Report On The International Workshop On The Biopharmaceutics Classification System (BCS): Scientific And Regulatory Aspects In Practice

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INTRODUCTION

The assessment of the safety and efficacy of multisource (generic) products involves a comparative study between the generic (test) products to be registered versus the innovator (reference) where their respective bioavailabilities are compared. Since the reference product would have been approved on the basis of clinical trials where the safety and efficacy of that product was established, the need to redo expensive and time consuming clinical trials to assess the safety and efficacy is considered unnecessary and instead, a surrogate measure whereby the concentration of drug in serum/plasma of human subjects is compared between the test and reference product is considered more appropriate. Comparative bioavailability studies between test and reference product involve the assessment of bioequivalence between a generic and innovator product in order to confirm the absence of a significant difference in the rate and extent to which the active ingredient or active moiety in pharmaceutically equivalent dosage forms becomes available at the site of action when administered at the same molar dose under similar conditions in an appropriately designed study in human subjects.

Such *in vivo* studies involve the use of healthy human subjects and various *in vitro* methods, such as dissolution rate determinations in particular, have been considered as potential models to predict *in vivo* performance. This is based on the premise that in order to elicit a response, the active ingredient in a dosage form must be released and subsequently dissolve in biological fluids in order to move to and become available at the site of action in the body. Hence the dissolution rate of dosage forms is one of several factors which can account for differences in performance between drug products administered in the same dosage form and same strength containing the same active ingredient. However, only when dissolution is the rate-limiting step will the measurement of dissolution rate provide useful information on drug product performance. Considerations of drug solubility and permeability are additional drug properties which influence product performance, both of which can be assessed *in vitro*.

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THE BIOPHARMACEUTICS CLASSIFICATION SYSTEM (BCS)

The BCS is a scientific framework for classifying drug substances based upon their aqueous solubility and intestinal permeability. When combined with the dissolution of a drug product, the BCS takes into account 3 major factors which govern the rate and extent of drug absorption from immediate release (IR) solid oral dosage forms (tablets/capsules), viz: dissolution rate, solubility and permeability.

According to the BCS, drug substances are classified as follows:

Class 1: High solubility-High permeability

Class 2: Low solubility-High permeability

Class 3: High solubility-Low permeability

Class 4: Low solubility-Low permeability

In addition, IR dosage forms are categorized as having rapid or slow dissolution. According to the BCS, when certain criteria are met, the classification system can be used as a drug development tool to assess bioequivalence *in vitro* thus obviating the need to perform *in vivo* studies in human subjects.

To-date, however, only drug products which fall in the Class 1 category, which contain highly soluble, highly permeable drug substances in IR solid oral dosage forms that exhibit rapid *in vitro* dissolution, may qualify for a waiver of *in vivo* bioequivalence studies.

INTERNATIONAL WORKSHOP PROGRAMME

This workshop was held at the Society Hall of the Royal Pharmaceutical Society in London on 8-9th October 2001 under the auspices of the International Pharmaceutical Federation (FIP) and the Academy of Pharmaceutical Sciences (APS), of Great Britain.

Dr. Gordon Amidon of the University of Michigan, USA described a mechanistic approach based upon the BCS for the absorption of drugs from IR and modified release dosage forms. He emphasized that in the case of Class1 drugs, gastric emptying is the rate-limiting step to drug absorption and that bioequivalence can thus be assured based on *in vitro* dissolution Class 1 drugs. He also discussed the possibility of extending the concept to Class 2 low solubility drugs with dissolution rate limited absorption provided the *in vitro* dissolution test reflects the *in vivo* solubilization and dissolution process. Such dissolution tests will require specific dissolution media including perhaps surfactants, in order to reflect *in vivo* processes for low solubility drugs.

Dr. A. Hussain's (USA Food and Drug Administration-FDA) presentation described the implications of gastrointestinal residence times on drugs with low permeability where incomplete absorption of such drugs may occur in spite of them having high solubility. This stressed the importance of carrying out dissolution rate testing in at least 3 different dissolution media with a pH range of 1.2, 4.5 and 6.8. If one of the products being compared exhibits a different dissolution rate in intestinal pH, then the effect of variable gastric emptying on *in vivo* dissolution will be an important consideration of that product's bioavailability.

Dr. Hong Zhao's, (also of the USA's FDA) presentation described a regulatory research project being conducted to evaluate the scientific evidence for waiving *in vivo* bioequivalence studies under various circumstances and to explore possible extensions of the BCS for such purposes. The project also involves an investigation to support modification of the BCS's solubility definition and consideration is being given to establishing another solubility category, *intermediate solubility*. The current solubility definition describes a solubility class boundary based upon the highest dose strength of an IR product. A drug substance is considered *highly soluble* when the highest dose strength is soluble in 250 ml or less of aqueous media over the pH range of 1-7.5. The volume estimate of 250 ml is derived from typical bioequivalence study protocols that prescribe administration of a drug product to fasting human subjects with a glass (about 8 ounces) of water. Similarly, the definition of *rapidly dissolving*, which currently relates to no less than 85% of the labeled amount of the drug substance dissolving within 30 minutes, is also being reconsidered.

Dr. M. Olling of the Medicines Evaluation Board of the Netherlands discussed the European guideline and acceptance of the BCS for waiving bioequivalence in the European Union. He reported that no application for waiving bioequivalence in the Mutual Recognition Procedure has been acceptable to date.

The second session of the workshop involved presentations which described evidence for waivers based upon the BCS.

