patches should be discussed in relation to the place(s) of administration, changing frequency and the need to avoid a place where a patch has been placed for a certain time. For instance, it may be difficult to find a place to administer a new patch if the patches are large, the changing frequency is high, and it is advised to avoid a place for several weeks after administration of a patch. Proposed change (if any): Please add this requirement.	Not accepted. Considered already addressed in the administration section 4.2.9.
Lines 286-288 Line 472	19	Comment: It is felt that temperature cycling studies should be mandatory rather than at consideration of the Applicant. Proposed change (if any): Please add this requirement.	Accepted. But not applicable to line 472.
Lines 313-315 Lines 382-384	19	Comment: The methods should also be discriminatory with regard to changes in the formulation. Proposed change (if any): Please add a bullet point with “formulation variables”	Not Accepted. Discrimination should be based on realistic variables. Discrimination based on changes in formulation for the developed product is considered unrealistic.
Line 317	19	Comment: More detailed guidance on the development of the dissolution test should be provided. Should skin conditions be mimicked?	Not accepted. Considered sufficient.

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		Proposed change (if any): Please add more detailed guidance.	
Lines 414-415	19	Comment: It is felt that composition, product manufacturing process, product batch numbers, drug substance batch numbers of clinical batches should also be listed. Proposed change (if any): Please add the above.	Not accepted. The requirements cannot be exhaustive.
Lines 467-482	19	Comment: -The suitability of the use of a transdermal patch should be discussed in view of the intended patient population and the possibility that they may remove the patches (e.g., children or patients with dementia). -Proposal also to consider: : “ease of opening of the sachet by individuals of the indicated populations” Proposed change (if any): Add bullet points to this section with the above requirements.	Not accepted. Considered addressed in the Administration section.
Lines 489-490	1	Comment: Transdermal manufacturing processes have been in existence with similar operating principles and unit operations for more than 30 years now. In many ways, they are no more complex than the processes used to manufacture other dosage forms.	Partially accepted. Transdermal patches, as well as some other dosage forms, are defined as complex dosage forms manufactured by non-standard processes. Nevertheless, in accordance with the draft guideline on process validation, data on 1 or 2 production scale batches may suffice where these are supported by pilot scale batches and by a history of consistent manufacture of products by essential equivalent

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			processes. However it should be noted that a manufacturer's own experience in the manufacture of specialised products or use of processes which might otherwise be considered "non-standard", might exempt them from the need to provide production scale process validation data at the time of submission provided sufficient supporting data are provided. This needs to be justified on a "case-by-case" basis, on the basis of appropriate pharmaceutical development data or by reference to similar products. The text below has been included: *"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/99738/2012)."*
Lines 501-502	1	Comment: Adhesives have a molecular weight distribution which is often characterized through an indirect measure (like inherent viscosity). Proposed change (if any): "For adhesive materials, the molecular weight (or an indirect measure of molecular weight like inherent viscosity), viscoelastic and adhesion /cohesion properties should be characterised and satisfactorily controlled."	Not accepted. One of the parameters used for characterisation of the adhesive should be the molecular weight; despite this analytical methods which correlate with the molecular weight can be used. Testing of inherent viscosity may be acceptable if the correlation with molecular weight is supported by data.
489-490	3	Comment: Please add the following wording after sentence in line 489-490.	Not accepted. The guideline for process validation, gives information about possible exclusion to provide production scale process validation data at time of submission.

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		Proposed change (if any): A manufacturer's own experience in the manufacture of transdermal patches including use of processes which might otherwise be considered "non-standard", might permit to define this production for this manufacturer **not** as a non-standard process and might exempt it from the need to provide production scale process validation data at the time of submission provided sufficient supporting data are provided.	Nevertheless, a non-standard process stay as it is to be a non-standard process of a complex dosage form. The new wording is: *"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/99738/2012)."* Citation of the guideline on process validation: *"…data on 1 or 2 production scale batches may suffice where these are supported by pilot scale batches, and by a history of consistent manufacture of products by essentially equivalent processes." … "However it should be noted that a manufacturer's own experience in the manufacture of specialised products or use of processes which might otherwise be considered "non-standard", might exempt them from the need to provide production scale process validation data at the time of submission provided sufficient supporting data are provided. This needs to be justified on a "case-by-case" basis, on the basis of appropriate pharmaceutical development data or by reference to similar products."*
495	3	Comment:	Accepted.

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		Typo. Proposed change (if any): If the material(s) is new or has not been previously authorised for transdermal use…	
517-518	3	Comment: Many approved transdermal patches are formulated to contain the drug substance in a sub-saturated state. This may be for the purpose of providing a larger surface area of contact with the skin, to improve permeation or to mitigate potential irritation concerns. Proposed change (if any): The occurrence of crystals throughout use in a transdermal patch is unwanted but sometimes unavoidable since the drug in adhesive or reservoir may be incorporated close to or even at its saturation limit.	Partly accepted. The text has been amended as follows: *"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 drug substance is intentionally dispersed within the matrix, at release a transdermal patch should show no signs of crystallization.* *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 packaging leaflet."*
526	3	Comment: Wording. Proposed change (if any): Since residual solvents may affect adhesion and permeation enhancement…	Accepted.
533	3	Comment: Please clarify whether specific skin irritation studies	The comment is acknowledged. No revision of the text is needed.

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		will be required or if data from skin safety studies with batches, where the impurities in question have been present, are sufficient.	Data from skin irritation studies with batches, where the impurities in question have been present, are sufficient.
516	4	Comment: only true, when a solution type system is considered. There are suspension type systems in the market. Proposed change (if any): crystallisation should be absent in the case of solution type systems.	Accepted. Text has been amended to: *"With the exception of suspension patches where the drug substance is intentionally dispersed within the matrix, at release a transdermal patch should show no signs of crystallization."*
489-491	5	Comment: In spite of transdermal patches being a complex formulation, a number of manufacturing steps applied in manufacture and production of transdermal matrix patches can today be considered to be standard or conventional processes for this dosage form. These include mixing processes, coating/drying/laminating processes, slitting processes and to a certain extent die cutting and pouch packaging. Since most manufacturing steps (coating/drying/laminating processes, slitting processes and to certain extent die cutting and pouch packaging) are applied in a continuous manner, a batch scale effect on product quality can be excluded at first. Consequently, the value of data on production scale batches to support the scale of routine production is limited and shall not be a principal	Previously discussed above.

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		requirement. It is suggested to assess the need for these data to be generated on a case-by-case basis. Proposed change (if any): Please amend this section as follows: "Transdermal patches are considered complex dosage forms **for which the manufacturing process may comprise non-standard manufacturing processes**. **Although of limited value for standard processes,** the scale of manufacture should be, **where relevant and on a case-by-case basis,** supported by manufacturing batch data at the proposed production scale."	
492 (See also 165/260/433)	5	Comment : Patch size, area and thickness are mentioned to be determined. It is pointed out, that area weight which may be considered to correlate with thickness can be determined more precisely. Proposed change (if any): Amend line 492 as follows: "In particular, the control of homogeneity and the **thickness and/or area weight** of the drug release and other layers, if present, together with the removal of residual solvents should be fully validated".	Partly accepted but patch thickness is considered a CQA. Text changed to: *"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."*
494	5	Comment: The term "laminates" seems inappropriate in this context and should be replaced by "films and foils".	Previously addressed. See above

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Proposed change (if any): 1) Amend title as follows: "4.4 Control of excipients, **films & foils**" 2) Define the terms "film & foil", "laminate" and "layer" under section Definitions, if both terms are to be used within the scope of this guideline (see also comment to line 160 & 213-215 & 224).	
495-496	5	Comment : This section should acknowledge that excipients used for other topical dosage forms (e.g. in topical creams, lotions) than transdermal patches, may also be considered as safe, if justified. Proposed change (if any): Please amend section as follows: "If the material(s) is new or has not been previously authorised for a transdermal use **or any other mode of topical administration (e.g. in topical creams, lotions)**, then full quality details should be provided […]"	Accepted. The text has been amended to: *"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 drug substance format."*
516-518	5	Comment : This sentence should specifically exempt suspension patches, where the drug substance is intentionally dispersed within the matrix. Proposed change (if any): Please amend as follows: "In general, **with the exception of suspension**	Accepted. The text has been amended to: *"With the exception of suspension patches where the drug substance is intentionally dispersed within the matrix, at release a transdermal patch should show no signs of crystallization."*

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		patches where the drug substance is intentionally dispersed within the matrix, at release a transdermal patch should show no signs of crystallization".	
532	5	Comment : It is not clear from this section whether the maximum daily dose, which is the basis to calculate the acceptable limits for degradation products, refers to the labelled drug content present in the patch or to the daily release rate of the transdermal patch. This needs clarification. Proposed change (if any): Please amend the sentence as follows: "[…] and qualified by reference to the maximum daily systemic dose of the drug substance **(i.e., nominal release rate per day)**, […]"	Accepted.
Line 487-488	9	Hold times and storage conditions of intermediate materials should be stated and justified, supported by appropriate stability and other relevant data. Comment: At this moment in time we do not have validated storage conditions, I think that is also not a current requirement	Not accepted. Possible critical process parameters should be identified. Intermediates of this complex dosage form are, if not otherwise justified, has an influence regarding the hold times and storage conditions and are therefore a critical process parameter. Data to justify these storage conditions and holding times are a prerequisite for the acceptance and authorisation of such a manufacturing process.
Line 489	9	Transdermal patches are considered complex dosage forms manufactured by non-standard manufacturing	Previously addressed. See above.

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		processes. Comment: this sentence sounds very strange to me. The part "...by non-standard manufacturing processes" is not clear for me.	
Lines: 514 - 515	9	Comment: ICH Q6A allows for different release and shelf life specifications. Proposed change (if any): Delete lines.	Not accepted. Differences in the limits between the release and shelf-life specification could be accepted if justified and qualified by clinical data.
489-490	10	Comment: Please add the following wording after sentence in line 489/490. Proposed change (if any): A manufacturer's own experience in the manufacture of transdermal patches including use of processes which might otherwise be considered "non-standard", might permit to define this production for this manufacturer **not** as a non-standard process and might exempt it from the need to provide production scale process validation data at the time of submission provided sufficient supporting data are provided.	Previously addressed. See above.
495	10	Comment: Typo. Proposed change (if any): If the material(s) is new or has not been previously authorised for transdermal use...	Previously addressed. See above.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
517	10	Comment: Typo. Proposed change (if any): The occurrence of crystals throughout use in a transdermal patch.	Previously addressed. See above.
526	10	Comment: Wording. Proposed change (if any): Since residual solvents may affect adhesion and permeation enhancement…	Previously addressed. See above.
533	10	Comment: Please clarify whether specific skin irritation studies will be required or if data from skin safety studies with batches, where the impurities in question have been present, are sufficient.	Previously addressed. See above.
Lines 519-520	11	Comment: Polymers tolerate by their viscosity regularly some degree of supersaturation. The appearance of crystallization may thus reveal a stronger lowering of effective concentration and be connected to considerable decrease in delivery rate. Proposed change ("track changes"): "Crystal formation is a visible quality deficiency which has a likely ~~may not have an~~ influence on the *in vivo* performance of the patch. Applicants should show pharmacokinetically and deduct thermodynamically if this effect may in their single case be small."	Not accepted. From the basis of historical data crystal formation may have <u>or</u> may not have influence on the *in vivo* performance of the patch.

