Meeting report: International Workshop on Implementation of Biowaivers based on the Biopharmaceutics Classification System (BCS)

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This paper reflects the scientific opinion of the authors and not the policies of the regulatory agencies and companies they work for.

INTRODUCTION

Even though the pivotal article stating the theoretical basis for a biopharmaceutics drug classification[1] was published almost 20 years ago, the extension of BCS-based biowaiver decisions to drugs belonging to other BCS classes, other than those showing high solubility and high permeability, has not yet reached a consensus among regulators, industrial scientists and academics. Also, within some jurisdictions, BCS principles have not yet been incorporated into legal frameworks and thus, have not been used to allow science- and risk-based regulatory flexibility.

This report provides a brief description of the presentations from the International Workshop on Implementation of Biowaivers based on the BCS in Buenos Aires, Argentine that took place on March 5-6, 2015. The meeting was co-sponsored by National University of La Plata, Confederación Farmacéutica Argentina, International Pharmaceutical Federation (FIP) and American Association of Pharmaceutical Scientists (AAPS). The main objectives of he meeting were to describe the state of the art with respect to in vitro and in silico tools to support waiving in vivo bioequivalence studies and to foster discussion about implementing BCS-based biowaiver decisions to support generic drugs registration in South America. 250 scientists from universities, the pharmaceutical industry and regulatory authorities took part in this meeting. The agenda of the workshop is listed in Table 1 and a picture of the speakers and moderators can be found in Figure 1..

THE PRESENTATIONS

The chair of the meeting, Prof. Pablo Quiroga, and the FIP CEO, Dr. Luc Besancon, opened the meeting and welcomed audience and speakers.

In Plenary Session 1, Dr. Vinod Shah presented the scientific principles of BCS and how US Food and Drug Administration (USFDA) incorporated them into its regulatory framework, firstly as an important tool for setting the requirements for supporting post-approval changes and, subsequently, for supporting new and abbreviated drug applications. Prof. Dr. Jennifer Dressman spoke about methods to characterize drug solubility according to BCS and pointed out some pitfalls found on the description of how to assess drug solubility using shake flask methods extracted from a CRO website. She also discussed the dose definition for drug solubility classification purposes. Using different dose definitions, “highest single therapeutic dose” or “highest dosage strength”, might lead to BCS class migration, such as in the cases of

metoclopramide and prednisone[2]. Prof. Dr. Peter Langguth reviewed currently available *in vitro* (e.g., Caco-2 and MDCK cells monolayers), *in situ* (e.g., rat intestinal perfusion model) and *in vivo* (e.g., human intestinal perfusion model, absolute bioavailability and mass balance) methods for assessing drug intestinal permeability. He cautioned about potential excipient effects on gastrointestinal motility as well as the possibility of them acting as competitors for some uptake and influx transporters, affecting drug absorption in a way that is not possible to anticipate by *in vitro* dissolution testing. This topic was further addressed by Prof. Dr. James Polli, who discussed about the risks of extending BCS-based biowaiver decisions to BCS Class 3 drugs, focusing on potential excipient effects on drug absorption. He presented some recent unpublished data from his research team, showing that even though some common excipients did not seem to affect permeability of cimetidine and acyclovir, which are P-glycoprotein substrates, they can impact *in vivo* dissolution, as was observed after administering formulations containing high amounts of HPMC and magnesium stearate. However, as long as *in vitro* experimental conditions are biorelevant, excipient effects such as the latter ones described could be anticipated. He also discussed that *in vitro* studies might be better than traditional pharmacokinetic studies for assessing bioequivalence between test and reference formulations highlighting the following advantages: a) reduced costs; b) *in vitro* dissolution tests directly assess product performance; c) ethical considerations and d) elimination of problems arising from inconclusive *in vivo* bioequivalence studies showing high type II error. Prof. Dressman also spoke about FIP Biowaiver Monographs, a project that was and is mainly intended to publish Biowaiver Monograph of drug substances which appear on WHO´s List of Essential Medicines and, occasionally, other drug substances finding very common use. The FIP Biowaiver Monograph reports all relevant data found in the open scientific literature, and also reviews critically the reliability of these published scientific data as well as identifying gaps. So far, 43 monographs have been published and many others are ongoing. Also, Prof. Dressman indicated that three of the ten most accessed articles in JPharmSci in 2014 were FIP Biowaiver Monographs, highlighting the worldwide relevance of the project. Prof. Dr. Leslie Benet was the last speaker of the first session. His presentation was pre-recorded since he had already accepted to attend another meeting on the same date. Prof. Benet explained that Biopharmaceutics Drug Disposition and Classification System (BDDCS) is a modification of BCS developed after identifying that there was a very good correlation between extent of drug absorption and extent of metabolism. He pointed out that there is no conflict between BCS and BDDCS but simply each system has a different purpose and utilizes a different measure of intestinal permeability. While the objective of the BCS is to predict *in vivo* performance

