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SCIENCE MEDICINES HEALTH

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Committee for Medicinal Products for Human Use (CHMP)

Concept paper on the need for revision of the note for guidance on modified release oral and transdermal dosage forms: section II (pharmacokinetic and clinical evaluation)

Agreed by Efficacy Working Party	April 2010
Adoption by CHMP for release for consultation	20 May 2010
End of consultation (deadline for comments)	31 August 2010

The proposed guideline will replace guideline CPMP/EWP/280/96

Comments should be provided using this [template](#). The completed comments form should be sent to EWPSecretariat@ema.europa.eu

Keywords	<i>Delayed release, prolonged release, food effect, pharmacokinetics, transdermal drug delivery systems (TDDS), guideline, EMA</i>
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1. Introduction

This concept paper refers to the Note for Guidance on the evaluation of Modified Release Oral and Transdermal dosage forms (CPMP/EWP/280/96).

The primary purpose of Section II of this guideline is to define the studies necessary to investigate the biopharmaceutic and pharmacokinetic properties of modified release and transdermal formulations in man and to set out general principles for designing, conducting and evaluating such studies.

The guideline only deals with oral formulations and transdermal dosage forms for systemic use containing chemically defined drug substances.

2. Problem statement

The guideline on Modified Release Oral and Transdermal Dosage Forms (CPMP/EWP/280/96) was adopted in 1999. Following the emergence of new scientific knowledge, this document requires a revision. Points to Consider on the Clinical Requirements of Modified Release Products Submitted as a Line Extension of an Existing Marketing Authorisation (CPMP/EWP/1875/03) was adopted in 2003. The revision aims to combine these two documents into one restructured guideline. Also aspects from the Q&A: Positions on specific questions addressed to the EWP therapeutic subgroup on Pharmacokinetics, point 2: Requirements for food-interaction studies for modified release formulations (EMA/618604/2008 Rev. 1) will be considered. Furthermore the revision of the Note for Guidance on the Investigation of Bioavailability and Bioequivalence (EWP/QWP/1401/98) generates the necessity of consequential adjustments.

3. Discussion (on the problem statement)

The following discussion points have been identified when reviewing the current guidelines:

3.1. The necessity to combine the current guideline with existing documents touching different aspects of modified release products (see section 2.) implies several aspects. The newly revised Note for Guidance on the Investigation of Bioequivalence (EWP/QWP/1401/98 rev1), the emergence of science as well as applications on new types of formulations require thorough discussions on:

- requirements for steady-state studies,
- primary pharmacokinetic parameters,
- possibility of widening (and narrowing) of acceptance ranges,
- requirements for food interaction studies,
- investigations on 'dose dumping' including the possible effect of alcohol,
- requirements for specific formulations, e.g. "timed - released" dosage forms,
- basic requirements for *in vivo* studies to establish *in vitro/in vivo* correlations, such as number of subjects, fed or fasting conditions, strength to be used, PK parameters etc,
- the role (possibilities and limitations) of *in vitro* dissolution data including *in vitro/in vivo* correlations,
- requirements for dose proportionality and acceptance of biowaiver in the case of several strengths.

3.2. It is aimed to compile a more comprehensive section on transdermal drug delivery systems (TDDS). This separate section should include issues like e.g.:

- specific requirements for bioequivalence studies for generic TDDS,

- requirements for the development of a new transdermal dosage form as a line extension or as a new drug substance,
- the role (possibilities and limitations) of *in vitro* dissolution test conditions,
- *in vitro* and *in vivo* methods to determine delivery rate,
- investigation of skin irritability, skin sensitisation and patch adherence during development of new and generic transdermal products,
- requirements on acceptable application sites,
- most relevant pharmacokinetic parameters to determine the rate and extent of absorption *in vivo*,
- dose proportionality and acceptance of biowaiver in the case of several strengths.

4. Recommendation

A revision of the already existing guideline is recommended. Some parts of the current guideline can be improved by rewording only whilst others need comprehensive review and modification in order to achieve a clear scientifically based document.

5. Proposed timetable

It is anticipated that a draft revision will be released 15 months after adoption of the Concept Paper. The public consultation on the draft revision will last for 6 months. Following the receipt of comments the revision will be finalised within approximately 6 months.

6. Resource requirements for preparation

The preparation will mainly involve the EWP Therapeutic subgroup on Pharmacokinetics (PK-EWP). The SWP will be consulted on specific aspects as appropriate (skin tests); topics overlapping with Section I of this guideline (like *in vitro* dissolution) will be handled in close cooperation with the QWP.

7. Impact assessment (anticipated)

The revised document will provide clearer and more systematic guidance for industry, academia and regulators. It is aimed to avoid misinterpretation of requirements and controversial assessments in European application procedures.

8. Interested parties

Academia and international scientific societies (e.g. EUFEPS).

9. References to literature, guidelines, etc.

1. Points to Consider on the Clinical Requirements of Modified Release Products Released as a Line Extension of an Existing Marketing Authorisation (CPMP/EWP/1875/03).
2. Note for Guidance on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev 1).