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495 - 496	13	Comment: Some pragmatism is necessary here. First transdermal use of an otherwise established excipient does NOT warrant a full dossier in drug substance format. Important is recognition of CQAs and any new risk factors for the proposed new use, and consideration if supporting information other than an appropriate specification may be necessary in the dossier.	Previously addressed. See above.
503 – 504	13	Comment: To avoid misunderstandings at dossier preparation/review, it should somewhere be unambiguously indicated whether a composition breakdown in the excipient section P4 of the dossier is considered adequate for adhesive mixtures, or if such is expected in P1 in the composition table(s).	In accordance to the above mentioned draft guideline on excipients *"…excipients presented as a mixture of compounds the following should be taken into consideration:* *i. Any bibliographical data on the chemistry and on the toxicology and the field in which the product is already used.* *ii. The Community provisions concerning additives in foodstuffs: any criteria which are based on the toxicological data, with cross-references to these data. The quality specifications which have been laid down in the directives are satisfactory as long as the routine control tests used are validated.* *iii. The international specifications (FAO/WHO/JECFA), and other publications such as the Food Chemical Codex.* *iv. For medicinal products for cutaneous use, data on the starting material in cosmetic products (see*

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			Directive 76/768/EEC, as amended). *v. Data concerning the toxicology of the novel excipient should be presented according to the dosage form and the route of administration of the medicinal product (if applicable).”*
Lines 495-496	14	Comment: / Proposed change: “If the material(s) is new or has not been previously authorized for transdermal use or for topical use, then full quality details should be provided according to the drug substance format.”	Previously addressed. See above.
516-523	16	Comment: A general statement about the presence or absence of patches is inappropriate, as some patch designed incorporate drug substance in solid, undissolved form. Any solid form of the drug substance in the patch must be characterized and appropriately documented, including stability studies, to perform according to the product profile.	Previously addressed. See above.
516 – 518	17	The patch design may actually include crystalline material.	Previously addressed. See above.
489-490	18	**Comment:** “Transdermal patches are considered complex dosage forms manufactured by non-standard manufacturing processes.” may not be applicable to all manufacturers/ manufacturing processes. Manufacturers with experience in the specific	Previously addressed. See above.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		manufacturing process of transdermal patches for which a marketing authorization application or a variation to a marketing authorization is submitted should be exempted from the requirement to submit process validation data with the submission. Hence, process validation could then be performed prior to launch. **Proposed change (if any)**: "Transdermal patches are **generally** considered complex dosage forms manufactured by non-standard manufacturing processes, **unless the drug product manufacturer has experience with this specific drug product manufacturing process. In this case, the manufacturing process might be considered not to be "non-standard" allowing exemption from the requirement to provide process validation data in the submission of a marketing authorization application/ variation application to a marketing authorisation."**	
517-518	18	**Comment**: Typo. **Proposed change (if any):** "The occurrence of crystals throughout **the shelf-life period** 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."	Previously addressed. See above.

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Lines 495-496	19	Comment: It should be made clear that the ASMF procedure cannot be used to provide (confidential) information on novel excipients. Instead, the manufacturer of the novel excipient may submit the information directly to the authorities in order to maintain confidentiality. Proposed change (if any): See above.	Not accepted. The active substance master file (ASMF) procedure is the only procedure available to provide confidential information directly to the EMA or national competent authorities. Please note that the ASMF procedure (former also known as Drug Master File procedure) is only foreseen for active substances. For novel excipients a dossier should be established containing the same data as that required for new active substances.
Lines 519-520	19	Comment: Proposal for statement that, in the cases that crystal formation does occur, it is recommended to also explain this in the SmPC in view of patient acceptance. Proposed change (if any): Add text as proposed above.	Previously addressed. See above.
Lines 550-553	1	Comment: Changes in the patch type (*e.g.*, drug-in-adhesive vs. reservoir), the presence or absence of an integrated overlay, and the patch size, area and thickness are all possible while still developing a bioequivalent transdermal product.	Accepted.
Lines 601-602	1	Comment: Transdermal manufacturing processes have been in existence with similar operating principles and unit operations for more than 30 years now. In many ways, they are no more complex than the processes used to manufacture other dosage forms.	Previously addressed. See above.
599	2	Comment: "Satisfactory" clinical safety: This is an	Accepted.

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		unspecific wording that would most likely not be accepted by e.g. ethics committees, if provided as a study aim in clinical study protocols. Proposed change (if any): Non-inferiority regarding clinical safety and local tolerance of the generic product should also be demonstrated.	Non-inferiority regarding clinical safety and local tolerance of the generic product should also be demonstrated.
646	2	Comment: "Peel adhesion" should be replaced by "Adhesion strength". In addition, the test on "Peel strength" should be added to the definitions, defined as the force required to separate the protective liner from the patch.	Not accepted. On the basis of a harmonised international standard, “Peel adhesion” is internationally understood as the force required to remove a transdermal patch from a test panel at a controlled angle and at a standard rate and condition. Thus, the term “Peel adhesion” does not need to be replaced.
581-589	3	Comment: Please see comments on lines 148-156.	Previously addressed. See above.
598	3	Comment: Please clarify reference - presumably, guideline CPMP/EWP/280/96/ Corr* is meant.	In line 598, following guideline reference is meant: EMA/CHMP/EWP/280/96 Rev. 1.
599	3	Comment: “Satisfactory” clinical safety: This is a very unspecific wording that would most likely not be accepted by e.g. ethics committees, if provided as a study aim in clinical study protocols.	Previously addressed. See above.

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		Proposed change (if any): Non-inferiority regarding clinical safety and local tolerance of the generic product should also be demonstrated.	
612	3	Comment: Please add wording as given below before line 612 in order to underline current industry practice on quality risk management. Proposed change (if any): The range of quality attributes which have to be verified in relation to a change incident should be evaluated by a risk assessment prior to any further activities.	Accepted.
615	3	Comment: Please clarify: Does this trigger the need to conduct a fully powered skin adhesion equivalence study including statistical evaluation?	If no comprehensible justification is available showing that the proposed change(s) will not affect skin adhesion, an in vivo skin adhesion equivalence study needs to be conducted.
615-616	3	Comment: The use of *in-vitro in-vivo* studies should be permitted where justified. Proposed change (if any): In addition, bioequivalence and *in vivo* skin adhesion equivalence studies may also be required, unless justified e.g. by the use of *in vitro in-vivo* studies.	Accepted.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
646	3	Comment: We suggest refining definitions in order to avoid ambiguities. "Peel adhesion" should be replaced by "Adhesion strength". In addition, the test on "Peel strength" should be added to the definitions, defined as the force required separating the protective liner from the patch. Proposed change (if any): Adhesion Strength. Peel strength: The force required to separate the protective liner from the patch.	Previously addressed. See above.
548	4	Comment: a generic drug application refers in all the toxicological and clinical results to the documentation of the originator. As these data, referring to the reason for transdermal delivery of the drug, are included in the originator's documentation, reference to these data should be sufficient.	Accepted.
568	4	Comment: this requirement needs a more precise definition of generics. If, in the case of transdermal systems, the released dose is the criterium for the strength, the requirement could be fulfilled. In Germany, the generic substitution, requires the same drug content, Also, the Narcotics Law requires the same dose.	The most important condition for substitution a generic transdermal patch in Germany is that the dosage strength must be the same. Variability to a certain extent with respect to overall drug substance content may be permitted according to German Narcotics Law, and this is comprehensible. Due to patent protection, some generic transdermal patches

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			must have another adhesive composition with a consequence that differences concerning absolute drug substance content may be unavoidable. No change to the text is required.
570	4	Comment: generics always have to deal with current patent protections. In some cases the use of specific adhesives with low solubility for the drug, e.g. silicones or polyisobutylenes or the like is patent protected by formulation patents. If may be necessary, in order to circumvent these patents, to use PSAs with higher solubilites, thus needing a different drug concentration, and or higher patch areas. This requirement would lead to an additional protection of the originator product and cannot be in the scope of cost reduction in the EU health systems.	The comment is acknowledged. The text does not need to be amended. It is anticipated that generic products will be manufactured with different adhesive systems compared to the innovator.
556-557	5	Comment : For generic medicines application, the term optimisation might not be reflecting the actual effort to match the release rate of the comparator product to demonstrate bioequivalence. Proposed change (if any): Please amend as follows: “The studies undertaken during the pharmaceutical development to optimise **or achieve suitable** in vivo release rate (mass delivered in vivo/unit area/unit	Accepted. The text has been amended to: *“The studies undertaken during the pharmaceutical development to determine in vivo release rate (mass delivered in vivo/unit area/unit time), drug substance utilisation and residual should be fully described.”*

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		time), drug substance utilisation and residual should be fully described."	
585 (see also 152 & 635-645)	5	Comment : The proposed definition for Patch area activity does not appear to provide any relevant information. Proposed change (if any): Please refer to comment for line 635-645 and proposal to amend the definition.	Previously addressed. See above.
591-593	5	Comment : Adhesive properties can only be properly evaluated during the clinical development program, since the in vitro test systems cannot be considered fully representative of the in vivo situation. The in vitro data may therefore not be correlated with those derived from in vivo tests. As such, achieving comparable in vitro results between a reference product and the product under development cannot be considered a scientific requirement. The same holds true for dissolution. Here, dissolution profiles can also be fairly different between two products yet the two medicinal products can be bioequivalent in vivo. Proposed change (if any): Please amend this section as follows: "[…] should be investigated and **the differences and** similarities in in vitro performance […] discussed, supported by appropriate data. Observed in vitro differences shall be addressed yet will typically not	Partly accepted. In lines 591-593 the claim of crucial quality characteristics is meant rather than an in vitro / in vivo correlation (IVIVC). Comparison of crucial quality characteristics of generic transdermal patch with those of the reference patch enables to conclude whether a comparable quality level can be achieved by the generic patch. Following addition to the text is considered reasonable: *"[…] should be investigated and **the differences and** similarities in **in vitro** performance […] discussed, supported by appropriate data."* The latter part of the proposed change is explanation and it goes without saying.

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		prejudge of in vivo performance and bioequivalence between two products which shall be assess on their own merit. ”	
594-595 in combination with line 582	5	Comment: It appears contradictory to have a requirement for the quality elements to be similar between the test and reference products whereas simultaneously it is clearly encouraged to minimize the absolute drug content of the patch by equal release rate (leading to minimised residual drug). Proposed change (if any**):** Line 595 may be deleted in this context.	Not accepted. Contradiction cannot be seen.
598	5	Comment: For generic applications, the QWP asks for non-inferiority compared to the reference product with respect to in-vivo skin adhesion. Since there is very poor information available in the public domain on possible non-inferiority margins for the different TDDS systems, a demonstration of statistical non-significance for the adhesion data should be adequate. Proposed change (if any): Please amend as follows: “To support a generic application, bioequivalence with the reference product should be demonstrated (see clinical guideline) and also non-inferiority **(absence of**	Accepted.

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		statistically significant difference) with respect to in vivo skin adhesion (see Annex II)".	
601	5	Comment : In spite of transdermal patches being a complex formulation, a number of manufacturing steps applied in manufacture and production of transdermal matrix patches can today be considered to be standard or conventional processes for this dosage form. We oppose the idea that the manufacturing process for transdermal patches is 'normally' considered complex, in respect to the current variation guidance. (See also comment to lines 489-491). Proposed change (if any): Please amend this section as follows: "**Certain steps of** the manufacturing process for transdermal patches can be considered complex, in respect to the current variation guidance. **Applicants should clearly identify those manufacturing steps which are to be considered non-standard**".	Previously addressed. See above.
605 (as well as 207 and 208)	5	Comment : Line 605 does not reflect that the thermodynamic activity of the drug substance might not be relevant for all formulations (e.g., formulations with drug substance in solution). Proposed change (if any): Amend line 605 as follows "Change in physicochemical state and / or	Not accepted. The bullet points should be kept with brief description. Therefore, further explanation is not deemed necessary.

