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**COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE
(CHMP)**

CONCEPT PAPER ON BCS-BASED BIOWAIVER

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	Biowaiver, guidance
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1. INTRODUCTION

The concept underlying the Biopharmaceutics Classification System (BCS) published by Amidon et al. in 1995 finally lead to introducing the possibility of waiving in vivo bioequivalence studies in favour of specific comparative in vitro testing in order to conclude bioequivalence of oral immediate release products with systemic actions. This approach is meant to reduce unnecessary in vivo bioequivalence studies however, is restricted to non-critical drug substances in terms of solubility, permeability, and therapeutic range, and to non-critical pharmaceutical forms. Although frequently discussed, BCS-based biowaivers are still rarely used probably attributed to uncertainties on both, pharmaceutical companies and regulatory authorities. Substantial differences of biowaiver dossiers and respective assessments contribute to the impression that a common understanding is lacking on a successful use of the BCS concept to support biowaivers. It is intended to reach an optimal and harmonised application of biowaiver principles within the European community by means of preparing an annex to the guideline on Bioavailability and Bioequivalence (1401/98).

2. PROBLEM STATEMENT

Section 5.1.1 of the Note for Guidance on the Investigation of Bioavailability and Bioequivalence describes basic criteria to be met by active pharmaceutical ingredients and drug products as prerequisites to use the biowaiver approach. With respect to the active substance the guideline paragraph addresses e.g. the risk of therapeutic failure and the possible evidence of bioavailability problems which is considered an unspecific request and difficult to be appropriately addressed in respective dossiers. Although high permeability is mentioned as referred to the BCS concept; linear and complete absorption is stated to be a favourable pharmacokinetic property. However, at the same time biowaiver extensions are frequently discussed and applied for focusing on substance solubility only. In addition, guideline recommendations are fairly arbitrary regarding drug product investigations, i.e., in vitro dissolution and evaluation of excipients. EU guideline limitations lead applicants to follow the FDA guideline on BCS-based biowaiver which may result e.g. in unnecessary cell culture investigations. On the other hand, there is no harmonised assessment of BCS-based biowaiver applications within the EU from the regulatory perspective even resulting in general rejection of respective applications.

3. DISCUSSION (ON THE PROBLEM STATEMENT)

The following discussion points can be defined when reviewing the current biowaiver criteria of the Note for Guidance on the Investigation of Bioavailability and Bioequivalence.

- Which characteristics are deemed indispensable to prove a **drug substance** eligible for the BCS-based biowaiver approach and what kind of data (literature and/or experimental) are acceptable, for instance (in addition to known guideline requirements):
 - Discuss ‘risk of bioinequivalence’.
 - Define dose to be investigated in terms of solubility.
 - Discuss whether BCS-based biowaiver may be acceptable within a restricted dose range due to solubility limitations, i.e., biowaiver for lower strengths and in vivo BE study for higher dose strengths.
 - Define permeability and/or absorption requirements.
 - Discuss/clarify acceptance or exclusion of biowaiver extensions, e.g., BCS based biowaiver for BCS class II and/or III drugs.

Drug product considerations

- Comprehensive description of in vitro dissolution requirements.
 - Experimental setting; method validation.
 - Evaluation of absence of product differences (or product ‘similarity’).
 - Delimitation from in vitro/in vivo correlations and quality control.

- Specify number of batches to be investigated.
- Specify evaluation of excipients.
- Clarification regarding fixed dose combinations and pro-drugs.
- Clarification on the applicability of the BCS-based biowaiver approach (generic applications, drug development, variations)

4. RECOMMENDATION

It is proposed to complement the current Note for Guidance on the Investigation of Bioavailability and Bioequivalence (CPMP/EWP/QWP/1401/98) with an annex to address the issue of BCS-based biowaiver.

5. PROPOSED TIMETABLE

It is anticipated that a draft CHMP document may be released 6 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 document will involve the EWP Therapeutic Subgroup on Pharmacokinetics and members of the QWP.

7. IMPACT ASSESSMENT (ANTICIPATED)

Anticipated Benefit to Industry and Other Interested Parties

Clarification of regulatory requirements will support optimal and harmonised use of the BCS-based biowaiver approach.

Anticipated Benefit to Regulatory Authorities

Consistent acceptance and assessment of BCS-based biowaiver applications supports a harmonised regulatory policy.

8. INTERESTED PARTIES

International scientific societies related to bioavailability/bioequivalence/pharmacokinetics and in vitro dissolution.

9. REFERENCES TO LITERATURE, GUIDELINES ETC

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