D. Dirk Barends of the National Institute of Public Health & The Environment, The Netherlands described his efforts of literature data mining, which can provide valuable evidence for waivers based upon the BCS. He is in the process of establishing a database which will record various properties of drugs and drug products including their formulations and bioequivalence assessment. Additional information includes chemical structural attributes, chirality, therapeutic indications, dose sizes, therapeutic window, polymorphism, pKa, partition coefficient, solubility, dissolution, permeability, absorption, distribution, metabolism and excretion information. Using atenolol, which is a class 3 drug, as an example he compared various generic formulations with the innovator product and showed that even differences in formulation with respect to the excipients used showed that as long as the drug product's dissolution rate is fast, no problems with respect to the absorption of this drug is likely. This is important information which could ultimately be used to obtain a biowaiver for class 3 drugs based upon *in vitro* dissolution rate coupled with solubility and permeability considerations.

Dr. James Polli of the University of Maryland's School of Pharmacy in Baltimore, USA described the efforts being made by the Product Quality Research Institute's (PQRI) BCS working Group. The main emphasis of this research is focused on drugs with high solubility but low permeability (class 3) which has resulted in 3 draft proposals which relate to the influence of common excipients on drug intestinal permeability, intestinal transit and absorption and criteria for dissolution profile similarity. He referred to

a list of excipients and their effects on permeability from studies using CACO 2 cell lines. More specifically the effect of lactose on formulations of atenolol, ranitidine, acyclovir, cimetidine and furosemide/hydrochlorothiazide was investigated and also the inclusion of the surfactant, sodium lauryl sulphate, the latter generally increasing permeability. These excipients also affect intestinal transit times of some drugs. The PQRI is currently collecting data on orally administered drugs which are ionizable. This information will be used to consider whether the current definition of *high solubility* can be broadened.The contention is that many ionizable drugs may fail this definition due to insufficient drug solubility in only a portion of the pH range which is stipulated over 1 – 7.5. He emphasized the fact that acidic drugs can have high solubility above pH of 5, yet lower solubility below pH=5 and drugs that are weak bases can have low solubility above pH of 6 yet high solubility below pH=6.

Dr. R. Roman of GlaxoSmithKline, USA presented 'in house' information where he showed that based upon the solubility, permeability and pharmacokinetics of a number of drugs under development, the criteria for receiving a BCS waiver as currently defined may be too restrictive. Examples were presented for drugs which exhibited complete or nearly complete absorption were not classed as having high solubility and high permeability and that almost without exception, drugs with pKa values within the range specified for the solubility determinations would be classified as having low solubility even though such drugs may be highly soluble in either simulated gastric or intestinal fluid. Similarly, such drugs would be unlikely to meet the dissolution criteria in at least one of the media specified in the BCS.

Session 3 involved the application of the BCS in drug development. Dr. Ron Borchardt of the University of Kansas in the USA described the use of cell culture models to predict oral absorption of drugs in humans and Dr. Potthaust of the Zentallaboratorium Deutsche Apotheker in Germany and co-workers presented a standardized protocol and database for *in vitro* permeability measures and some results. The objective of this research was to understand the reasons for reported variabilities of permeability of drugs when generated by the CACO-2 model from different laboratories. A rank order with respect to apparent permeability was generated for 3 drugs, propranolol, atenolol and the marker FITC-dextran with known absorption by 5 laboratories employing the CACO-2 model.

Dr. H. Junginger of the Center for Drug Research, Leiden University, The Netherlands described *in vitro* models to establish *in vitro-in vivo* correlations based on the BCS. His presentation focused on correlating dissolution and permeability in order to predict *in vivo* performance.

Dr. Brian Henry of Pfizer's Global Research and Development in Michigan, USA discussed the application of the BCS in drug development. He described how *in vitro* studies on new compounds can be used as rudimentary tests to help choose compounds with therapeutic potential for further product development and showed the cost-effectiveness of this approach.

Dr. K. Midha presented results from investigations involving the bioavailability of nicotine from chewing gum dosage forms. Using the amount of nicotine remaining after chewing as an *in vitro* measure of release, these data were correlated with *in vivo* bioequivalence data obtained using the same test and reference products. The relationship between the chew-out (*in vitro*) and the *in vivo* bioequivalence study was discussed.

The final session, session 4, included presentations on challenges and approaches in BCS.

Dr. B. Abrahamsson of AstraZeneca R&D, Sweden discussed the industry perspectives on the BCS. He emphasized the advantages and benefits provided by the BCS, which resulted in minimization of drug exposure to large panels of human subjects and in some cases, shortened drug product development time in addition to large cost savings.

Dr. V. Shah of the USA's FDA described how the dissolution test had undergone a shift from its initial role as a quality control tool in regulatory perspectives. Dissolution rate testing has the potential to predict drug product performance for certain drug candidates under specific conditions and in association with other physicochemical properties such as solubility and permeability. Whilst preliminary data confines biowaivers to class 1 drugs only, additional considerations are given to risk assessment such that dissolution can be used as a surrogate marker for drug blood concentrations for products, which are considered *low risk*.

The workshop presented current information on the use of the BCS and several new proposals were made regarding modifications and 'fine tuning' of the current system. These included, amongst others, the need to reconsider the current class 2 solubility definition by perhaps increasing the volume to greater than 250 ml, modifying the fraction of dose absorbed (currently greater than 90%) in the case of high permeability drugs (80% being considered as being more realistic) and also revising the definition for class 3 permeability. The definition of *rapidly dissolving* was also revisited (85% in 30 min as opposed to 85% in 15 min). Also the range of pH values to be used for the solubility determinations was suggested to be constrained to pH 1-6.8 since beyond pH 6.8, such media would probably be not relevant for weak bases as much of the drug would already have been absorbed. The relevance of pH 1-4 for weak acids was also considered to be not relevant. Weakly acidic drugs would generally not be absorbed in such regions of low pH. The use of physiologic media and inclusion of surfactants were also discussed.