Annex III: Biopharmaceutics Classification System (BCS) Based Biowaiver

I. Introduction

The BCS (Biopharmaceutics Classification System)-based biowaiver approach is meant to reduce *in vivo* bioequivalence studies, *i.e*., it may represent a surrogate for *in vivo* bioequivalence. *In vivo* bioequivalence studies may be exempted if an assumption of equivalence in *in vivo* performance can be justified by satisfactory *in vitro* data.

Applying for a BCS-based biowaiver is restricted to highly soluble active pharmaceutical ingredients with known human absorption and considered not to have a narrow therapeutic index (see Section 3.1.9). The concept is applicable to immediate release, solid pharmaceutical products for oral administration and systemic action having the same pharmaceutical form. However, it is not applicable for sublingual, buccal, and modified release formulations. For oral dispersible formulations the BCS-based biowaiver approach may only be applicable when absorption in the oral cavity can be excluded.

BCS-based biowaivers are intended to address the question of bioequivalence between specific test and reference/comparator products. The principles may be used to establish bioequivalence in applications for generic medicinal products, extensions of innovator products, variations that require bioequivalence testing, and between early clinical trial products and to-be-marketed products.

In situations where multiples strength formulations have been submitted for BCS based biowaiver, comparative dissolution should be provided for all the strength.

II. Summary Requirements

BCS-based biowaiver are applicable for an immediate release finished pharmaceutical product if:-

- the active pharmaceutical ingredient has been proven to exhibit high solubility and complete absorption (BCS class I; for details see Section III) and

- either very rapid (> 85 % within 15 min) or similarly rapid (85 % within 30 min) *in vitro* dissolution characteristics of the test and reference product has been demonstrated considering specific requirements (see Section IV.1) and

Annex III: Biopharmaceutics Classification System (BCS) Based Biowaiver

- excipients that might affect bioavailability are qualitatively and quantitatively the same. In general, the use of the same excipients in similar amounts is preferred (see Section IV.2).

BCS-based biowaiver are also applicable for an immediate release finished pharmaceutical product if:-

- the active pharmaceutical ingredient has been proven to exhibit high solubility and limited absorption (BCS class III; for details see Section III) and

- very rapid (> 85 % within 15 min) *in vitro* dissolution of the test and reference product has been demonstrated considering specific requirements (see Section IV.1) and

- excipients that might affect bioavailability are qualitatively and quantitatively the same and

- other excipients are qualitatively the same and quantitatively very similar (see Section IV.2).

Generally the risks of an inappropriate biowaiver decision should be more critically reviewed (e.g. site-specific absorption, risk for transport protein interactions at the absorption site, excipient composition and therapeutic risks) for products containing BCS class III than for BCS class I active pharmaceutical ingredient.

III. Active Pharmaceutical Ingredient

Generally, sound peer-reviewed literature may be acceptable for known compounds to describe the active pharmaceutical ingredient characteristics of importance for the biowaiver concept.

Biowaiver may be applicable when the active substance(s) in test and reference products are identical.

Biowaiver may also be applicable if test and reference contain different salts provided that both belong to BCS-class I (high solubility and complete absorption; see Sections *III.1* and *III.2*). Biowaiver is not applicable when the test product contains a different ester, ether, isomer, mixture of isomers, complex or derivative of an active substance from that

Annex III: Biopharmaceutics Classification System (BCS) Based Biowaiver

of the comparator product, since these differences may lead to different bioavailabilities not deducible by means of experiments used in the BCS-based biowaiver concept.

The active pharmaceutical ingredient should not belong to the group of 'narrow therapeutic index' drugs (see Section 4.1.9 on narrow therapeutic index drugs).

III.1 Solubility

The pH-solubility profile of the active pharmaceutical ingredient should be determined and discussed. An API is considered highly soluble when the highest single **therapeutic dose** as determined by the relevant regulatory authority, typically defined by the labeling for the innovator product, is completely dissolved in 250 ml of buffers within the range of pH 1 – 6.8 at 37±1 °C. This demonstration requires the investigation in at least three buffers within this range (preferably at pH 1.2, 4.5 and 6.8) and in addition at the pKa, if it is within the specified pH range. Replicate determinations at each pH condition may be necessary to achieve an unequivocal solubility classification (e.g. shake-flask method or other justified method). Solution pH should be verified prior and after addition of the active pharmaceutical ingredient to a buffer.

III.2 Absorption

The demonstration of complete absorption in humans is preferred for BCS-based biowaiver applications. For this purpose complete absorption is considered to be established where measured extent of absorption is ≥ 85 %. Complete absorption is generally related to high permeability.

Complete drug absorption should be justified based on reliable investigations in human. Data from either:-

- absolute bioavailability or
- mass-balance

studies could be used to support this claim.

When data from mass balance studies are used to support complete absorption, it must be ensured that the metabolites taken into account in determination of fraction absorbed are formed after absorption. Hence, when referring to total radioactivity excreted in urine, it should be ensured that there is no degradation or metabolism of the unchanged active pharmaceutical ingredient in the gastric or intestinal fluid. Phase 1 oxidative and Phase 2

Annex III: Biopharmaceutics Classification System (BCS) Based Biowaiver

conjugative metabolism can only occur after absorption (i.e. cannot occur in the gastric or intestinal fluid). Hence, data from mass balance studies support complete absorption if the sum of urinary recovery of parent compound and urinary and faecal recovery of Phase 1 oxidative and Phase 2 conjugative drug metabolites account for ≥ 85 % of the dose.

