European Medicines Agency

London, 24 May 2007
Doc. Ref. EMEA/CHMP/EWP/200943/2007

COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE (CHMP)

RECOMMENDATION ON THE NEED FOR REVISION OF (CHMP) <NOTE FOR GUIDANCE ON THE INVESTIGATION OF BIOAVAILABILITY AND BIOEQUIVALENCE > CPMP/EWP/QWP/1401/98

AGREED BY EFFICACY WORKING PARTY	May 2007
ADOPTION BY CHMP FOR RELEASE FOR CONSULTATION	24 May 2007
END OF CONSULTATION (DEADLINE FOR COMMENTS)	31 August 2007

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KEYWORDS	Bioavailability, bioequivalence, guidance

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1. INTRODUCTION

The Note for guidance (NfG)[1] on the investigation of bioavailability (BA) and bioequivalence (BE), for products with a systemic effect, defines requirements for bioavailability and bioequivalence studies regarding necessity, design, conduct, evaluation, and reporting. Discussion during mutual recognition procedures (MRP) and decentralised (DC) procedures revealed that several issues in the NfG may be differently interpreted by Member States. Better clarity on these issues should improve the understanding of the Guideline, and as a result may increase the consensus between Member States during the MRP and DC procedures.

2. PROBLEM STATEMENT

Firstly, the NfG is outdated in some aspects, since the coming into force of the new pharmaceutical legislation with the new amendment of Directive 2001/83/EC. Furthermore, bioavailability and bioequivalence are two different topics that need to be distinguished and each deserves specific attention because requirements for bioavailability and bioequivalence may differ. Guidance on bioavailability in the NfG is limited. This should be improved and extended. On the other hand, regulatory experience has shown that guidance on bioequivalence needs further harmonisation within the European Union. This was already recognised and a Q & A document has been released recently (http://www.emea.europa.eu/pdfs/human/ewp/4032606en.pdf).

In addition, in the last decade the analytical methods have been improved in such a way that the guidance and requirements on the analytes to be measured need to be updated. Similarly, experience gained in the Biopharmaceutics Classification System (BCS) allows further recommendations on biowaivers.

3. DISCUSSION (ON THE PROBLEM STATEMENT)

The following discussion points have been defined when reviewing the current NfG on the Investigation of Bioavailability and Bioequivalence in order to improve the harmonisation:

- Specific recommendations on BA will be given. Requirements on exploratory and confirmatory BA and BE studies will be differentiated in separate sections of the guidance document
- Recommendations on BE in the current guidance will be updated with regard to:
    - the concept of essential similarity which has changed since the new legislation with reference to the recent Directive amendment (Directive 2004/27/EC) and relevant guidelines
    - under which circumstances a parallel design may be used
    - under which circumstances a sequential design may be used
    - the study design for drugs with dose and time dependent pharmacokinetics
    - the acceptability of steady state designs
    - the analytes to be measured and to be taken into account in the assessment of bioequivalence
    - the need of enantiomeric bioanalytical methods
    - requirements for potency correction of Test and Reference products
    - study design/dosing instructions for particular dosage forms (e.g., orodispersible tablets)
    - dissolution test conditions

1. The term “NfG” has been replaced by “Guideline”. The latter term will be applied in the revision process of this document.

- proportionality of compositions

- Incorporation and adaptation of other topics discussed in the recent Question and Answer document:
  - the assessment of Cmax in bioequivalence studies
  - whether the acceptance range of BE limits (90% CIs) can be extended
  - requirements on how to handle outliers
  - inclusion of the borders of the 90% CI
  - the use of a non-parametric statistical method
  - in which cases metabolites have to be measured and to be taken into account in the bioequivalent assessment
  - the definition of highly variable drugs
  - the selection of the strength to be measured
  - standardisation with regard to food intake for studies under fed conditions
  - the use of urinary data for bioequivalence assessment
- BCS concepts and biowaiver requirements will be revised and expanded in a separate Annex/section

4. RECOMMENDATION

It is proposed to revise the current Note for Guidance on the Investigation of Bioavailability and Bioequivalence (CPMP/EWP/QWP/1401/98) to provide an updated NfG on the above-mentioned issues.

5. PROPOSED TIMETABLE

It is anticipated that a draft CHMP document may be released 12 months after adoption of the Concept Paper. It will be later released for 6 months of external consultation and finalised within 6 months.

6. RESOURCE REQUIREMENTS FOR PREPARATION

The preparation of this document will involve the EWP Therapeutic Subgroup on Pharmacokinetics and the QWP.

7. IMPACT ASSESSMENT (ANTICIPATED)

Anticipated Benefit to Industry and Other Interested Parties

Revision of the Note for Guidance on the Investigation of Bioavailability and Bioequivalence should improve understanding of the Guideline and lead to a more consistent interpretation of regulatory requirements, which can result in improved design and success of bioequivalence studies.

Anticipated Benefit to Regulatory Authorities

Revision of the Note for Guidance on the Investigation of Bioavailability and Bioequivalence should improve consistent acceptance and assessment of bioequivalence studies and lead to an increased consensus between Member States leading to a reduced number of referrals.

8. INTERESTED PARTIES

Academia and international scientific societies related to bioavailability, bioequivalence, pharmacokinetics and in vitro dissolution.