European Medicines Agency

COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE
(CHMP)

CONCEPT PAPER FOR AN ADDENDUM TO THE NOTE FOR GUIDANCE ON THE
INVESTIGATION OF BIOAVAILABILITY AND BIOEQUIVALENCE:

EVALUATION OF BIOEQUIVALENCE OF HIGHLY VARIABLE DRUGS AND DRUG
PRODUCTS

AGREED BY EFFICACY WORKING PARTY	April 2006
ADOPTION BY CHMP	27 April 2006
END OF CONSULTATION (DEADLINE FOR COMMENTS)	31 July 2006

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KEYWORDS	Pharmacokinetics

1.   SCOPE AND INTRODUCTION

A drug product is called highly variable if its intra-individual (i.e. within-subject) variability is larger than 30%. The evaluation of bioequivalence of highly variable drugs and drug products (HVDP) is a well-known problem to industry and regulatory agencies. Due to the statistical characteristics of the widely applied equivalence test, the higher the within-subject variability the more difficult it is to satisfy the regulatory criterion with a reasonably sized trial. In the current framework the only way to overcome this problem is to design a bioequivalence trial with a higher number of volunteers than the usual 16 to 32. The purpose of this document is to describe alternatives to demonstrate bioequivalence of HVDP and to discuss their regulatory acceptability. In particular, the concept of scaled or standardized average bioequivalence (SABE) will be discussed. This approach extends the currently applied procedure of average bioequivalence and uses the within-subject variation of the reference product for standardisation.

2.   PROBLEM STATEMENT

The Note for Guidance on the Investigation of Bioavailability and Bioequivalence states under 3.6.2 that a test product is considered to be bioequivalent to a reference product, i.e. an average bioequivalence (ABE) is demonstrated, if the 90% confidence interval for the ratio of the two geometric means (GMR), for both AUC and C_{max}, falls between 0.80 and 1.25. Wider regulatory cut off values for C_{max} are allowed in certain cases but should be clinically justified or should refer to a defined HVDP. At the EU level, no clear regulatory guidance exists on how to proceed, especially for AUC, when the reference product is deemed to behave as a HVDP. This leads to different regulatory practices among Member States. The current document is designed to bring some harmonisation in this regard.

3.   DISCUSSION POINTS

- What are the best methods to provide evidence that a medicinal product is a highly variable drug product (HVDP)?

- Describe different approaches to bioequivalence of HVDP, with benefits and drawbacks for regulatory purposes.

- For the scaled average bioequivalence (SABE) concept:

  o   Define the recommended study designs.

  o   Define the acceptance range for this new approach.

  o   Suggest the recommended statistical and computational analyses, including the estimation of the within-subject variances of the two formulations and the determination of bioequivalence. A technical appendix will describe the recommended computational methods.

  o   Decide whether any additional constraints are necessary.

  o   Decide what to do if the within-subject variance ratio shows that the test product is more variable than the reference product.

  o   Decide how to define and how to handle outliers with this approach.

4.   RECOMMENDATION

It is proposed to complement the current Note for Guidance on the Investigation of Bioavailability and Bioequivalence (CHMP/EWP/QWP/1401/98) with an addendum addressing the issue of highly variable drugs and drug products (HVDP).

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 3 months.

6.   RESOURCE REQUIREMENTS FOR PREPARATION

The preparation of this addendum will involve the EWP (Therapeutic Subgroup on Pharmacokinetics).

7.   IMPACT ASSESSMENT (ANTICIPATED)

- Anticipated Benefit to Industry and Other Interested Parties

Clearer regulatory guidance decreases the uncertainties related to drug development requiring bioequivalence studies.

- Anticipated Benefit to Regulatory Authorities

It will result in a more consistent assessment of bioequivalence trials and therefore be helpful in a harmonised regulatory policy.

8.   INTERESTED PARTIES

International scientific societies in statistics and in pharmacokinetics.

9.   REFERENCES

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