The BCS system was first introduced in 1995. A four-category model for drug classification based on an assessment of drug solubility and permeability was proposed. It was anticipated that this could form the basis for the waiver of in vivo bioavailability and bioequivalence studies. The United States Food and Drug Administration (FDA) subsequently published guidance for highly soluble, highly permeable (BCS Class I) drugs, defining the regulatory criteria for biowaivers, as did the National Institute of Health Sciences in Japan. Thereafter, the World Health Organization (WHO) and European Medicines Agency (EMA) published guidelines for biowaivers for BCS class I and class III (high solubility, low permeability) drugs. Subsequently, the FDA updated its guidance to include both class I and III drugs.

Extensive BCS biowaiver assessments on essential drugs have been carried out by the International Pharmaceutical Federation (FIP). It has published 45 monographs – mostly for highly soluble compounds (BCS class I and III), but also for some BCS class II drugs, i.e. diclofenac, ibuprofen, and nifedipine; some BCS class IV drugs, i.e. furosemide and ciprofloxacin; and some that are not definitively assignable to any one class. For example, isoniazid and quinidine are BCS class I/III; amitriptyline and quinine are BCS class I/II; efavirenz is BCS class II/IV; and prednisone cannot be assigned into any BCS class.

There have been proposals to modify the BCS system based on drugs’ metabolic profiles, i.e. transporter/eﬄux mechanisms. Wu and Benet demonstrated that for drugs showing high intestinal permeability rates (BCS class I/II) the main route of elimination in man was via metabolism, while drugs exhibiting poor intestinal permeability rates (class II/IV) were principally eliminated unchanged. They suggested that a biopharmaceutics drug disposition classification system (BDDCS) could help to predict the relevance of drug transporters in deﬁning drug disposition, in addition to predicting drug–drug interactions.

Butler and Dressman proposed the Developability Classiﬁcation System (DCS), which is intended to have a greater focus on drug developability criteria. In particular, the importance of intestinal solubility in biorelevant media, i.e. fasted state simulated intestinal fluid (FaSSIF); the synergistic nature of solubility and permeability in the small intestine; and an assessment of the drug substance particle size required to address dissolution rate limited absorption. The DCS system was then validated by assessing the in vivo performance of a number of test compounds and this demonstrated that DCS has greater utility than the BCS system in predicting which factors are critical to in vivo performance.

The role of dissolution

In vitro dissolution testing is used to complement any biowaiver request. Dissolution analysis of the test and reference products are assessed at three different pH values (normally pH 1.2, 4.5 and 6.8), to reﬂect the extremes of physiological pH. The dissolution proﬁles can be compared for similarity using the f2 test. Recent FDA guidance on dissolution requirements for biowaivers recommends using 500ml of media in the comparative dissolution tests. Historically, media volume for apparatus one and two are 900ml, although volumes between 500ml and 1,000ml are still acceptable. It would appear that the purpose of this change is to make the media volume more biorelevant as, under fasting conditions, the typical volume of gastric (250ml) and intestinal media (250ml) is 500ml. While laudable in its aims, there isn’t a huge amount of scientific data to support the routine use of this reduced media volume and the concern is that the hydrodynamics within the dissolution vessel may be adversely impacted. In addition, this proposed change is not aligned with EU, Japanese or WHO requirements for dissolution media volume.

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.

References

1. Original references can be found online at www.europeanpharmaceuticalreview.com