

Guidelines for the preparation of biowaiver monographs for J Pharm Sci & FIP Website

Aims of the monographs

The goals of these monographs are:

1.

To gather and organize all relevant data on a particular Active Pharmaceutical Ingredient (API) which have to be taken into consideration when a decision is to be made as to whether a new formulation of that API (either a reformulation or a new, multi-source product) needs to be tested in an *in vivo* bioequivalence study, or whether a biowaiver is appropriate and can be recommended.

Relevant data are likely to include: solubility, pharmacokinetics (especially with respect to absorption and bioavailability) and permeability of the API and the dissolution of dosage forms as per current BCS rules; the therapeutic use and therapeutic window of the API; any history of problems with BA/BE and, if it exists, data on excipient interactions. In specific cases, it may be desirable to introduce and discuss further information relevant to a biowaiver decision.

In general it is expected that the risks associated with an inappropriate biowaiver decision will be addressed. In this context, risks are defined not only as the probability of reaching an incorrect decision with respect to applicability of the biowaiver but also with respect to the ramifications of this decision in terms of public health and risks to individual patients.

2.

To assess the validity of the present BCS Guidances on the basis of the gathered data. To illustrate some of the possibilities: the results may show that there is a need to re-define the present BCS Classes (e.g. relax permeability requirements or D:S limits), to invoke other dissolution test conditions than those currently recommended or to change the specifications used for dissolution test results.

3.

To assess the biopharmaceutical relevance of dissolution testing according to the compendial method in the USP (where one exists).

From the above, it should be clear that these monographs are NOT intended to be used solely to produce databases according to the present BCS rules, but rather give more general guidance on the necessity (or lack thereof) of performing in vivo bioequivalence studies for the approval of new formulations of the API under consideration.

The list below contains various elements that might be important to the above-mentioned deliberations, and a proposal for their organization. However, this list is not „set in stone“. In some cases, certain elements may not be relevant to the discussion and in other cases, some important elements might not be covered with this list. Any data or considerations important to the risk assessment of a biowaiver should be included.

Data sourcing

The structure of the monographs is that of a classical scientific literature review, including the publicly available Summary of Product Characteristics (SmPCs) (sometimes known as Product Information Leaflets (PILs)).

To locate information it is recommended to use the approach of Lindenberg et al, Eur J Pharm Biopharm 58 (2004) 265–278. A search in PubMed using as keywords: absolute, absorption, aqueous, bioavailability, permeability, pharmacokinetics, solubility and the name of the API, in different combinations, would be a good starting point. Whenever possible, original literature is to be consulted in order to evaluate the quality of the data. Data from secondary sources can be included for completeness or when original literature cannot be located. When no data on an item has been found, this should be stated.

Although these monographs are basically literature reviews, some authors might want to add relevant results of their own experimental work, for instance, on the solubility of the API. On a limited scale, these experimental results can be fitted into the monograph, if the experimental methodology used is standard. A brief description of the methodology (preferably with a reference to a more detailed description) should be sufficient.

Style and format

The style is that of the J Pharm Sci, consult the Instructions to Authors. However, there is no need to go deep into the details of these Instructions, as the corresponding author (Dr. Dirk Barends) will check the style.

It would be helpful to deliver the references to the corresponding author in the form of EndNote or a Reference Manager database.

Organization („template“) for the monograph

Titel

Biowaiver Monographs for Immediate Release Solid Oral Dosage Forms:xxxx

Abbreviations

Abbreviations in use of this series are:

BCS	Biopharmaceutics Classification System
IR	Immediate Release
MA	Marketing Authorization
BE	Bioequivalence
GI	Gastrointestinal
API	Active Pharmaceutical Ingredient
BA	Bioavailability
DE	Germany
NL	The Netherlands
FI	Finland

Note that bioequivalence is abbreviated by BE, bioequivalent is not abbreviated.

Abstract

Please use the following as a *starting point* for constructing the Abstract (noting that in specific cases it may be necessary/desirable to deviate from the text as written):

Literature (and experimental) data relevant to the decision to allow a waiver of in vivo bioequivalence testing for the approval of immediate release (IR) solid oral dosage forms containing „API“ are reviewed. According to the current Biopharmaceutics Classification System (BCS), „API“ would be assigned to Class X . Also, API`s therapeutic use and therapeutic index, its pharmacokinetic properties, data related to the possibility of excipient interactions and reported bioequivalence/ bioavailability problems are taken into consideration. On the basis of this evidence, a biowaiver can currently be [recommended] / [recommended, provided that] / [cannot be recommended].

Keywords

Suggested: „API“; Absorption; Biopharmaceutics Classification System (BCS); Permeability; Solubility.

INTRODUCTION

Suggested wording:

A monograph based on literature data is presented on “API”, with respect to its biopharmaceutical properties and the risk of waiving in vivo bioequivalence testing in the approval of new Immediate Release (IR) solid oral dosage forms containing “API” (“biowaiving”), including both reformulated products and new, multisource products. The purpose and scope of this series of monographs were discussed previously {reference to: Vogelpoel H, Welink J, Amidon GL, Junginger HE, Midha KK, Möller H, Olling M, Shah VP, Barends DM. Biowaiver monographs for Immediate Release solid oral dosage forms based on Biopharmaceutics Classification System (BCS) literature data: verapamil hydrochloride, propranolol hydrochloride, and atenolol. J Pharm Sci 2004;93(8):1945-56}. Briefly, the aim is to evaluate all pertinent data available from literature sources, to assess the risk of such a biowaiver (risk being defined as both the chance of arriving at an incorrect biowaiver decision, and an assessment of the likely impact of such an incorrect biowaiver decision on public health and individual patient risks) and recommend whether a biowaiver can be recommended or not.