In addition highly soluble active pharmaceutical ingredients with incomplete absorption, i.e. BCS-class III compounds, could be eligible for a biowaiver provided certain prerequisites are fulfilled regarding product composition and *in vitro* dissolution (see also Section *IV.2* Excipients). The more restrictive requirements will also apply for compounds proposed to be BCS class I but where complete absorption could not convincingly be demonstrated.

Reported bioequivalence between aqueous and solid formulations of a particular compound administered via the oral route may be supportive as it indicates that absorption limitations due to (immediate release) formulation characteristics may be considered negligible. Well performed *in vitro* permeability investigations including reference standards may also be considered supportive to *in vivo* data.

IV. Finished pharmaceutical product

IV.1 In vitro Dissolution

IV.1.1 General Aspects

Investigations related to the medicinal product should ensure immediate release properties and prove similarity between the investigative products, i.e. test and reference show similar *in vitro* dissolution under physiologically relevant experimental pH conditions. However, this does not establish an *in vitro*/*in vivo* correlation. *In vitro* dissolution should be investigated within the range of pH 1 – 6.8 (at least pH 1.2, 4.5, and 6.8). Additional investigations may be required at pH values in which the drug substance has minimum solubility. The use of any surfactant is not acceptable.

Test and reference products should meet requirements as outlined in Section 3.1.2 of the main guideline text. In line with these requirements it is advisable to investigate more than one single batch of the test and reference products.
Comparative *in vitro* dissolution experiments should follow current compendial standards. Hence, thorough description of experimental settings and analytical methods including

Annex III: Biopharmaceutics Classification System (BCS) Based Biowaiver

validation data should be provided. It is recommended to use 12 units of the product for each experiment to enable statistical evaluation. Usual experimental conditions are e.g.:-

- Apparatus: paddle or basket
- Volume of dissolution medium: 900 ml or less
- Temperature of the dissolution medium: 37±1 °C
- Agitation:
  - paddle apparatus - usually 50 rpm
  - basket apparatus - usually 100 rpm
- Sampling schedule: e.g. 10, 15, 20, 30 and 45 min
- Buffer: pH 1.0 – 1.2 (usually 0.1 N HCl or SGF without enzymes), pH 4.5, and pH 6.8 (or SIF without enzymes); (pH should be ensured throughout the experiment; Ph.Eur. buffers recommended)
- Other conditions: no surfactant; in case of gelatin capsules or tablets with gelatin coatings the use of enzymes may be acceptable.

Complete documentation of *in vitro* dissolution experiments is required including a study protocol, batch information on test and reference batches, detailed experimental conditions, validation of experimental methods, individual and mean results and respective summary statistics.

IV.1.2 Evaluation of in vitro dissolution results

Finished pharmaceutical products are considered ‘very rapidly’ dissolving when more than 85 % of the labelled amount is dissolved within 15 min. In cases where this is ensured for the test and reference product the similarity of dissolution profiles may be accepted as demonstrated without any mathematical calculation.

Absence of relevant differences (similarity) should be demonstrated in cases where it takes more than 15 min but not more than 30 min to achieve almost complete (at least 85 % of labelled amount) dissolution. *F2*-testing (see Annex I) or other suitable tests should be used to demonstrate profile similarity of test and reference. However, discussion of dissolution profile differences in terms of their clinical/therapeutical relevance is considered inappropriate since the investigations do not reflect any *in vitro/in vivo* correlation.

Annex III: Biopharmaceutics Classification System (BCS) Based Biowaiver

IV.2 Excipients

Although the impact of excipients in immediate release dosage forms on bioavailability of highly soluble and completely absorbable active pharmaceutical ingredients (i.e., BCS-class I) is considered rather unlikely it cannot be completely excluded. Therefore, even in the case of class I drugs it is advisable to use similar amounts of the same excipients in the composition of test like in the comparator product.

If a biowaiver is applied for a BCS-class III active pharmaceutical ingredient excipients have to be qualitatively the same and quantitatively very similar in order to exclude different effects on membrane transporters.

As a general rule, for both BCS-class I and III active pharmaceutical ingredients well-established excipients in usual amounts should be employed and possible interactions affecting drug bioavailability and/or solubility characteristics should be considered and discussed. A description of the function of the excipients is required with a justification whether the amount of each excipient is within the normal range. Excipients that might affect bioavailability, like e.g. sorbitol, mannitol, sodium lauryl sulfate or other surfactants, should be identified as well as their possible impact on:-

- gastrointestinal motility
- susceptibility of interactions with the active pharmaceutical ingredient (e.g. complexation)
- drug permeability
- interaction with membrane transporters

Excipients that might affect bioavailability should be qualitatively and quantitatively the same in the test product and the comparator product.

V. Fixed Combinations (FCs)

BCS-based biowaiver are applicable for immediate release FC products if all active substances in the FC belong to BCS-class I or III and the excipients fulfil the requirements outlined in Section IV.2. Otherwise, *in vivo* bioequivalence testing is required.