European Medicines Agency

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COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE (CHMP)

CONCEPT PAPER/RECOMMENDATION ON THE NEED FOR REVISION OF (CHMP) NOTE FOR GUIDANCE ON THE INVESTIGATION OF DRUG INTERACTIONS (CPMP/EWP/560/95)

AGREED BY EFFICACY WORKING PARTY	July 2008
ADOPTION BY CHMP FOR RELEASE FOR CONSULTATION	24 July 2008
END OF CONSULTATION (DEADLINE FOR COMMENTS)	31 October 2008

Comments should be provided electronically in word format to EWPSecretariat@emea.europa.eu using this template

KEYWORDS	*Interactions, inhibition, induction, enzyme, transport protein*

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INTRODUCTION

The present Note for guidance on the Investigations of Drug Interactions was written in the nineties when the knowledge about pharmacokinetic processes determined by drug metabolism and interactions had evolved to a point where it was time to start requesting drug-interaction studies based on mechanistic theory. Now, 10 years later, more knowledge has been gained about these mechanisms and about the methodologies used for studying interaction potential and extrapolating the results of such studies to other drug combinations. The requests from Regulatory Agencies during evaluation of applications for Marketing Authorisation have been driven by science rather than requirements stated in the guideline, leading to inconsistencies between Member States. In addition, in some areas, science has evolved to a point where it is time to take a step forward.

1. PROBLEM STATEMENT

The Note for Guidance document needs to be updated in several areas to be in line with current knowledge as well as to give a more clear description on which studies are needed in which situation, how these should be performed and interpreted.

2. DISCUSSION (ON THE PROBLEM STATEMENT)

There are three main types of drug interaction based on pharmacokinetic, pharmacodynamic and pharmaceutical actions; the following are examples of areas which need to be updated. A number of other areas will also need revision. Furthermore, a restructuring of the guideline may be necessary.

Food interactions

More detailed information on requirements for food interaction (both meal and drinks) studies should be given.

Metabolism

How to determine the main enzymes involved in metabolism in general and in special populations (e.g. poor metabolisers, renal impairment, differences in the amount of the enzymes in the races).
Characterising enzymes involved in formation and elimination of active metabolites significantly contributing to the efficacy and safety.
Characterisation of metabolism catalysed by non-CYPs or phase II enzymes.

Enzyme inhibition

In vitro inhibition studies: design issues, parameters to be estimated (including non-specific binding, and inactivation constant, etc).
Relevance of *in vitro* inhibition results for the *in vivo* situation.
Need to investigate inhibition potency for quantitatively important metabolites *in vivo*.
Design aspects on *in vivo* interaction studies, including timing.
Possibility of minimizing interactions by the use of staggered dosing.

Enzyme induction

For which drugs are induction studies required?
Which kind of studies, *in vitro* or *in vivo*, are required?
Design aspects for *in vitro* studies (e.g. number of livers, positive controls, what to measure).
Interpretation of the *in vitro* induction results.
Design aspects of *in vivo* studies, including timing.
Extrapolating the results to other non-studied enzymes based on mechanistic knowledge.

Transport proteins

When should transport and effects on transporters be studied?
In vitro methods and general design requirements.
Requirements of *in vivo* interaction studies.

Presentation of information on interaction in the SPC

Considering the increasing amount of information on interactions, it should be investigated how best to present information and recommendations in the SPC taking into account healthcare professionals' expectations.

3. RECOMMENDATION

The Working Party recommends revising the current Note for Guidance on the Investigation of Interactions to provide an updated NfG giving clear and updated advice in this area.

4. PROPOSED TIMETABLE

It is anticipated that a draft CHMP document may be released 12 months after adoption of the Concept Paper. The draft document will then be released for 6 months of external consultation and following the receipt of comments it will be finalised within approximately 6 months.

5. RESOURCE REQUIREMENTS FOR PREPARATION

The preparation will involve the EWP Therapeutic Subgroup on Pharmacokinetics (PK-EWP) and specific pharmacokinetics assessors experienced in this field. External experts on specific methodologies will be contacted when needed. One rapporteur will be involved and the document is predicted to be discussed on 4-5 PK-EWP meetings and on two EWP meetings.

6. IMPACT ASSESSMENT (ANTICIPATED)

An update of the guideline will be of benefit for industry as the intention is to give updated advice on the entire interactions part of the development program. It will also lead to a more consistent assessment between the different Member States.

7. INTERESTED PARTIES

Academia and international scientific societies related to drug metabolism, transport and drug interactions.
The EMEA CHMP Healthcare Professionals Working Group will be consulted in particular regarding presentation of information in the SPC.