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		thermodynamic activity of the drug substance **as a consequence of decreased solubility within the matrix (where relevant and appropriate)**".	
612-615	5	Comment : While the proposed method to support the change is appropriate in lines 612 -615, it is not acceptable that in any case a bioequivalence study is required by default. Proposed change (if any): **"In addition, bioequivalence and in vivo skin adhesion equivalence studies may be required in some specific cases; not performing these studies would however need to be justified."**	Not accepted. Line 616 states "[...], unless extensively justified." This already implies that not in all cases a bioequivalence study is required.
622+	5	Comment : **The proposed definition of 'cold flow' cannot be accepted as proposed in the draft guideline**. It more or less describes the impact of cohesive strengths on quality attributes and dark ring formation. Proposed change (if any): Please replace the current definition by the following one: **"Cold flow refers to a dimensional change /deformation of the polymeric matrix under constant load and temperatures within the working range. Cold flow (or creep) is caused by the polymer molecules creeping towards stronger bonds and is thus the basis of adhesion**	Partially accepted. The text has been amended as follows: *"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."*

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		of e.g. polymer mixtures to materials or skin. However, the balance of adhesive and cohesive properties should be carefully adjusted, because significant cold flow may affect handling of the patch by sticking to the sachet or patches may leave a sticky residue around the patch."	
634	5	Comment : The text between brackets does not provide added value and should preferably be deleted. Proposed change (if any): Please delete the text into brackets: ~~**"(preferably per hour)**~~"	Accepted.
635-645	5	Comment : The patch area activity appears as a value failing to provide any relevant additional information. According to the equation provided, the nominal released quantity expressed as percentage (=normalized to 100) is divided by the patch size. Taking into account that – usually – dosage strength is adjusted with patch size (mainly resulting from a laminate of equal qualitative and quantitative composition), this leads to different patch area activity values. It is proposed to calculate the percentage of released quantity, referring to the nominal drug content of the patch. Alternatively, the residual drug content (e.g. mg) can be compared – on the same dosage strengths.	Not accepted. The proposed change is not a suitable replacement for the Patch Area Activity calculation.

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		The patch size may also be compared between two products, e.g. by calculating the size ratio of new and established product on the same dosage strength or by simply comparing the size in cm^2. Proposed change (if any): We suggest amending the definition of Patch area activity so that the percentage of released quantity refers to the nominal drug content of the patch. In this context it may be considered to re-name to Patch activity.	
654	5	Comment: For consistency purposes, please adapt the guideline definition to that of the European Pharmacopoeia. Proposed change (if any): Please replace by Ph. Eur. Monograph on dosage forms, Patches, transdermal.	Accepted.
NEW	5	Comment : A definition for laminate shall be provided. Proposed change (if any): Please insert: **“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**	Accepted.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		backing film).”	
NEW	5	Comment : A definition for layer shall be provided. Proposed change (if any): Please insert: “**A layer is a single coherent composite. More than one layers form a laminate. Transdermal patches consist of several layers as e.g. release liner, drug-in-adhesive, drug-controlling membrane or backing film**.”	Accepted.
598	8	**Comment:** Line 598 of the draft guideline requires demonstration of non-inferiority to the reference product with respect to in vivo skin adhesion. Line 615 in contrast mentions “in vivo skin adhesion equivalence studies”. In contrast, lines 911-918 seem to suggest a descriptive evaluation only. A non-inferiority study or equivalence would require a non-inferiority/equivalence margin to be defined, which seems very difficult, and might require very large sample sizes. Furthermore, other than descriptive evaluations would not be consistent with lines 873-875 that allow the combination of such studies with pharmacokinetic	Not accepted. Non-inferiority boundaries should be fixed. In the event that these boundaries are not available, descriptive evaluation is deemed suitable. Re-wording of the term “non-inferiority” is not considered necessary.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		studies. **Proposed change:** It is proposed to re-word “non-inferiority with respect to in vivo skin adhesion” to read “comparable adhesive properties in vivo”.	
615	8	**Comment:** Line 615 mentions “bioequivalence and in vivo skin adhesion equivalence studies”. **Proposed change:** As suggested for line 598, it is proposed to re-word to read “bioequivalence and comparable adhesive properties in vivo”.	Not accepted. Re-wording of the term “non-inferiority” is not considered necessary.
516	9	Proposed change (if any): change from “…no signs of crystallization” to “…no signs of crystallization if the product is expected to not have crystals (below saturation)”.	Previously addressed. See above.
610	9	Comment: Delete in vitro permeation. (see comments above regarding variability of intro skin permeation studies.	Previously addressed. See above.
614	9	Comment: Delete in vitro permeation. (see comments above regarding variability of intro skin permeation studies.	Previously addressed. See above.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
647	9	Proposed change (if any): change from "…a patch from a surface" to "…a patch from a standardized surface like stainless steel".	Accepted.
658	9	Proposed change (if any): change from "…preparation to the skin" to "…preparation to the skin. The active substance(s) can be incorporated directly into the adhesive matrix to form a matrix designed delivery device".	Previously addressed. See above.
661	9	Proposed change (if any): change from "…by a rate-controlling membrane" to "…by a rate-controlling membrane and a pressure sensitive adhesive".	Accepted.
665	9	Proposed change (if any): change from "…may also be a solution or dispersion…" to "…may also be a solution or solid dispersion…"	Accepted.
581-589	10	Comment: Please see comments on lines 148-156.	Previously addressed. See above.
598	10	Comment: Please clarify reference - presumably, guideline CPMP/EWP/280/96/ Corr* is meant.	In line 598, the following guideline reference is meant: CPMP/EWP/QWP/1401/98 Rev.1
599	10	Comment: "Satisfactory" clinical safety: This is a very unspecific wording that would most likely not be accepted by e.g. ethics committees, if provided as a study aim in clinical study protocols.	Previously addressed. See above.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Proposed change (if any): Non-inferiority regarding clinical safety and local tolerance of the generic product should also be demonstrated.	
612	10	Comment: Please add wording as given below before line 612 in order to underline current industry practice on quality risk management. Proposed change (if any): The range of quality attributes which have to be verified in relation to a change incident should be evaluated by a risk assessment prior to any further activities.	Previously addressed. See above.
615	10	Comment: Please clarify: Does this trigger the need to conduct a fully powered skin adhesion equivalence study including statistical evaluation?	Previously addressed. See above.
646	10	Comment: We suggest refining definitions in order to avoid ambiguities. "Peel adhesion" should be replaced by "Adhesion strength". In Addition, the test on "Peel strength" should be added to the definitions, defined as the force required separating the protective liner from the patch. Proposed change (if any): Adhesion Strength. Peel strength: The force required to separate the protective liner from the patch.	Previously addressed. See above.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
622-626	14	Comment: Cold flow: the appearance of adhesive surrounding the patch is more an aesthetic attribute than a quality one; it may happen that the patch performances (pharmacokinetics, efficacy) could not be influenced by a limited cold flow, especially when hot wearing conditions are met. On the other hand, cold flow is also influenced by the wear duration.	Previously addressed. See above.
565-567	17	We question the relevance of this.	The comment is acknowledged. Investigation of suitable adhesion properties is crucial for the active substance diffusion from the patch into the skin. To find out the most suitable amount of enhancer is on the one hand important for the desired active substance penetration through the skin, on the other hand the chosen amount of enhancer should not essentially affect the adhesion properties of the transdermal patch.
568-572	17	Vague.	The comment is acknowledged. No amendment to the text is required.
615-616	18	**Comment**: Please clarify whether the following “In addition, bioequivalence and *in vivo* skin adhesion equivalence studies should also be required, unless extensively justified.”does trigger the need to conduct a fully powered skin adhesion equivalence study including statistical evaluation. Statistical powering might not be possible.	Previously addressed. See above.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
590-595	19	Comment: What are the acceptance criteria with respect to comparative drug release / dissolution, in vitro skin permeation and adhesion / cohesive and viscolelastic properties? Proposed change (if any): Please add the requirements.	The comment is acknowledged. No amendment to the text is required. Suitable acceptance criteria should be set by the applicant, depending on the outcome of corresponding tests with the reference transdermal patch.
Lines 600-611	19	Comment: Changes in the manufacturing site, equipment, and batch size can also have a significant impact. Proposed change (if any): Please add bullet points with the above.	Not accepted. These three aspects may already be considered in the fourth bullet point. Thus, separate enumeration is not deemed necessary.
722-723	2	Comment: The requirement of typically six replicates or more for pivotal experiments is not in line with the OECD technical guideline 428, which requires data from a minimum of four replicates. Proposed change (if any): Typically, four replicates may be used, or more for pivotal experiments.	The comments are acknowledged. This comment is not endorsed. More than 4 replicates are needed.
796	2	Comment: We suggest dropping this requirement. From a data protection perspective, the identity of skin donors has to remain concealed from the lab using the skin for experiments. Therefore, as the identity of donors is not known, there is no way of unambiguously determining whether two skins are derived from the same donor.	The comments are acknowledged. This comment is not endorsed. When sourcing human skin tissue this information is provided by the hospital.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
801-802	2	Comment: For multi-day patches, *in vitro* skin permeation should be carried out for more than 24 hours. Skin does not necessarily deteriorate after 24 hours. Duration should be appropriate for the formulation under test.	The comments are acknowledged. This comment is endorsed and the text will be revised accordingly.
803-804	2	Comment: We suggest replacing "been compromised" with "deteriorated to an extent not conducive to sound testing".	The comments are acknowledged. This comment is endorsed and the text will be revised accordingly.
844-845	2	Comment: We suggest rephrasing in order to avoid repeated use of percentages and the word "interval" for different items. Proposed change (if any): 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 comments are acknowledged. This comment is endorsed and the text will be revised accordingly.
706	3	Comment: Please clarify on the requirement of "fresh" human skin and whether this means that no frozen and defrosted skin may be used? In practice, most skin used in the lab for skin permeation studies will not be fresh.	The comments are acknowledged. This comment is endorsed and the text will be revised accordingly.
718	3	Comment:	The comments are acknowledged.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Please clarify whether tritiated water is meant. Due to restrictions in use of radioactive materials and due to the availability of other methods to perform skin integrity testing, this rather appears to be an option for academic settings, but not for routine industrial pharmaceutical development. Proposed change (if any): Tritiated.	This comment is endorsed and the text will be revised accordingly.
722	3	Comment: The requirement of typically six replicates or more for pivotal experiments is too large. (Against the background of the difficult supply with suitable human skin material). The OECD technical guideline 428 requires data from a minimum of four replicates. Proposed change (if any): four replicates.	Previously addressed. See above.
746	3	Comment: Please align with definition of sink conditions in Ph.Eur.: Definition of sink conditions as concentrations less than 10 % of maximum solubility of analyte in the receptor solution should be aligned with Ph.Eur., where sink conditions are defined as 10-33% of maximum solubility [Ph.Eur. 5.17.1].	The comments are acknowledged. This comment is endorsed and the text will be revised accordingly.
755-758	3	Comment: To us, performance of a mass balance study is not	Accepted.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		required for the typical experimental set up, where a comparison of different formulations is intended. Proposed change (if any): Delete lines 755-758.	
768	3	Comment: Transport validation is a very strict requirement and not strictly necessary, as integrity of skin will be verified prior to use (cf. lines 771-772).	The comments are acknowledged. This comment is endorsed and the text will be revised accordingly.
775	3	Comment: Please rephrase, as the meaning is unclear: When administered, transdermal patches themselves are occlusive.	The comments are acknowledged. This comment is endorsed and the text will be revised accordingly.
791	3	Comment: cf. comment on line 718.	The comments are acknowledged. This comment is endorsed and the text will be revised accordingly.
796	3	Comment: We kindly request to drop this requirement. Supply with suitable human skin material is difficult and due to the lack of correlation between in vitro permeation studies and in vivo permeation data this requirement cannot be fulfilled. From a formal perspective, the personal data like the identity of skin donors cannot be disclosed by the lab when providing skin specimen for in vitro experiments. Therefore, as the identity of donors is unknown, it is practically impossible whether two skin specimens are derived from the same donor or not.	Previously addressed. See above.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Proposed change (if any): Delete line 796.	
799	3	Comment: From our experience, 15 or 30 minutes is too early as permeation starts after a lag time that is typically not less than 30 min. Proposed change (if any): Minimum of 5 suitably timed receptor sampling time points.	The comments are acknowledged. This comment is endorsed and the text will be revised accordingly.
801	3	Comment: For multi-day patches, in-vitro skin permeation should be carried out for more than 24 hours. Skin does not necessarily deteriorate after 24 hours. Duration should be appropriate for the formulation under test.	Previously addressed. See above.
802-804	3	Comment: The current wording is apodictic and would disallow the use of data where any difference in skin integrity during measurement has taken place. However, suitable limits will have to be permitted. Proposed change (if any): Longer periods should be justified in respect to *in vivo* use and satisfactory data to show that the integrity of	Previously addressed. See above.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		the skin has not deteriorated to an extent not conducive to sound testing should be provided.	
805	3	Comment: cf. comment on line 775.	The comments are acknowledged. This comment is endorsed and the text will be revised accordingly.
806-808	3	Comment: cf. comment on line 755. Proposed change (if any): Delete lines 806-808.	Accepted.
823	3	Comment: Please state this requirement more precisely as not all parameters to be validated according to ICH Q2 are relevant to the test methods used here.	This comment is not endorsed. Analytical methods should be validated according to ICH Q2.
827-828	3	Comment: Please state more precisely, whether the coefficient of variation of the entire test including sample preparation etc. has to meet the given limits, or only the cv for the analytical method.	This comment is not endorsed. The variability refers to the permeation study results.
843-845	3	Comment: Rephrase to avoid repeated use of percentages. Proposed change (if any): 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	Previously addressed. See above.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		claim of equivalence, unless justified.	
848, 850	3	Comment: Typo. Proposed change (if any): Delete “1” at end of lines 848 and 850.	This comment is endorsed and the text will be revised accordingly.
850	3	Comment: The measurements conducted here are not within the scope of GLP according to Directive 2004/10/EC. Therefore we do not feel that it is appropriate to *exclusively* mandate observance of GLP-standards. Proposed change (if any): A declaration of compliance with the principles of Good Laboratory Practice or operation under another suitable quality system, e.g. GMP.	This comment is endorsed and the text will be revised accordingly.
851-853	3	Proposed change (if any): The technical ability of the performing lab is intrinsically verified during method execution.	This comment is not endorsed. Due to the large high variability resulting from the skin it will be very difficult to acertain technical ability during method execution.
854	3	Comment: We kindly request to delete this requirement for those institutions, where skin permeation testing is conducted in the same units that are conducting formulation and	The comment is acknowledged. Evidence of a satisfactory quality system should be provided.

