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Committee for Medicinal Products for Human Use (CHMP)

Concept paper on a revision of the Guideline on the investigation of drug interactions

Agreed by Pharmacokinetic Working party	October 2016
Adopted by CHMP for release for consultation	23 March 2017
Start of public consultation	7 April 2017
End of consultation (deadline for comments)	30 June 2017

The proposed guideline will replace 'Guideline on the investigation of drug interactions (CPMP/EWP/560/95/Rev. 1 Corr. 2**)'.

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

Keywords	*Interaction, guideline, metabolism, inhibition, induction, transport, enzyme, transport protein, transporter, absorption, food, distribution, PBPK, herbal, SmPC*

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1. Introduction

The first revision of the Guideline on the investigation of drug interactions (CPMP/EWP/560/95/Rev. 1 Corr. 2**) was adopted by the CHMP in June 2012. This concept paper proposes a further update to reflect recent scientific knowledge and experience in applying the guideline since it came into force.

2. Problem statement

This guideline should be updated at the present time with new recommendations in order to ensure continued relevance for the investigation of drug interactions. There are also areas where existing requirements could be clarified.

3. Discussion (on the problem statement)

The following items have been identified and would need to be addressed in the revised guideline:

New recommendations on:

- Inhibition and induction of enzymes in the intestine: specifying cutoffs for poorly soluble drugs.
- Specific in vitro study design recommendations for in vitro induction studies: number of concentrations to study.
- Transport as rate limit for elimination: in vivo study design considerations.
- The addition of a table to present in vitro drug-drug interaction (DDI) information.
- Specifying a cutoff (two-fold) for the inhibition constant 'Ki' shift to conclude mechanism based inhibition, including details regarding the pre-incubation duration.
- In vitro induction screening: update on study design recommendations.
- Transporter inhibition screening: update of the list of transporters to screen from a pharmacokinetic perspective.
- Transporter inhibition screening: update of some cutoffs for determining in vivo relevance of in vitro inhibition.

Clarifications on:

In vitro studies:

- The need to know whether the (unbound) target concentration was maintained in an in vitro system during the incubations.
- The use of Bile Salt Export Pump (BSEP) inhibition data.
- How to calculate the unbound inlet concentration.
- How to verify adequate sensitivity of the system for in vitro induction studies.

In vivo studies and labelling:

- How to present the mass balance study results: adding a recommendation on how to illustrate the elimination of a drug schematically.
- Discussing the text on interaction studies with oral contraceptives for potential teratogens.

- Specification of the presently recommended duration of in vivo studies of CYP3A4 induction[1].

4. Recommendation

The PKWP and CHMP recommend revising the Guideline on the investigation of drug interactions. Points that will be addressed are listed in section 2 and 3 of this Concept Paper.

5. Proposed timetable

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

6. Resource requirements for preparation

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

7. Impact assessment (anticipated)

The revised guideline will be up-to-date and be easier to understand in terms of the recommendations on the investigation of drug interactions. This will benefit pharmaceutical industry in their clinical pharmacology development as well as regulatory agencies involved in assessment.

8. Interested parties

Academia, pharmaceutical industry, healthcare professionals, regulatory agencies including the FDA and PMDA.

9. References to literature, guidelines, etc.

1. PKWP Questions & Answers 2.7:
http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/q_and_a/q_and_a_detail_000179.jsp&mid=WC0b01ac0580aff2ec