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ICH M9: Biopharmaceutics Classification SystemBiowaivers

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Introduction

The International Conference on Harmonization (ICH) M9: Biopharmaceutics Classification System-based Biowaivers,[1,2] was adopted in mid-June 2016. A biowaiver allows for *in vitro* testing to be used in lieu of in vivo bioavailability and/or bioequivalence studies to facilitate product approval, where solubility and permeability are not expected to impede bioavailability. ICH M9 will therefore minimize unnecessary in vivo studies in man and allow greater public access to vital medicines. However, this approach is not always universally aligned or recognized.

The Role of Biowaivers

In certain cases regulatory applications using biowaivers are permissible. Submissions can be either based on BCS, *in vitro* - in vivo correlation (IVIVC), *in vitro* - in vivo relationship (IVIVR) or simply on an *in vitro* dissolution profile comparison. Examples of the BCS, IVIVC or IVIVR biowaiver approach[3] include:

- in support of generic product entry versus the innovator product
- in support of regulatory submission, i.e. changing the product type during development (capsules to tablets, etc.)
- in support of over-encapsulated comparator products, that are often used in pivotal clinical studies
- in support of bridging between the product used in pivotal clinical studies and the 'to be marketed' commercial product
- in support of product line extensions (PLEs) for different clinical populations, i.e. pediatric or geriatric products
- in support of post-approval changes

History and Evolution of BCS

The BCS was introduced in 1995[4] to facilitate the introduction of biowaivers into the regulatory lexicon. The BCS scheme is a 4-box model for drug product assessment based on an evaluation of the drug solubility and permeability. There are four classifications: BCS class 1 (highly soluble and highly permeable), class 2 (poorly soluble and highly permeable), BCS class 3 (highly soluble and poorly permeable) and BCS class 4 (poorly soluble and poorly permeable).

The US Food and Drug Administration (FDA) then published regulatory guidance for BCS Class I drugs describing the essential regulatory standards for biowaivers.[5] The National Institute of Health Sciences in Japan also published similar guidance.[6,7] Thereafter, the World Health Organization (WHO)[8] and European Medicines Agency (EMA)[9,10] followed suite and notably addressed the possibility that BCS class 3 compounds could also be included. This prompted updates

in Japan[11] and the US[12] to try and align the international biowaiver guidance.

A comprehensive series of BCS biowaiver evaluations for essential drugs have been carried out and published by the International Pharmaceutical Federation (FIP).[13] FIP have currently published 45 monographs, and they are mostly of highly soluble compounds, i.e. BCS class 1 and 3.

There have been some suggestions to modify the BCS system based on the metabolic profile of the medicinal compound, in particular transporter and efflux mechanisms. Wu and Benet[14] showed that for those drugs exhibiting high intestinal permeability rates, i.e. BCS class 1/2 compounds, the main route of drug elimination in humans was via metabolism. In contrast, those drugs showing poor intestinal permeability rates in man, i.e. BCS class 3/4 compounds, were principally eliminated unchanged in man.[15]

In 2010, Butler and Dressman proposed a Developability Classification System (DCS),[16] which was intended to have a greater focus on drug developability criteria, rather than just biowaivers. The DCS system stresses the importance of dose, and on intestinal solubility in biorelevant media, i.e. FaSSIF (Fasted State Simulated Intestinal Fluid). DCS utilizes a value of 500mL for the volume of available gastrointestinal fluids; whereas, BCS only uses the gastric volume, i.e. 250mL (as a consequence some BCS 2 compounds become DCS 1). The DCS also accounts for the synergistic nature of solubility and permeability. DCS defines a solubility limited absorbable dose (SLAD) and also provides for an assessment of the drug substance particle size to address dissolution rate limited absorption. This leads to a subdivision of the DCS class 2 compartment into DCS 2a (dissolution rate limited absorption) and DCS 2b (solubility limited absorption). DCS has a greater ability than the BCS system in predicting the factors that are critical to in vivo performance. The system also has significant utility in predicting the appropriate formulation strategy based on DCS categorization.

The Role of *In Vitro* Dissolution Testing

In vitro dissolution testing is always used to support any biowaiver request. Comparative dissolution testing of both the test and reference compounds are assessed at three different pH values. The dissolution profiles are then compared for equivalency or similarity using the f2 test.[8,10,11] Interestingly, the recent FDA guidance on dissolution requirements for biowaivers[12,15] recommends 500mL of media should be used in the comparative dissolution tests. However, this proposed change isn't aligned with EU,[10] Japanese[11] or WHO[8] requirements for dissolution media volume. Historically, the media volume for apparatus 1 and 2 was 900mL, even though volumes between 500 and 1000mL are still deemed to be acceptable.[18,19] It would appear that this modification is to make the dissolution media volume more biorelevant, as under fasting conditions the typical total volume of gastric (250mL) and intestinal media (250mL) compartments are 500mL.[16] Whilst commendable in its objectives, there isn't a huge amount of scientific data in support of the routine use of reduced media volume in a production setting. The concern would be that the hydrodynamics within the dissolution vessel may be adversely impacted as it will be working at the bottom end of its design range.[20]

ICH M9: Potential Discussion Points

As the new ICH guidance evolves towards step 4 ratification (target 2Q 2019), several areas of debate/contention are apparent.