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		analytical development and is included in the overall quality system of this organisation.	
706 - 796	4	To our knowledge and experience in Germany it is not possible to get commercial samples of freshly dermatomed human skin, with reference to the organ trade law. There are limited, very expensive, sources which offer either freeze dried or frozen skin sample, with very limited capacities, and questionable legal basis. It is not possible to get high and reproducible qualities in sufficient amounts, which will be necessary for the number of tests, as proposed by this draft guideline. It is agreed, that in order to save animal or human tests skin permeation tests are necessary when changes at a given product are made, or a waiver for bioequivalence study is proposed, but for routine tests, be it in stability tests or quality control, the use of human skin should not be expected.	The comments are acknowledged. As stated in section 4.2.6.2, 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.
708-710	4	In general, even on the same type of skin, the comparison of different patch types, i.e. reservoir vs matrix may be completely misleading, because of water uptake into the sin and moreover into the patch from the acceptor, leading to precipitation at the patch/skin interface with matrix patches, whereas reservoir patches can prevent this by their solvent content. This also happens when you compare a supersaturated matrix system with a sub-saturated system. In vivo this water diffusion is much more	The comments are acknowledged. No amendment to the text is required.

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		restricted, thus such experimental difficulties do not occur under clinical condition. Before one has adjusted his in vitro permeation model with in vivo results, a justification of the chosen model often is speculative. Taking this into consideration, the in vitro skin permeation model in general only compares thermodynamic activities of drugs, when present in comparable patch systems. Otherwise, the unavoidable water uptake alters the drug solubilities.	
724	4	This diffusion area is rather small. What is recommended to test reservoir patches that cannot be cut?	This comment is endorsed and the text will be revised accordingly.
775	4	The request for unoccluded test conditions should only be made for non-occlusive patches. Occlusive patches cover the whole skin area of 0,5 to 2 cm^2	This comment is endorsed and the text will be revised accordingly.
704-709	5	Comment : The choice of the skin model is the full responsibility of the scientist / development department and should be justified considering the *specific scope of the respective experiments*, this also includes the body area from which the skin samples derives from. Proposed change (if any): Please amend this section to reflect the above responsibility of the scientist / development department and the need for justification of the choice.	This comment is endorsed and the text will be revised accordingly. Lines 704-705 have been deleted.
714-716 &	5	Comment :	This comment is endorsed and the text will be revised

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771-772 & 790		Skin integrity tests can typically lead to stress to the skin tissue and prove time consuming. Therefore, especially during early development – e.g. screening – a visual check of the skin tissue should be accepted as sufficient. In case of use of prepared skin (fresh or stored), it should be demonstrated according to the present draft guideline, that skin samples for skin permeation experiment are not damaged by preparation. Therefore skin integrity should be determined before the experiment. Neither the OECD Guideline for the Testing of Chemicals 428, adopted 13th April 2004, nor the present Guideline request performance of a certain analytical method to describe skin property. The OECD Guidance no. 28 lists determination of Transepidermal Water Loss (TEWL), determination of transdermal epidermal electrical resistance (TEER) and penetration experiments of tritiated marked water as accepted test method for pre-study integrity evaluation. Publication of F. Netzlaff, University of Saarbrücken, 2006 (dissertation) reflects the actual state of science and states that use of TEWL is not suitable for detection of local and limited skin damages. Only an overall deterioration of the skin barrier can be recognized with this test method, which would easily be recognized too by visual examination of the skin	accordingly. Skin integrity test should be performed prior to start of the experiment only. The method employed may include TEWL, resistance or visual inspection (but not accepted for pivotal studies).

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		preparation intended for use. Therefore measurement of TEWL before permeation experiment provides no additional information compared to visual examination. The use of tritiated marked water is based on determination of water flux through the skin via calculating water permeability coefficient from a dataset established over a number of hours (Dugard et al., 1984; Roper el al.; 2000; Scott et al. 1992). This procedure requires treatment of skin preparation with solutions, potentially resulting in modification of skin status e.g. by swelling. Therefore a possible effect of treatment with the used solution on skin integrity by the test itself cannot be excluded. Additionally, according to directive 96/29/ of the Council of the European Union, dated 13 May 1996, the use of radioactive molecules like tritiated water has to be justified by demonstrating that this test method reveals to a benefit (economic, social or other) compared to other test methods acting without radioactive substances. Furthermore special requirements regarding safety at work for laboratory use of radioactive substances have to be fulfilled when applying this test method. Thus the use of tritiated water is not regarded as a suitable method for testing of skin integrity prior to use. Compared to the use of tritiated water, determination of electrical resistance is regarded as a more effective method (D. Davis, R. Ward, J. Heylings, Multi-species	

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		assessment of electrical resistance as a skin integrity marker for in vitro percutaneous absorption studies, Toxicology in Vitro 18 (2004) 351-358) to investigate skin integrity prior to permeation experiment. Although skin is brought into contact with solution too, this method may be regarded as suitable, since the measurement itself needs only a short time and the used 0.9% sodium chloride solution is not expected to alter skin barrier properties. **In summary**, visual testing of skin allows recognition of mechanical damages. Minor changes in skin integrity may remain undiscovered – this is a comparable situation to that which exists in clinical studies in man. The determination of TEWL and water flux by use of tritiated water are regarded as not suitable for the above listed reasons. Measurement of electrical resistance is described in literature as an effective and reliable method. In order to confirm skin integrity after performance of permeation experiment the present draft guideline requests a further assessment of skin integrity (line 715 sqq.). It is noted that removal of test formulations, especially in case of transdermal systems, is in many cases not possible without performing a certain strip effect to the skin surface at the same time due to adhesive properties of the vehicle. Therefore skin properties may be changed as a	

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		consequence of removal and measurement of skin integrity does not provide valid information about the skin status at the end of the permeation experiment. In conclusion assessment of skin integrity after performance of permeation experiment should be renounced. Proposed change (if any): The sections 714-716 & 771-772 & 790 should be amended to reflect that **the extent and method to investigate the skin tissue samples used for permeation experiments is the responsibility of the scientist / development department and that it should be described in the scope of the experiment**. It should also be acknowledged that, especially during (early) formulation screening / drug candidate screening, it may be appropriate to run more experiments and accept a considerable uncertainty regarding the skin integrity. Especially since relevant damages may be seen in unusual high drug fluxes of single profiles.	
731-735 in connection with 746	5	Comment : It is recommended to avoid organic co-solvents in the acceptor fluid whenever possible. The guidance should be revised to allow maximum concentration in the fluid to up to e.g. 30% (sink conditions) as only up to 10% (ideal sink conditions). This would allow preventing that the skin barrier is artificially destroyed by the co-	This comment is endorsed and the text will be revised accordingly.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		solvents. Also, a pH shift of the fluid for basic/acidic molecules may be taken into account. Proposed change (if any): Please revise this section in line with the above comment. Please add the following definitions: - sink (NMT 30% of solubility, see also USP 35 chapter <1092> or Ph. Eur. 2.9.3) and - ideal sink condition (NMT 10% of solubility) shall be defined within the guidance document.	
768	5	Comment: The validation of the transport of skin tissue, which may originate from a variety of clinical sites is considered to be out of scope. It is however acknowledged, that the transport of the skin may be a critical step that requires adequate control. Proposed change (if any): Please amend this sentence by the following: “The storage and transport of the skin should be defined **and appropriately controlled**”.	This comment is endorsed and the text will be revised accordingly.
794-795	5	Comment : This section is unclear and should preferably be reworded. Proposed change (if any): Please amend as follows: “Number of replicates: the choice of the number of	This comment is endorsed and the text will be revised accordingly.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		samples should be **justified with regard to the scope of the experiment."**	
797	5	Comment : This bullet point seems overly prescriptive. The anatomical region concerned should allow other body locations than the three listed in the present draft guideline. Based on current experience, human skin derived from, for example, the upper arm, may also be appropriate for skin permeation experiments. Proposed change (if any): This section should be reworded so as to allow other body regions. "Skin anatomical region – **e.g.** abdominal, breast, back, arms **(non-exhaustive)**".	Previously addressed. See above.
799	5	Comment: The sampling scheme should be specified according to the expected permeation profile considering the lower limit of quantification of the analytical method. Therefore, for many drug substances and depending on the skin tissue, relevant lag times may be observed with quantifiable drug concentrations in the acceptor fluid at significantly later time points than those suggested in the draft guideline. Proposed change (if any): Please delete the end of the section as follows: "Minimum of 5 receptor sampling time points, including	This comment is endorsed and the text will be revised accordingly.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		an early time point~~**, e.g. 15 to 30 min**~~".	
806-807 838-839	5	Comment The determination of the mass balance is in many experiments not of primary interest and should be limited to specific scientific questions. Moreover, recovery rate especially from the skin tissue and the individual drug content of the test item (e.g. patch segment) may bear relevant variation, so that a fixed acceptance range for a mass balance is not acceptable. E.g. Ph. Eur. 2.9.40. allows individual dosage units with drug contents of 85% or 115% of labelled claim, solely this may burst the acceptance range for mass balance of 90-110%. Please refer also to comment to lines 755-757. Proposed change (if any): Please amend this section as follows: 'Unoccluded conditions The mass balance should be determined**,** if the recovery is not within the 90-110% range, **where necessary with regard to the scope of the experiment**. The overall recovery **range for** the drug substance **should be determined and justified, where applicable**."	Previously addressed. See above.
821	5	Comment : The analytical methods should be demonstrated to be selective.	Not accepted. The current wording is clear.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Proposed change (if any): Please amend this section as follows: "the stability indicating power of the method should be assessed. **The method should be demonstrated as selective**."	
828	5	Comment: Skin models are intended to be as close as possible to real conditions. During a clinical trial a CV significantly higher than 10% would be expected. Consequently, for human skin a CV of 10% appears as an underestimation of what would be accepted in vivo. Proposed change (if any): Please amend the sentence as follows: "[…] for human skin a coefficient of variation **significantly higher** than 10% can be expected".	Not accepted. The current wording reflects the fact that for human skin a CV greater than 10% can be expected.
843-845	5	Comment: The straightforward adoption of bioequivalence criteria to apply to in vitro skin permeation experiments does not appear appropriate nor relevant. These criteria can solely be applicable to clinical BE trials in subjects. If two products are to be compared appropriate statistical tools should be applied as e.g. t-test or t-test with Welch correction to resolve Behrens-Fischer problem, if applicable. Appropriate levels of significance are to be applied. Proposed change (if any):	Not accepted. The relevant text has been revised to state: *"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."*