GENERAL CHARACTERISTICS

- „API`s“ INN name, WHO name and chemical name

- structure (as a Figure)
- stereochemistry (if applicable)
- salts, esters, polymorphs
 - Where relevant, define which stereoisomers/salts/esters/polymorphs are covered by this monograph

therapeutic indication

- therapeutic indication
- therapeutic Index
 - Wide dosing range ?
 - Adverse drug reactions (ADRs) after overdose?
 - Need to monitor blood levels?

CHEMICAL PROPERTIES

Solubility

- in water
 - Solubility in organic solvents are not relevant.
- in aqueous buffers
 - Most relevant to the bio waiver discussion would be: pH 1.2, pH 4.5, pH 6.8.
- dose:solubility ratio for WHO dose at pH 1.2 pH 4.5, pH 6.8
 - In many cases, data in this field will be incomplete. If so, this should be stated, indicating which data are missing*

Polymorphism

Partition coefficient

State which organic solvent was used to determine logP. If only the distribution coefficient (logD) is known, give this with the pH value at which it was determined.

pKa

State whether the compound is a weak acid, weak base or does not ionize under usual gastrointestinal conditions (i.e. has no pKa below 9).

Available dose/tablet

- WHO recommended dose
- strengths available on studied market(s) and special dosing instructions (e.g. with food) on that market
 - Name the market(s) that were studied.

PHARMACOKINETIC PROPERTIES

- absolute bioavailability versus i.v.
 - Describe how studies were done (was radioactive API used?)
report animal data only if no human data is available.
- relative bioavailability versus oral solution
 - Describe how studies were done (was radioactive API used?)
report animal data only if no human data is available.
- human permeability data?
- CaCo II cell permeability data.
 - Was a validation set included in the study?
- Distribution, metabolism, elimination

Not extensive, because only „nice to know“ Only a short summary on the volume of distribution, protein binding, serum half-life, plasma clearance, elimination half-life, extent of biotransformation.

DOSAGE FORM PERFORMANCE

Excipients

- excipients present in registered innovator drug product or market leader in studied market(s)
- excipients present in other registered IR drug products. A table with excipients present in registered products in DE, FI and NL will be provided to the first author(s) by the corresponding author for this section. Publicly available data from the home countries of the first authors, if available from SmPCs, can be added, but added data must conform to the format of the table provided.
- in vivo comparisons of different formulations
 - Are the compositions of these formulations known? Their in vitro dissolution? By which method?
- any there reports of bioavailability and/or bioequivalence problems with formulations?

Dissolution

- USP dissolution methodology
- Comparative studies of different formulations in vitro
 - Known attempts to optimize dissolution from the dosage form: e.g. micronization of drug, addition of surfactants to formulation....

DISCUSSION

Solubility

- discuss quality of the data
- D:S ratios for maximum available dosage strength and for WHO dosage strength
- Any D:S changes with pH?
- conclusion about classification with respect to solubility according to the current BCS criteria

Permeability

- discuss quality of the data
- discuss concordance of data
 - Do the permeability data support the absorption data?
 - Variability in fraction absorbed among studies and within studies.
- concentration/dose – dependent absorption?
 - If appropriate, mechanism of absorption.
- evidence for an GI absorption window?
- conclusion about classification with respect to permeability, where possible, according to the current BCS criteria

Risks with respect to excipient and/or manufacturing variations

- discuss the evidence for and hence the likelihood of an influence on bioavailability of excipients and/or manufacturing methods (particle size, hydration state, polymorphic forms, compression force etc.). Is there evidence to suggest that there are *bioinequivalencies* among products already in the marketplace?

- discuss the usefulness of surrogate techniques (comparative dissolution tests) to detect differences in such effects among formulations.

Patient's risks associated with bioinequivalence

- Discuss data on the therapeutic indication („critical use“?) and therapeutic index („narrow therapeutic index“?) and discuss how crucial it is for new formulations of “API” to be bioequivalent to the reference product in terms of patient safety.
Does that hold for AUC (total exposure), C_{max} (rate of exposure), both?
- What conclusions, if any, can be drawn for IR drug products which conform to the USP dissolution test specification (if one exists)?
Is the USP test similar to the tests recommended in the BCS/Biowaiver Guidances?
Have USP tests been shown to discriminate between bio(in)equivalent formulations appropriately?

CONCLUSION

- BCS classification for “API” under the present BCS rules
Stipulate degree of certainty of classification.
- Can a biowaiver be recommended? Under which restrictions?
Where applicable, comment on current BCS rules and class boundaries
What are the risks associated with associated with inappropriate application of the biowaiver?
- When a biowaiver is recommended, recommend the surrogate in vitro testing to be performed, and suggest sensible acceptance criteria.
Where applicable, comment on current BCS comparative dissolution testing rules
Is compliance to the USP dissolution test method and specifications appropriate/sufficient?
- When the formulation is found to be bioequivalent, established by in vitro or in vivo testing, can you make recommendations for in vitro dissolution testing for the batch-to-batch control?
Is the USP dissolution test method and specification appropriate, i.e. sufficiently biorelevant, for batch to batch control purposes?