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SCIENCE MEDICINES HEALTH

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Committee for Medicinal Products for Human use (CHMP)

Concept paper on the development of a guideline on quality and equivalence of topical products

Draft agreed by Quality Working Party	December 2014
Adopted by CHMP for release for consultation	26 February 2015
Start of public consultation	22 April 2015
End of consultation (deadline for comments)	22 July 2015

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Keywords	Therapeutic equivalence, bioequivalence, pharmaceutical equivalence, generic and hybrid medicinal products, locally applied, locally acting products, topical products, dermatological use, *in vitro*, quality, CHMP

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Problem Statement

Topical products are exemplified by medicines for cutaneous use; but in broadest scope, they are locally applied, locally acting products. They can be applied to any of the diverse external surfaces of the body that may present a physiological barrier to drug absorption e.g. skin, eye, ear.

The site of local action for topical products may be:

- External - on the surface of the physiological barrier;
- Internal - at and about the physiological barrier; and
- Regional - beyond the physiological barrier in adjacent tissues.

The bioavailability of the active substance at the site of action from topical products is known to be affected by the active substance's physicochemical properties, the topical formulation design, the manufacturing process and the means and patient preference of dose administration. In addition, it is known that the vehicle itself may influence the condition to be treated e.g. moisturisers and emollients.

For topical products, small changes in formulation, dosage form, administration or manufacturing process may significantly influence the efficacy and/or safety and this presents challenges to the prediction of therapeutic equivalence at time of marketing authorisation application and during management of variations to marketing authorisations after approval.

Clinical trials are in principle necessary to demonstrate therapeutic equivalence, but other models may be used, if adequately validated[1]. In many cases, these other models have exhibited poor accuracy, sensitivity, reproducibility, *in vitro in vivo* correlation and have been unable to provide convincing evidence to predict therapeutic equivalence.

1. Discussion (on the Problem Statement)

Quality of Topical Products

In recent years, the assessment of topical products has evolved. It has become evident that their quality needs to be thoroughly understood and characterised, supported by a robust manufacturing process and control strategy. In addition, the designated shelf life needs to be based not only on physical, chemical and microbiological stability, but also, when necessary, on evidence of stable *in vitro* performance to assure equivalence throughout storage.

Sound product development is necessary to characterise and achieve adequate product quality; reference to clinical studies to justify inadequate product development or poor product quality should be avoided.

Equivalence of Topical Products

At present, for most topical products, demonstration of pharmaceutical equivalence is normally not sufficient to predict therapeutic equivalence. However, a waiver of the need to provide therapeutic equivalence data may be acceptable in the case of solutions, e.g. eye drop solutions, nasal spray solutions or cutaneous solutions[2].

Extension of this waiver to other pharmaceutical forms may be possible, if based on an extended concept of pharmaceutical equivalence combined with additional measures of equivalence, using

suitable *in vitro* and *in vivo* models and methods, and evidence of equivalence with respect to the method and means of administration.

An extended concept of pharmaceutical equivalence could be developed based on appropriate comparative quality data with the relevant reference medicinal product, including qualitative and quantitative composition, microstructure, physical properties, product performance and administration. The comparative data need to be representative, the test methods appropriate and validated, and equivalence acceptance criteria adequate.

The additional measures of equivalence currently available include *in vitro* drug release through an artificial membrane and / or human skin membrane to determine the rate and extent of drug release or permeation, *in vivo* tape stripping to determine dermatopharmacokinetics and possibly microdialysis. Furthermore, when drug absorption to the blood compartment from the site of application is sufficiently high, then comparative pharmacokinetic studies should be supportive of equivalence. Other methods might also be valid for some specific medicinal products.

The scientific rational as to how these methods may be used to support a claim of therapeutic equivalence needs to be developed, taking account of the site of action of the active substance(s). The advantages and disadvantages of each method need to be considered. Method limitations may be addressed by employing a battery of different techniques, but, in any case, this needs to be fully explored and understood to avoid inappropriate use and claims.

Method variability, sensitivity and discrimination power also need to be addressed. It is acknowledged that some methods may show some inherent variability, e.g. skin used in permeation studies, but variability can also be due to poor conduct and inadequate validation. All studies should follow best practice and quality assurance principles, which should be established and described.

In addition, possible limitations of this approach e.g. products with narrow therapeutic index and / or significant systemic side-effects, and safety requirements, including local tolerance studies, should be considered in the guideline.

Bioequivalence is generally not a suitable way to show therapeutic equivalence for topical products[1], due to limited systemic bioavailability. When studies are needed to demonstrate therapeutic equivalence, a topical medicinal product, developed to be pharmaceutically and therapeutically equivalent to an innovator product should be submitted as a "hybrid medicinal product"[3].

The guideline will aim to develop a systematic approach to describe methods or combinations of methods for the prediction of therapeutic equivalence, when taken with evidence of extended pharmaceutical equivalence.

2. Recommendation

The scope of the guidance should focus on locally acting, locally applied products for cutaneous use, and other routes, if possible and appropriate.

The new guideline should address the quality requirements of topical products, containing new or known active substances, throughout their marketing life.

The concept of pharmaceutical equivalence for topical products should be developed and extended to include e.g. qualitative and quantitative equivalence of formulation, physical properties and microstructure, administration and *in vitro* drug release properties.

Guidance on alternative *in vitro* and *in vivo* methods that characterise the bioavailability of the active substance to the local site of action should be developed.

The guideline should consider the application of an extended pharmaceutical equivalence with alternative *in vitro* and *in vivo* models and methods to predict therapeutic equivalence with reference medicinal products, *in lieu* of therapeutic equivalence studies in patients.

3. Proposed Timetable

The Concept Paper will be released for 3 months external consultation.

Following the receipt of Concept Paper comments, the draft Guideline will be prepared and released for 6 months external consultation.

The draft Guideline will be revised in light of comments received, finalised and published.

4. Resource requirements for preparation

The preparation will mainly involve the Quality Working Party (QWP), with support from other Working Parties and expertise from academia, as necessary.

5. Impact assessment (anticipated)

The new guideline will provide guidance for pharmaceutical industry and regulatory authorities that is in line with current knowledge.

6. Interested Parties

Academia, international scientific societies, pharmaceutical industry

7. References to literature, guidelines, etc.

1. Note for Guidance on the clinical requirements for locally applied, locally acting products containing known constituents CPMP/EWP/239/95;

2. Guideline on the Investigation of Bioequivalence CPMP/EWP/QWP/1401/98 Rev. 1/ Corr ** Appendix II, Locally acting and locally applied products).

3. Notice to Applicants, Revision 4, Volume 2A, Procedures for Marketing Authorisation, Chapter 1, Marketing Authorisation, June 2013, Chapter 5.3.2.2, Application in accordance with paragraph 3 of Article 10 ("hybrid “medicinal product);