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		"For comparison of products, relevant permeation parameters, e.g. flux, should be statistically compared **using appropriate statistical tools**."	
850	5	Comment : Many laboratories performing skin permeation experiments hold a manufacturing licence and apply a GMP quality system in the lab. Therefore, it does not appear justified to additionally implement a GLP quality system. This should be reflected within this guidance document. Proposed change (if any): Please amend this section as follows: "**the existence of an appropriate quality management system**"	This comment is endorsed and the text will be revised accordingly.
Line 706	6	Comment: 1) The skin site used in *in vitro* studies should be determined based on the intended clinical application site. 2) Literature suggests that rat and human skin are dissimilar. Proposed changes: It is recommended to use fresh human skin ~~from breast or abdomen.~~ 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	This comment is endorsed and the text will be revised accordingly.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		should be justified.	
Line 706	9	Proposed change (if any): ... to use freshly prepared human skin...	This comment is not endorsed. The wording has been corrected to exclude the need to perform the skin studies using fresh skin since frozen skin is acceptable.
Lines 721-723	9	Comment: Number of skin donors should be added here.	This comment is not endorsed. This information is stated in the text.
Line 783	9	Comment: I am not an expert in skin permeation studies, but have used bi-carbonate buffer for organ bath experiments in the past, is this not allowed?	The comments are acknowledged. This specific question should be addressed through scientific advice.
Line 786	9	Comment: humidity of the laboratory room?	This comment is endorsed and the text will be revised accordingly.
Lines 798-799	9	Comment: suggest adding guidance on the selection of time points with respect to the cumulative fraction permeated.	This comment is not endorsed. Time points should be decided based on study requirements.
Lines 800-804	9	Comment: Suggest adding guidance with respect to the maximum cumulative fraction that should have permeated at the end of the experiment.	This comment is not endorsed. Maximum cumulative fraction permeated at the end of the experiment depends upon the transdermal patch under investigation.
Lines 822-823	9	Comment: Suggest adding Bioanalytical Limit of quantification should be less than 1% permeated, to be able to detect lag-time.	The comment is acknowledged, but text not revised. It is intended that further guidance will be published.
Line 834	9	Comment: a slope suggests a linear relationship, which should preferably be true for the larger part of the curve. Suggest adding some guidance on lag-time and less constant permeation rates.	The comment is acknowledged, but text not revised. It is intended that further guidance will be published.
682	10	Comment: Due to limited availability of human skin, high variability of biological material etc. we kindly	This comment is not endorsed. It is not the intention of the guideline to use them as

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		request to preserve in vitro skin permeation studies as a tool for development and not to make them a QC-tool, as intended by this draft guideline, We suggest to reference to OECD technical guideline 428 on skin permeation tests for more formal tests providing e.g. supportive data for variations, and eliminate any requirements for tests during early stage development. Proposed change (if any): Delete Annex I.	a quality control tool. However, 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. Annex I will not be deleted.
706	10/3	Comment: Please clarify on the requirement of "fresh" human skin and whether this means that no frozen and defrosted skin may be used? In practice, most skin used in the lab for skin permeation studies will not be fresh.	This comment is endorsed and the text will be revised accordingly.
718	10/3	Comment: Please clarify whether tritiated water is meant. Due to restrictions in use of radioactive materials and due to the availability of other methods to perform skin integrity testing, this rather appears to be an option for academic settings, but not for routine industrial pharmaceutical development. Proposed change (if any): tritiated.	Previously addressed. See above.
722	10/3	Comment: The requirement of typically six replicates or more for pivotal experiments is too large. (Against	This comment is not endorsed. More than 4 replicates are needed.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		the background of the difficult supply with suitable human skin material). The OECD technical guideline 428 requires data from a minimum of four replicates. Proposed change (if any): four replicates.	
746	10/3	Comment: Please align with definition of sink conditions in Ph.Eur.: Definition of sink conditions as concentrations less than 10 % of maximum solubility of analyte in the receptor solution should be aligned with Ph.Eur., where sink conditions are defined as 10-33% of maximum solubility [Ph.Eur. 5.17.1].	This comment is endorsed and the text will be revised accordingly.
755	10/3	Comment: To us, performance of a mass balance study is not required for the typical experimental set up, where a comparison of different formulations is intended. Proposed change (if any): Delete lines 755-758.	Previously addressed. See above.
768	10/3	Comment: Transport validation is a very strict requirement and not strictly necessary, as integrity of skin will be verified prior to use (cf. lines 771-772) Proposed change (if any): “The storage and transport of the skin should be described ~~and validated~~.”	This comment is endorsed and the text will be revised accordingly.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
775	10/3	Comment: Please rephrase, as the meaning is unclear: When administered, transdermal patches themselves are occlusive.	This comment is endorsed and the text will be revised accordingly.
791	10/3	Comment: cf comment on line 718.	Previously addressed. See above.
796	10/3	Comment: We kindly request to drop this requirement. Supply with suitable human skin material is difficult and due to the lack of correlation between in vitro permeation studies and in vivo permeation data this requirement cannot be fulfilled. From a formal perspective, the personal data like the identity of skin donors cannot be disclosed by the lab when providing skin specimen for in vitro experiments. Therefore, as the identity of donors is unknown, it is practically impossible whether two skin specimens are derived from the same donor or not. Proposed change (if any): Delete line 796.	This comment is not endorsed. When sourcing human skin this information is provided by the Hospital.
799	10/3	Comment: From our experience, 15 or 30 minutes is too early as permeation starts after a lag time that is typically not less than 30 min. Proposed change (if any): Minimum of 5 suitably timed receptor sampling time points.	This comment is endorsed and the text will be revised accordingly.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
801	10/3	Comment: For multi-day patches, in-vitro skin permeation should be carried out for more than 24 hours. Skin does not necessarily deteriorate after 24 hours. Duration should be appropriate for the formulation under test.	Previously addressed. See above.
802-804	10/3	Comment: The current wording is apodictic and would disallow the use of data where any difference in skin integrity during measurement has taken place. However, suitable limits will have to be permitted. Proposed change (if any): Longer periods should be justified in respect to *in vivo* use and satisfactory data to show that the integrity of the skin has not deteriorated to an extent not conducive to sound testing should be provided.	Previously addressed. See above.
805	10/3	Comment: cf comment on line 775.	This comment is endorsed and the text will be revised accordingly.
806-808	10/3	Comment: cf comment on line 755. Proposed change (if any): Delete lines 806-808.	Previously addressed. See above.
823	10/3	Comment: Please state this requirement more precisely as not all parameters to be validated	Previously addressed. See above.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		according to ICH Q2 are relevant to the test methods used here.	
827-828	10/3	Comment: Please state more precisely, whether the coefficient of variation of the entire test including sample preparation etc. has to meet the given limits, or only the cv for the analytical method.	Previously addressed. See above.
843-845	10/3	Comment: Rephrase to avoid repeated use of percentages. Proposed change (if any): 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.	Previously addressed. See above.
848, 850	10/3	Comment: Typo. Proposed change (if any): Delete “1” at end of lines 848 and 850.	Previously addressed. See above.
850	10/3	Comment: The measurements conducted here are not within the scope of GLP according to Directive 2004/10/EC. Therefore, we do not feel that it is appropriate to *exclusively* mandate observance of GLP-standards.	Previously addressed. See above.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Proposed change (if any): A declaration of compliance with the principles of Good Laboratory Practice or operation under another suitable quality system, e.g. GMP.	
851-853	10/3	Comment: Proposed change (if any): The technical ability of the performing lab is intrinsically verified during method execution	Previously addressed. See above.
854	10/3	Comment: We kindly request to delete this requirement for those institutions, where skin permeation testing is conducted in the same units that are conducting formulation and analytical development and is included in the overall quality system of this organisation.	Previously addressed. See above.
682-870	11	Comment: The fine-tuned recommendations give the impression as if a bias-free comparison, even a surrogate for bioequivalence might be achievable, which to my experience is rarely the case. Detailed adhesion behaviour, humidity influences, layers of skin available for diffusion, all these may strongly differ. Proposed change (if any): Limit applicability of skin	Not accepted. Annex I is also applicable to cutaneous formulations and hence the scope is broader than what would be expected for transdermal patches.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		permeation studies to the pre-clinical field, to make be best prognosis in absence of clinical data. Further on, skin permeation results are likely to be contradictory to the real situation and even do not correlate well (as silently accepted in line 693) between formulations.	
Annex 1 Line 850	14	Comment: / Proposed change: “A declaration of compliance with the principles of Good Laboratory Practice or Good Manufacturing Practice.”	Previously addressed. See above.
Lines 867-869	14	Comment: add reference to Directive 2003/94/EC (GMP).	Previously addressed. See above.
Lines 706-709	15	**Comment:** Skin from the human torso (breast or abdomen as well as back) is appropriate for use, although other anatomical locations may be used with justification (e.g. if relevant to the intended clinical use). It is recommended not to use the term non-viable, and instead describe the use of appropriately stored (e.g. cryopreserved) ex vivo human skin, in instances where freshly excised human skin is not practical to utilize. Skin from other species (such as pig) can be used, however, we would recommend not using rodent skin due to its high permeability, which may be less discriminatory toward formulation differences. Our opinion is that the use of artificial/synthetic	Previously addressed. See above.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		membranes is not recommended. **Proposed change (if any):** It is recommended to use human skin from the torso (breast, abdomen or back). If the use of freshly excised skin is unfeasible, appropriately stored (e.g. cryopreserved) *ex vivo* human skin, or skin from another species such as a pig can be used. The choice of skin model used throughout the development should be justified.	
Lines 714-716; 771-772; 793	15	**Comment:** Although post-experiment assessment of skin integrity can be assessed and discussed, we would not recommend a requirement that it be shown to be satisfactory for the experiment to be considered valid. Interpretation of the post-experimental skin integrity results would be problematic because the removal of the adhesive transdermal system from the skin is likely to remove stratum corneum in a manner analogous to skin stripping (which is known to diminish the skin barrier function.). Furthermore, drug or matrix components of the transdermal system may have altered the skin barrier during use, and/or the influence of occlusion by the transdermal system may have altered the skin barrier during use. In addition, the process of post-experimental integrity testing (e.g. tritiated water testing) may alter the distribution and recovery of drug from the skin, particularly where a surface wash is performed to	Previously addressed. See above.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		account for the amount of residual drug on the skin surface following removal of the transdermal system (e.g. when mass balance procedures are included). **Proposed change (if any):** We would not recommend a post-experimental skin barrier integrity test.	
Lines 721-723; 796	15	**Comment:** We recommend no less than 3 donors whenever feasible, because with only 2 donors, there will inherently be one high and one low donor. The inclusion of a 3rd donor affords for a minimum representative assessment of the skin permeation level, which may be particularly critical depending upon inter-individual variability, and better facilitates the calculation of a representative average and standard error for the data. We believe that 3 donors with even 4 replicates each (12 diffusion cells) provides more valuable data than 2 donors with 6 replicates each (also 12 diffusion cells).	This comment is not endorsed. There are difficulties in sourcing human skin and therefore a minimum of 2 donors is recommended. If feasible, a higher number of donors should be used.
Lines 725-726; 787-788	15	**Comment:** We recommend a clarification that the skin surface temperature be at 32°C, not the diffusion cell. The skin surface temperature may be suitably verified prior to dose application using an infrared thermometer.	This comment is endorsed and the text will be revised accordingly.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
Lines 733; 811-812	15	**Comment:** We would not recommend the use of alcohol in the receptor solution, as it may alter the skin's barrier function. The non-ionic surfactant Oleth-20 (a.k.a. Volpo) was shown by Dr. Bob Bronaugh at FDA to provide suitable solubility without compromising the skin barrier. A small amount (typically 0.1%) of provides more than adequate solubility for the vast majority of hydrophobic compounds. Occasional compounds necessitate a slightly higher percentage of Oleth-20 (e.g. 0.2% to 0.5%).	This is acknowledged. To be further investigated. Further guidance will be published.
Lines 800-804	15	**Comment:** The expectation that skin integrity will deteriorate after 24 hrs may not be valid. The stratum corneum, which serves as the predominant layer controlling the rate of delivery from the transdermal system, is a very rugged membrane. Independently, experimental techniques such the use of receptor solution containing antibiotics can mitigate deterioration of the epidermis and dermis across longer study durations (e.g. 7 days). Other experimental procedures such as the use of sterile techniques and/or nutrient media with freshly excised skin may also mitigate deterioration beyond 24 hours. Independently, certain transdermal systems may require greater than 24 hrs to achieve steady-state delivery, and durations representative of the clinical	Previously addressed. See above.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		use duration may be necessary in order to evaluate or compare the sustained performance of the transdermal system across multiple days.	
706-709	16	Comment: The barrier function of the skin is maintained by the stratum corneum, therefore, although fresh human cadaver skin may be used, frozen cadaver skin is also an acceptable alternative for use in skin permeation studies.	Previously addressed. See above.
797	16	Comment: Limitation of skin source to abdomen, back, or breast is inappropriate as skin samples from the extremities or other anatomical sites may be appropriate depending on the product under investigation.	Previously addressed. See above.
798-99	16	Comment: The time points for collection of samples during permeation studies must be selected based on the performance of the individual patch. The recommended “early time points” is inappropriate for some patches.	The comments are acknowledged. The text will be revised accordingly.
817-818	16	Comment: The statement is made that skin permeation studies must discriminate “critical manufacturing parameters that are known to have an	The comment is acknowledged. Nevertheless, some data to demonstrate that the test is discriminating is considered necessary. It is known