Supportive Data for BCS Assessment

Solubility

The biggest area of contention centers on whether the solubility should be based on the highest therapeutic dose or whether it should be based on the highest strength of the medicinal product. The antimalarial drug quinine sulfate[21] has a maximum therapeutic dose from the product label of 648mg; whereas, the highest dose strength is 324mg/capsule. The target dose/solubility (D/S) ratio based on the gastric volume is ≤ 250mL. Quinine sulfate shows greater solubility at acidic pHs. A summary of the solubility, D/S and BCS assignment in various media of differing pH's is given in Table 1.

Table 1. Solubility, D/S and BCS assignment of quinine sulfate in various media (derived from Strauch et al., 2011)[21]

Media	Solubility (mg/mL)	D/S[c] mL (based on 324mg – highest strength)	BCS[d] Assignment	D/S mL (based on 648mg – highest dose)	BCS Assignment
SGF[a]	12.0	27	1	54	1
SIF[b]	1.3	249	1	498	2

a. SGF simulated gastric fluid, pH 1.2
b. SIF simulated intestinal fluid, pH 6.8
c. D/S dose/solubility ratio
d. BCS Biopharmaceutics Classification System

Therefore, quinine sulfate is a BCS class 1 compound across all physiologically relevant pH's based on the highest capsule strength criterion. In contrast, quinine sulfate is a BCS class 1 compound at acidic pH's, but a BCS class 2 compound at neutral pH's, based on the highest dose criterion.

However, if the D/S ratio was based on the total gastrointestinal volume, i.e., ≤500 mL;[16] then quinine sulfate would be a DCS class 1 compound - based on both highest strength and highest dose calculations, although in the latter case, the drug is borderline at pH 6.8.

There are other examples of commercial drugs (such as ibuprofen) where DCS classification changes from DCS 1 to 2 at higher doses, and it also increasingly common for new chemical entities (NCE's) in phase 1 to straddle DCS 1 to 2b across the range of doses intended for dose escalation.

Permeability

ICH M9 will need to harmonize the different approaches to assessing permeability, i.e. *in vitro* or in vivo assessments. In addition, the cutoff between high and low permeability often prompts debate and is currently "≥ 85% or more of an administered dose based on a mass balance determination (along with evidence showing stability of the drug in the GI tract) or in comparison to an intravenous reference dose".[12] Quinine sulfate is often reported to be highly permeable.[21] However, the absolute bioavailability after oral dosing was reported to be between 76%[22] or 88%;[23] which would make this drug a borderline case. However, because quinine sulfate is extensively hepatically metabolized,[24] the absolute bioavailability only represents a minimum estimate of the fraction of drug absorbed and as < 5% of the oral dose is found in the feces, this provides auxiliary evidence of high permeability.[25] This example shows how difficult it can be, even for a well-established drug, such as quinine sulfate, to unambiguously define a permeability classification.

Published Literature

Strauch et al.[21] indicated that, "a biowaiver cannot be recommended for new quinine immediate-release multisource products or major postapproval changes of already marketed quinine products, and in such cases, BE should be evaluated using an in vivo BE study." In contrast, Wu and Benet[14] classified quinine sulfate as a class I drug using their BDDCS system, i.e. highly soluble and extensively metabolized and therefore a likely candidate for a biowaiver approach.

Setting the Requirements for *in vitro* Dissolution Testing

In vitro dissolution testing will be a prerequisite for any biowaiver. Currently, there are two different criteria for high solubility compounds; either Q = 80% after 30 minutes (BCS class 1) or Q = 80% after 15 minutes (BCS 3). Given the well-established and poor hydrodynamic mixing capabilities[28] of pharmacopoeial dissolution apparatus (particularly USP II) it makes little sense to apply different specification limits, particular as both BCS class 1 and 3 compounds are highly soluble. Since it is practically impossible to perform any meaningful comparability assessment between two dissolution profiles with Q values centered at 15 minutes, Q=80% after 30 minutes may be preferred for both.

Pharmaceutical Equivalents

Thus far biowaivers have been restricted to pharmaceutical equivalents and primarily to BCS class I compounds. There has been widespread concern regarding the effect of different excipients on the permeability and thereby the bioavailability of different formulations. For example, FDA[12] guidance states, “Unlike for BCS class 1 products, for a biowaiver to be scientifically justified, BCS class 3 test drug product must contain the same excipients as the reference product. This is due to the concern that excipients can have a greater impact on absorption of low permeability drugs.”

Whilst it is certainly true that “certain excipients, such as surfactants (e.g., polysorbate 80) and sweeteners (e.g., mannitol or sorbitol) may be problematic”, it is by no means true that all excipients can adversely influence absorption.29 It is likely that the various precepts defined in the “scale up and post approval change” (SUPAC)30 guidance documents will be useful in assessing the likely impact of any change.

Where a medicinal product is marketed in several strengths, i.e. amitriptyline, which has four strengths: 10, 25, 50 and 75mg, does this mean that the BCS based biowaiver has to be performed on all four strengths? Or can the applicant bracket the strengths, i.e. 10 and 75mg or if all four strengths are compositionally similar and there is evidence of linear pharmacokinetics in the proposed dosing range, can the applicant use one strength, i.e. 75mg?

Conclusion

ICH M9 will provide comprehensive recommendations to support a BCS assessment of medicinal products and the potential for biowaiver relief. The aim of ICH M9 is to prevent unnecessary in vivo bioequivalence studies being performed due to conflicting regional recommendations on the acceptability of BCS based biowaivers. This results in increased drug development costs and unnecessary exposure of healthy human volunteers to medicinal products. However, the challenges facing ICH M9 are significant and a target date of 2Q 2019 for step 4 implementation may be difficult to achieve.

References

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