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Committee for Medicinal Products for Human use (CHMP)

Concept paper on the development of a guideline on the demonstration of therapeutic equivalence for locally applied and locally acting products in the gastrointestinal tract

Agreed by Pharmacokinetics Working Party	May 2013
Adopted by CHMP for release for consultation	19 September 2013
Start of public consultation	1 October 2013
End of consultation (deadline for comments)	31 December 2013

The proposed guideline will replace 'The Note for guidance on the clinical requirements for locally applied, locally acting products containing known constituents' (CPMP/EWP/239/95).

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

Keywords	Therapeutic equivalence, gastrointestinal, locally applied and locally acting, *in vitro*, pharmacokinetic, bioequivalence, guideline, CHMP

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1. Introduction

The Note for guidance on the clinical requirements for locally applied, locally acting products containing known constituents (CPMP/EWP/239/95) [in the following called 'guideline'] provides general recommendations on the clinical requirements for respective formulations with known active substances. This concept paper discusses the need to expand the guidance on locally applied and locally acting gastrointestinal products.

2. Problem statement

Following recent development, there is a need to expand the existing guideline regarding the approaches for the demonstration of therapeutic equivalence of locally applied and locally acting gastrointestinal products.

3. Discussion (on the problem statement)

During the recent years the assessment of locally applied and locally acting products has evolved. It has become evident that the investigation of therapeutic equivalence based on clinical or pharmacodynamic endpoints is demonstrative of equivalence only if the study shows assay sensitivity. This requires not only demonstrating that the investigational product is superior to placebo, but also that different doses of the investigational product and the reference product elicit a quantitatively different clinical or pharmacodynamic response.

At the same time, it has been agreed that drug release and availability at the site of action are the major factors determining the clinical response for locally applied and locally acting products containing the same drug. Therefore, all available models or endpoints that are described in the existing guideline (clinical, pharmacodynamic, local availability, in vitro or animal models) are considered surrogates of drug release and availability at the site of action.

The difficulty in showing a significant dose-response curve with clinical or pharmacodynamic endpoints has illustrated that alternative methods or models (including in vitro and in vivo methods) may have a higher sensitivity to detect differences between products containing the same drug. Therefore, therapeutic equivalence of locally applied and locally acting gastrointestinal products could be demonstrated using these models. The conditions under which these alternatives provide valid surrogates of in vivo release and availability at the site of action would have to be defined.

Experience on these alternative models, either individually or in combination, for the purpose of demonstrating therapeutic equivalence in locally applied and locally acting gastrointestinal products have recently been gained. Based on this experience, a systematic approach could be identified to define the most sensitive model or combinations of models for the demonstration of therapeutic equivalence in those products. Alternative methods might also be valid for some specific products. Again, the setting of these methods would have to be defined.

4. Recommendation

The current guideline defines the general requirements for all locally acting and locally applied products. This new guideline will address when and how to employ particular models to demonstrate therapeutic equivalence for gastrointestinal products (e.g. in vitro comparisons and pharmacokinetic comparisons) apart from clinical trials.

5. Proposed timetable

The Concept Paper will be released for 3 months external consultation. Following the receipt of comments, the draft Guideline will be consolidated and released for 6 months external consultation.

6. Resource requirements for preparation

The preparation will mainly involve the Pharmacokinetics Working Party (PKWP).

7. Impact assessment (anticipated)

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

8. Interested parties

Academia, international scientific societies (e.g. EUFEPS), pharmaceutical industry

9. References to literature, guidelines, etc.

N/A