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		impact on bioavailability of the product". Such relationships are generally unknown and untested as products with critical defects are not tested in bioavailability studies.	that the manufacturing process can significantly affect the product performance.
838-839	16	Comment: Mass balance need not be performed on all studies.	Previously addressed. See above.
693 -695	17	What is the justification for this statement?	This is applicable for most transdermal patches, however, it might be different for cutaneous products.
706	17	Why recommend fresh skin and then use a barrier integrity test (717), but also then state that non viable is also acceptable? The only time when it is really necessary to use fresh tissue is when considering skin metabolism.	Previously addressed. See above.
706-709	17	This statement cannot be justified for all models based on the literature and it should be amended.	The comments are acknowledged. The text will be revised accordingly.
724	17	Does this preclude the use of larger area cells than 2 cm2? There should be no maximum limit. A minimum limit may make sense related to any analytical method.	The comments are acknowledged. The text will be revised accordingly.
724-730	17	What other than diffusion cells could be used?	This comment is not clear.
727-730	17	There should be no preference for static or dynamic systems. As it states, viability may be maintained using flow, but it's not the flow that's doing all of this it's the receptor fluid. A simple statement of static or	Not accepted. The text does not state any preference for static or dynamic systems.

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		flow through cells systems being applicable would be better.	
732	17	Aqueous buffer will not maintain viability, so why use viable tissue (See line 706).	The comments are acknowledged. The text will be revised accordingly.
733-4	17	The solubility of the drug in receptor fluid should be confirmed. Ethanol water will stop viability, so why use fresh skin. The concentration of the solubilising excipients should be included – as long as the receptor fluid does not affect the skin integrity (ethanol water does) (states this in 736).	This comment is not endorsed. This requirement is in the revised text.
734-8	17	This is in OECD 428 too. This relates to static and not flow. Even then, as long is solubility is not rate limiting, you do not need 10-fold. For many drugs, this will be impossible and they will not penetrate anyway.	The comments are acknowledged. The text will be revised accordingly.
736-738	17	It may not be possible to avoid inclusion of solubilising agents.	The comment is acknowledged. No need to revise the text.
753	17	Most likely to be LC-MS rather than HPLC.	The comments are acknowledged. The text will be revised accordingly.
755-7	17	Mass balance, so need to have analytical method validated in multiple matrices, for mass balance, will also need to know residual in the patch.	The comment is acknowledged. No need to revise the text.
758	17	The term “satisfactory” is not defined and needs to be specified.	Previously addressed. See above.
759-60	17	Use a lab with experience and demonstrated knowledge. Variability is often more related to the donor and site than anything else. Poorly prepared tissue and performed studies will provide a poor result.	The comment is acknowledged. No need to revise the text.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
768	17	And validated – why? The method requests a barrier test, this will identify damaged tissue (or at least skin with a poor barrier function – it may of course be intact). Why transport and storage when recommended to use fresh?	The comments are acknowledged. The text will be revised accordingly.
769	17	Not full thickness, should be dermatomed or epidermis (epidermis cannot be viable).	The comment is acknowledged. No need to revise the text.
785-6	17	Static not flow.	The comments are acknowledged. The text will be revised accordingly.
789	17	Why humidity? There will be patients living in low and high humidity areas. Humidity is difficult to control (not impossible), it is unlikely to impact on delivery of a drug from a sealed patch.	The comments are acknowledged. The text will be revised accordingly.
791	17	Tritiated.	The comments are acknowledged. The text will be revised accordingly.
793	17	Why? – the integrity may have been damaged by the patch and this is not the purpose of the study. If you perform a barrier test, they will impact on further movement of the drug.	Previously addressed. See above.
795	17	Statistically significant – likely to be many more than 6. Cosmetics guideline states dose 12 cells (eg 6 donors in duplicate) and at the end have at least 8 useable data points (from at least 4 donors). Very good for inter and intraindividual variability.	The comment is acknowledged. No need to revise the text.
796	17	Not enough, must be at least 4, there is such great inter and intra individual variability.	Previously addressed. See above.
797	17	OK, but does depend on the hospital – fresh skin is	Previously addressed. See above.

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		preferred so should not be cadaver.	
799	17	15 min and 30 min, surely there will be a lag time? With flow, you can easily have 15, 30, 45, 60 and hourly timepoints. Need to decide on timepoints based on study requirements.	Previously addressed. See above.
805	17	It is a patch, so it is occluded.	The comments are acknowledged. This comment is endorsed and the text will be revised accordingly.
806-808	17	90-110% may not reflect realistic recovery values. These numbers need to be related to typical experimental conditions. Are they drawn from guidance documents for other routes of delivery?	Previously addressed. See above.
808	17	This reads as taken from OECD 428. This is impossible, if we do not measure material in patch.	This comment is not endorsed. This requirement is in the revised text.
809-828	17	As alluded to, there is already guidance on bioanalysis.	This comment is not endorsed. The bio-analysis guideline should be read in conjunction with this guideline for further guidance.
811-815	17	The text here is vague and ambiguous and will not provide much guidance.	This is not a comment but a statement. No need to revise the text.
830	17	Reproducibility – remember this is human tissue and we should expect variability. When duplicates are from the same donor, it is easier to assess variability, but even then human skin varies greatly due the scars, hair (follicle) density and the washing processes that each individual uses in everyday life. Surgeons are interested in the tissue they leave behind and not the material they remove (although they are usually very good!).	This is not a comment but a statement. No need to revise the text.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
832	17	Outliers are important, this is human tissue	This is not a comment but a statement. No need to revise the text.
839	17	Residual in patch now included – noted.	This is not a comment but a statement. No need to revise the text.
851-853	17	The design of caffeine, benzoic acid, testosterone tests are also related to formulation dose levels and washing procedures, they do not relate to comparing patches. Published data for these reference chemicals do not comply with either test guidelines or with the design of the actual test for that particular test item.	This is not a comment but a statement. No need to revise the text.
706	18	**Comment**: What is meant by “fresh”? Does this mean no frozen and defrosted skin may be taken? Though the use of fresh skin is preferable, this is not always possible.	Previously addressed. See above.
722-723	18	**Comment:** The requirement to typically use six replicates, or more for pivotal experiments is unrealistic in light of the difficulty to obtain sufficient suitable human skin material. The OECD technical guideline 428 requires data from a minimum of four replicates. **Proposed change (if any):** “Typically, ~~six~~ **four** replicates may be used,….”	Previously addressed. See above.
768	18	**Comment:** The validation of the skin transportation is not deemed to be necessary, in particular as integrity of skin needs to be verified (ref lines 721-723).	Previously addressed. See above.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Proposed change (if any): "The storage and transport of the skin should be described ~~and validated~~."	
849-853	18	**Comment**: Typically, these *in vitro* permeation studies are performed under GMP conditions. Furthermore, the described measurements are not within the scope of GLP according to Directive 2004/10/EC. Compliance with GMP is considered appropriate. **Proposed change (if any)**: "A declaration of compliance with the principles of Good Laboratory Practice~~1~~ **or Good Manufacturing Practice**." [Please delete "1" at the end of line 848 as well.]	Previously addressed. See above.
872	2	Comment: The topics between quality aspects of TDDS (to be discussed in the present guideline) and safety aspects (to be discussed in the clinical guideline to be published) are not easily distinguishable. We suggest reconsidering the appearance of detailed guidance on clinical performance in the quality guideline as opposed to the clinical guideline, where we feel it might be more appropriately discussed.	Annex 2 has been transferred to the clinical guideline.
886-888	2	Comment: We would appreciate more detailed information on how such assessment should be conducted in clinical practice.	Annex 2 has been transferred to the clinical guideline.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
899	2	Comment: We suggest deleting this line. It is very challenging to prepare photographs in a clinical setting with sufficient precision and repeatability to allow them to be used as a tool for validation of scores assigned by the investigator, as suggested here.	Annex 2 has been transferred to the clinical guideline.
902-908	2	Comment: We suggest modifying these limits as follows below (reference to FDA). Proposed change (if any): Set the increments as “equal or larger than 90 %”, “equal or larger than 75 % but less than 90 %”, ”equal or larger than 50 % but less than 75 %”, ”less than 50 % or detached”.	Annex 2 has been transferred to the clinical guideline.
911-913	2	Comment: The requirement to have no instances of patch detachment is very strict. Clinical experience shows that a considerable subset of the population has skin characteristics where transdermal patches do not stick at all. Proposed change (if any): In general, a mean adherence of greater than 90% should be expected and detachments in a maximum of 20 % of subjects should be seen.	Annex 2 has been transferred to the clinical guideline.
682	3	Comment:	Annex 2 has been transferred to the clinical guideline.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Due to limited availability of human skin, high variability of biological material etc. we kindly request to preserve in vitro skin permeation studies as a tool for development and not to make them a QC-tool, as intended by this draft guideline, We suggest to reference to OECD technical guideline 428 on skin permeation tests for more formal tests providing e.g. supportive data for variations, and eliminate any requirements for tests during early stage development. Proposed change (if any): Delete Annex I.	
871	3	Comment: General remark: The topics between quality aspects of TDDS (to be discussed in the present guideline) and safety aspects (to be discussed in the clinical guideline to be published) are not easily distinguished. EMA is requested to reconsider the appearance of detailed guidance on clinical performance in the quality guideline as opposed to the clinical guideline, where we feel it might be more appropriately discussed.	Annex 2 has been transferred to the clinical guideline.
876-878	3	Comment: Typo; sentence appears in duplicate.	Annex 2 has been transferred to the clinical guideline.
900-908	3	Comment: Please drop the 5 % increments; these are too tight to	Annex 2 has been transferred to the clinical guideline.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		be applied with reasonable effort in a clinical setting. The wording should be kept simple. Proposed change (if any): The scores for adhesion of transdermal patches should be scaled as indicated below: • less than 70 % adheres or patch detachment is regarded as significant patch adhesion failure.	
911-912	3	Comment: Clinical experience shows that a considerable subset of the population has skin characteristics where transdermal patches do not stick at all. Proposed change (if any): In general, a mean adherence of greater than 90 % should be expected and instances of complete detachment should be discussed and evaluated.	Annex 2 has been transferred to the clinical guideline.
913	3	Comment: We suggest adding a statement on bioequivalence studies, requesting non-inferiority for cumulative adhesive behaviour for generic formulations compared to reference products to be demonstrated.	Annex 2 has been transferred to the clinical guideline.
886 - 888	5	Comment: This section is unclear. The data expected could represent a collection of information of events that	Annex 2 has been transferred to the clinical guideline.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		might have happened during an adhesion study which is not designed to explicitly address these issues. As a consequence, not much information will be collected and reports will be highly coincidental. Designing additional separate studies that explicitly address all the aspects mentioned seems to be rather excessive. Proposed change (if any): Please delete lines 886-888.	
890-891	5	Comment: Transdermal patches should be applied as proposed, i.e. according to what is described in the Summary of Product Characteristics. The following sentence reads "Patch reinforcement such as over-taping is not allowed." Since there are a number of e.g. fentanyl transdermal patches where over-taping is allowed according to the respective SmPC, the two sentences are in contradiction. Proposed change (if any): Please amend this section as follows: "Patch reinforcement such as over-taping is not allowed **unless referred to in the SmPC."**	Annex 2 has been transferred to the clinical guideline.
892	5	Comment : It is unclear what "*other scales of measurement*" are referring to. Proposed change (if any):	Annex 2 has been transferred to the clinical guideline.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		The final guideline should provide some examples of non-visual measurements which can be applied for in vivo skin adhesion assessment and thus clarify the meaning of this sentence.	
895	5	Comment : It is unclear in which cases photo-documentation is required. The current wording can be interpreted in such a way that photographs should be taken for all subjects. If this is correct, one time point (e.g. immediately prior to removal) should be sufficient. Proposed change (if any): Please amend this section so as to clarify expectations.	Annex 2 has been transferred to the clinical guideline.
898	5	Comment : Patch adherence assessment should be done in a differentiated manner depending on the patch application duration. Assessment once daily should be sufficient in many cases, e.g. if patch is applied for at least 4 days. Please specify the required minimum number of assessments. Proposed change (if any): “The frequency of assessment should be ~~**more than**~~ **at least once daily, if one patch is applied for at least four days. Otherwise, additional observations should be available.”**	Annex 2 has been transferred to the clinical guideline.
899	5	Comment : According to current experience, assessment of	Annex 2 has been transferred to the clinical guideline.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		adhesion by photographs is very unreliable and not suitable to validate the direct visual assessment. Proposed change (if any): Please delete this sentence.	
900 - 908	5	Comment: Scaling of scores for adhesion of transdermal patches in 5% increments does not appear appropriate in practice. As a mean adherence of >90% should be expected (see line 911), the meaning of assessing 5% increments does not make sense. Additionally, it has to be considered that e.g. dependent of transparency, colour and shape of the patches, this scoring may not be feasible. Patches usually do not detach at one specific point but on several points at the same time and it is not possible to decide whether all detachment sited together sum up to 5% or a 10% detachment. Proposed change (if any): Please amend this section so that the recommended scoring mimics that referred to in the FDA Guidance for Industry, Skin Irritation and Sensitization, Testing of Generic Transdermal Drug Products: **0 = ≥ 90% adhered (essentially no lift off of the skin)** **1 = ≥ 75% to < 90% adhered (some edges only lifting off of the skin)** **2 = ≥ 50% to < 75% adhered (less than half of the system lifting off of the skin)**	Annex 2 has been transferred to the clinical guideline.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		3 = < 50 % adhered but not detached (more than half of the system lifting off of the skin) **4 = patch detached (patch completely off the skin)**	
909	5	Comment : The opportunity to fix patches in pharmacokinetic or efficacy studies once they exceed a certain detachment threshold should be considered. Proposed change (if any): Please amend section as follows "[…] that completely detach during the study **(or are fixed by additional measures after inacceptable detachment as defined in the protocol of a pharmacokinetic or efficacy study)** the score should be carried forward […]"	Annex 2 has been transferred to the clinical guideline.
911 - 913	5	Comment : In case of longer application periods (e.g. 4 to 7 days) more than 90% detachment is not unusual based on current experience. For generic medicinal products, the level of detachment should be evaluated in light of the reference product behaviour. Proposed change (if any): Please amend as follows: "In general, a mean adherence of ~~**greater than**~~ **75 –** 90 % **(depending on the period of application)** should be expected […]"	Annex 2 has been transferred to the clinical guideline.
917	5	Comment :	Annex 2 has been transferred to the clinical guideline.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		In situations where fixing of patches is allowed (which is usually the case in pharmacokinetic or efficacy studies), the number of patches in which fixing was necessary should be evaluated instead. Proposed change (if any): Please amend this section accordingly.	
918	5	Comment : We consider a valid statistical analysis of in vivo skin adhesion as meaningful only when non-inferiority boundaries can be applied in the case of generic applications. If the non-inferiority boundaries are not known, a descriptive analysis seems appropriate. Proposed change (if any): Please amend this section accordingly.	Annex 2 has been transferred to the clinical guideline.
876-878	8	**Comment:** The draft guideline requires adhesiveness testing in vivo with the smallest and the largest patch sizes as a minimum. It is proposed to require adhesiveness testing in vivo only for one patch size for the following reasons: • For matrix patches, the patches of the different sizes are based on the same laminate. Therefore, differences in adhesion properties between different patch sizes, if any, detected during such studies would not be due to the formulation, but rather to	Annex 2 has been transferred to the clinical guideline.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		the properties of the skin area used for application. Such differences would be observed to the same extent for the test and the reference product based on the size of the patch and the skin area used. • Depending on the drug substance, it may not be possible to perform an adhesiveness study with the highest strength in healthy volunteers due to safety concerns (e.g. for narcotic drugs). The guideline suggests in line 875 that adhesiveness studies may also be performed in patients. However, such studies would be less discriminative due to lack of adequate standardization (e.g. with regard to physical stress on the patch in patients lying in bed, showering, bathing; limited possibility to standardize the evaluation of adhesiveness in a multi-center study, probably involving critically ill patients). A well-controlled study would hardly be possible under such a setting. Whenever possible adhesiveness studies should only be performed in healthy subjects. • This proposal is also in line with US FDA requirements. US FDA requires adhesiveness testing in only one patch size according to the "Bioequivalence Recommendations for Specific Products" for transdermal patch products (http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm075207.htm; examples of products: Clonidine, Fentanyl, Methylphenidate, Nitroglycerin, Rivastigmine,	

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Rotigotine, Selegeline). The strength to be tested for adhesiveness is mostly the strength used in the bioequivalence study. Depending on the safety profile of the substance, this can either be the highest or a lower strength. In general, it is proposed to assess adhesiveness properties with the largest patch. However, in line with the Guideline on the Investigation of Bioequivalence (CPMP/QWP/EWP/1401/98 Rev. 1), it should be allowed to use a lower strength if the highest strength cannot be administered to healthy volunteers for safety/tolerability reasons. **Proposed change:** The text should be re-worded in the following way: “For transdermal patches covering a range of different dosage strengths, as a minimum, one patch size should be tested in vivo. In general, the largest patch size should be used; however, use of a smaller patch size is acceptable, if the largest patch cannot be administered to healthy volunteers for safety/tolerability reasons.”	
876-878	8	**Comment:** The sentence „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*.“ is written in duplicate in these lines,	Annex 2 has been transferred to the clinical guideline.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		once with addition of “as a minimum". **Proposed change:** If you do not agree with the comment above on line 876-878, please delete one of the two sentences.	
879-888	8	**Comment:** The paragraph should be re-worded to add clarity. It is assumed that “the sites of application” and “transdermal patch application” need to be carefully defined, but these items do not seem to be “elements of assessment”. **Proposed change:** As explained above.	Annex 2 has been transferred to the clinical guideline.
880	8	**Comment:** For generic applications the patch should only be administered to one site of application.	Annex 2 has been transferred to the clinical guideline.
882	8	**Comment:** Between the word “release” and “liner” there is an “l” too much.	Annex 2 has been transferred to the clinical guideline.
882	8	**Comment:** Please provide more detailed guidance on how these assessments should be performed.	Annex 2 has been transferred to the clinical guideline.
884-885	8	**Comment:**	Annex 2 has been transferred to the clinical guideline.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Please provide more detailed guidance on how the assessments of cold flow, patch movement or displacement and wrinkling should be performed.	
886-888	8	It seems that the requirements outlined here refer to new applications. However, they should not apply for generic applications. This is also not in line with the statement that adhesiveness properties can be evaluated within clinical pharmacokinetic studies (line 873-874). The conditions mentioned here are not feasible in a pharmacokinetic study setting. It is not possible to send the study subjects to saunas or let them use any topical treatment as this would impact the pharmacokinetic parameter assessment. **Proposed change:** It should be specified that such requirements only apply to new applications, and are not relevant for generic products.	Annex 2 has been transferred to the clinical guideline.
890	8	**Comment:** According to the draft guideline, the transdermal patch should be used as proposed and patch reinforcement such as over-taping is not allowed. The text should add clarity for products that contain not only the active patch, but an overlay that is to be used for reinforcement according to the SmPC.	Annex 2 has been transferred to the clinical guideline.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		In this case, it is suggested to perform the adhesion studies with the overlay, because this is the route of application as proposed in the SmPC. This should also be adhered to in bioequivalence studies that may be combined with adhesion studies. **Proposed change:** Please add: “In case a product can be used with an overlay to ensure adequate adhesion, the adhesion studies are to be performed using this overlay in accordance to the SmPC.”	
892	8	**Comment:** Further guidance on the accepted “justified visual or other scales of measurement” would be appreciated.	Annex 2 has been transferred to the clinical guideline.
899	8	**Comment:** The draft guideline proposes that the adherence should be supported by analysis of photographs, to show validity of the method. **Proposed change:** As suggested in line 895, photographs should only be used supportively, as a valid evaluation of adhesion properties based on photographs is hardly possible.	Annex 2 has been transferred to the clinical guideline.
900-908	8	**Comment:** Does this scale signify that any adhesion less than 70% is regarded as complete detachment and both	Annex 2 has been transferred to the clinical guideline.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		scenarios (less than 70% adheres (e.g. 60%) and total patch detachment) are treated the same way - as patch adhesion failure? **Proposed change:** There should be 2 scores for the point in line 908. One for “less than 70% of the patch area adheres” and one for “total patch detachment”.	
902-908	8	**Comment:** A score numbering should be added to the 5% increments E.g. “Score 6 = more than 95 % of the patch area adheres; Score 5 = more than 90 % of the patch area adheres; Score 4 = more than 85 % of the patch area adheres…”	Annex 2 has been transferred to the clinical guideline.
911-913	8	It is written that *a mean adherence of greater than 90% should be expected*, but in line 598 of the draft guideline *non-inferiority* to the reference product should be demonstrated. **Proposed change:** Please specify that the requirement of > 90% adhesion is only applicable to new applications. For generic products, an adhesion comparable to the reference product should be achieved.	Annex 2 has been transferred to the clinical guideline.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
918	8	**Comment:** Please provide details regarding the requested statistical assessment. For the reasons given in the comment to line 598, it is suggested that descriptive statistics should be sufficient. **Proposed change:** Please re-word: “A critical assessment and **descriptive** statistical analysis should be provided.”	Annex 2 has been transferred to the clinical guideline.
919	8	**Comment:** The draft guideline requires “similar reports” “for the other in vivo assessment elements”. It is understood that “similar reports” means frequency tables with scores. It is understood that “the other in vivo assessment elements” refer to the assessment of residue formation on release liner removal and on transdermal patch removal, to cold flow, patch movement or displacement and wrinkling. **Proposed change:** If frequency tables for various scores of these items are required, it should be specified what sort of scores should be used for these items. Otherwise, it is proposed to document these items only	Annex 2 has been transferred to the clinical guideline.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		with a “yes/no” question.	
920	8	**Comment:** Please re-word “… critical assessment and **descriptive** statistical analysis …”	Annex 2 has been transferred to the clinical guideline.
Annex 2	8	**Comment:** For generic products, a bioequivalence study will normally be performed with the highest strength and the originator product. In this study, adhesion properties will usually also be evaluated. If you do not agree to the comments to lines 876-878 (adhesiveness testing of only one patch size), the lower strength will usually need to be covered with a separate adhesion study. **Proposed change**: Annex 2 should provide further guidance for the design of such an adhesion study for a generic transdermal system (that is not part of a bioequivalence study), in particular if such a study should only investigate • the lowest strength of the generic product or • compare the lowest and the highest strength of the generic product or • compare the lowest strength of the generic product with the lowest strength of the reference product.	Annex 2 has been transferred to the clinical guideline.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
877	9	Delete repeat sentence. "For transdermal…"	Annex 2 has been transferred to the clinical guideline.
882	9	Delete "l" so that line reads "…release liner…"	Annex 2 has been transferred to the clinical guideline.
886	9	Comment: Robustness of product to normal behaviour – this may be difficult to standardise and to study	Annex 2 has been transferred to the clinical guideline.
900	9	Comment: The 5% increments appear to be small for accurate assessment. Proposed change (if any):rather propose categorisation as presented by the FDA.	Annex 2 has been transferred to the clinical guideline.
911	9	Comment: is adherence absolute or in comparison with a reference? The number of 90% may be very high.	Annex 2 has been transferred to the clinical guideline.
918	9	Comment: Can the agency give some more detail on the type of statistics that would be expected.	Annex 2 has been transferred to the clinical guideline.
919	9	Comment: can the agency give examples of what type of assessment would be expected especially as some of these circumstances as in 886 may be difficult to standardise.	Annex 2 has been transferred to the clinical guideline.
Annex 1 pgs 22- 28	9	Comment: Above please find comments for Lines 359-363.	Annex 2 has been transferred to the clinical guideline.
871	10	Comment: General remark: The topics between quality aspects of TDDS (to be discussed in the present guideline) and safety aspects (to be discussed in the clinical guideline to be published) are not easily distinguished. EMA is requested to reconsider the appearance of detailed guidance on clinical performance in the quality guideline as opposed to the clinical guideline, where	Annex 2 has been transferred to the clinical guideline.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		we feel it might be more appropriately discussed.	
876-878	10	Comment: Typo; sentence appears in duplicate.	Annex 2 has been transferred to the clinical guideline.
899	10	Comment: Please delete line 899. It is very challenging to prepare photographs in a clinical setting with sufficient precision and repeatability to allow them to be used as a tool for validation of scores assigned by the investigator, as suggested here. Proposed change (if any): Delete line 899.	Annex 2 has been transferred to the clinical guideline.
900-908	10	Comment: Please drop the 5 % increments; these are too tight to be applied with reasonable effort in a clinical setting. Depending on the patch size it might become impossible to differentiate between single 5% increments by visual inspection. In case of use of more sophisticated methods to measure the percentage adhered, a negative bias due to the measuring method might be introduced. Proposed change (if any): The scores for adhesion of transdermal patches should be scaled as indicated below: equal or larger than 90 %”,	Annex 2 has been transferred to the clinical guideline.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		“equal or larger than 75 % but less than 90 %”, ”equal or larger than 50 % but less than 75 %”, ”less than 50 % or detached	
911-912	10	Comment: Clinical experience shows that a considerable subset of the population has skin characteristics where transdermal patches do not stick at all. Proposed change (if any): In general, a mean adherence of greater than 90 % should be expected and instances of complete detachment should be discussed and evaluated.	Annex 2 has been transferred to the clinical guideline.
913	10	Comment: We suggest adding a statement on bioequivalence studies, requesting non-inferiority for cumulative adhesive behaviour for generic formulations compared to reference products to be demonstrated.	Annex 2 has been transferred to the clinical guideline.
900-920	13	Comment: It may be impractical to try to score the adhesion of transdermal systems in 5% increments while conducting an *in vivo* adhesion study. In addition, a there is some inconsistency between the statements in line 908 that less that 70% adherence is considered a significant patch adhesion failure and the statement in line 911 that a mean adherence of greater than 90% should be expected, with no incidence of detachment seen. Proposed change:	Annex 2 has been transferred to the clinical guideline.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		A broader scale has been proposed in another transdermal product draft guidance, which is more realistic to observe: The recommended scoring system for adhesion of transdermal patches is indicated as follows: 0 = ≥ 90% adhered (essentially no lift off the skin) 1 = ≥ 75% to < 90% adhered (some edges only lifting off the skin) 2 = ≥ 50% to < 75% adhered (less than half of the patch lifting off the skin) 3 = > 0% to < 50% adhered but not detached (more than half of the patch lifting off the skin without falling off) 4 = 0% adhered - patch detached (patch completely off the skin) It could also be more clearly stated that this Annex applies to a clinical investigation *in vivo* adhesion study referenced as part of drug development in P2, and is not necessarily meant to be taken in full as a commercial specification for product release or shelf life in P5. In principle, if the assessment shows limited cold flow or adhesion/transference concerns, it should be possible to justify in P5 that no or different specifications are required for routine commercial product control.	
Annex 2 Lines 872-920	14	Comment: as this guideline is addressing the quality requirements for the transdermal patches, it may be more appropriate to detail the *in vivo* adhesion in the clinical Guideline (EMA/CPMP/EWP/280/96 Corr1) that	Annex 2 has been transferred to the clinical guideline.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		has just been released for comments.	
Lines 873-920	14	Comment: it makes sense to rely on the relationships between patch adhesiveness and patch efficacy; on the other hand, it remains relevant to take into account that only a small portion of the drug substance is finally released from the patch.	Annex 2 has been transferred to the clinical guideline.
Lines 876-878	14	Comment: it is asked to conduct *in vivo* skin adhesion using both the smallest and the biggest patch sizes as the worst cases situation; this situation is also depending on the site of application.	Annex 2 has been transferred to the clinical guideline.
Lines 900-908	14	Comment: the scoring scale for assessing adhesion has very narrow increments which do not match the 10% increment used to set up the expected target (mean score greater than 90%). The clinical relevance of such small increments in the loss of adhesion to the treatment effectiveness may depend on the size, the structure, the strength of the transdermal patch. In addition in studies* having assessed adhesion, the 5-point scale recommended in Appendix B of the FDA Guidance “Skin Irritation and Sensitization Testing of Generic Transdermal Drug Products” (Dec 1999) was used. *References:	Annex 2 has been transferred to the clinical guideline.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		- Gomez-Panzani E. et al - Application and maintenance habits do make a difference in adhesion of Alora® transdermal systems. Maturitas 35 (2000) 57–64 - Erianne J.A., Winter L.Jr. Comparison of the local tolerability and adhesion of a new matrix system (Menorest@) for estradiol delivery with an established transdermal membratie system (Estraderm TTS®). Maturitas 26 (1997) 95-101 - Wokovich A.M., et al. Transdermal drug delivery system (TDDS) adhesion as a critical safety, efficacy and quality attribute; European Journal of Pharmaceutics and Biopharmaceutics 64 (2006) 1–8 Proposed change: “The choice of the validated scoring system and the method applied to assess the adhesion of transdermal patches should be fully justified.” In case it would be considered useful to add a scale, it could be added “The following scale is provided as an example of a scoring system.”	
886-888	16	Comment: The robustness of the patch under conditions of normal use should be derived based on Phase 3 clinical trial use. Controlled studies may be conducted, as appropriate, based on risk analysis and the instructed conditions of use for the individual products.	Annex 2 has been transferred to the clinical guideline.
900-909	16	Comment: Assessment of patch adhesion in	Annex 2 has been transferred to the clinical guideline.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		increments of 5% cannot be adequately performed. Loss of adhesion may only be grossly estimated by visual inspection of the applied patch.	
876-878	18	**Comment**: Based on a scientific rationale it should be possible to test only one patch size. Please remove redundant/duplicate text. **Proposed change (if any):** "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*, **unless justified by a scientific rationale that testing of one patch size is sufficient and representative for the other patch sizes**. ~~For transdermal patches covering a range of different dosage strengths the smallest and the biggest patch sizes should be tested *in vivo.*~~"	Annex 2 has been transferred to the clinical guideline.
879-881 886-888	18	**Comment**: Regarding the elements of assessment: • The sites of application → assessment of all potential sites of application will be a huge undertaking depending on the number of sites and if exploratory or not. • Transdermal patch application → this needs some further clarification. What is actually meant herewith? • • …….	Annex 2 has been transferred to the clinical guideline.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		• ……. • 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. → As above, if this is meant to be powered, this means an enormous effort to show all this. Exploratory analyses should be feasible. It would be good to have some clarification on the nature of the data that should be provided.	
900-908	18	**Comment**: An evaluation of adhesiveness according to a scale with 5% increments during an in-vivo study is unrealistic with adequate accuracy. The 5% increments are far too small and it will be difficult or - depending on the patch size - even impossible to differentiate between single steps by visual inspection. In case of more 'invasive' methods to measure the percentage of adhesiveness, this increases the danger of a negative bias of the method on adhesiveness results. It is recommended to apply the FDA score for evaluation of adhesiveness. **Proposed change (if any):** "The scores for adhesion of transdermal patches should be scaled ~~in 5 % increments~~ **according to FDA**	Annex 2 has been transferred to the clinical guideline.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		scores for adhesiveness 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.~~ • **equal or larger than 90 % (score 0)** • **equal or larger than 75 % but less than 90 % (score 1)** • **equal or larger than 50 % but less than 75 % (score 2)** • **less than 50 % or detached (score 3)”**	