of drug products, BDDCS was proposed to serve as a basis for predicting the importance of transporters in determining drug bioavailability and disposition. In his opinion, any difference between BCS and BDDCS is not due to the systems *per se*, but in the ambiguous definition permeability stated by US-FDA, which define a kinetic parameter, intestinal permeability, in terms of a thermodynamic measure, extent of drug absorption.

In Plenary Session 2 Dr. Vinod Shah reviewed metrics currently available to compare dissolution profiles. These can be categorized as model-independent or model-dependent methods. He highlighted that the f2 metric, initially proposed by Moore and Flanner based on mean-squared difference[3] and further statistically developed through mathematical scaling by Shah and co-workers,[4-5] ended up being the simplest and broadly accepted mathematical approach to compare dissolution profiles, based on the assumption that an average difference of up to 10% between two dissolution profiles is not significant. Dr. Shah also emphasized that since the f2 factor is calculated using mean percentage of drug dissolved at each sampling time point, high variability may bias the mean estimates. This can be overcome by using bootstrap method to build 90% confidence intervals.[4] Nevertheless, standardization of simulation techniques in this field is still lacking. Prof. Dr. Bertil Abrahamson presented some experimental examples and suggestions of how clinical relevance of dissolution testing can be achieved in the context of Quality by Design (QbD), emphasizing that *in vitro* dissolution testing together with BCS considerations could provide a key link between manufacturing/product design variables and clinical safety/efficacy in QbD. Also, Prof. Dr. Abrahamson pointed out that IVIVR and physiologically base pharmacokinetic models (PBPK) can be useful tools to build "safe spaces" aiming to achieve regulatory flexibility which, in turn, may facilitate continuous improvement of both drug product and manufacturing process.[6] Prof. Pablo Quiroga used the equation for calculating risk priority number (RPN) in Failure Mode and Effects Analysis (FMEA), firstly suggested by Kubinga and co-workers[7] as a useful tool for supporting biowaivers, to assess the risks of extending BCS-based biowaiver decisions to BCS Class 2 drugs. He focused on the element of the risk equation related to the capacity of detection and reviewed the literature to identify whether current set of experimental conditions recommended by BCS guidelines could anticipate the bioequivalence outcome for poorly soluble and highly absorbed drugs. Some issues related to the dynamic acidification of the thin diffusion layer in response to ionization of some weak acids, which in turn can affect the dissolution of the drug product itself, which do not seem to be captured by the high buffer capacity dissolution media were raised.[8] This led to the conclusion that the

current capacity of detection would need to be improved to allow a biowaiver for BCS Class 2 drugs. Prof. Peter Langguth was the last speaker of the afternoon session and spoke about predicting food effects on the oral drug product performance using BCS. He presented several examples, highlighting an influence of food on intestinal drug metabolism and uptake and efflux transport system and a negative food effect on BCS Class 3 drugs, mainly affecting drug substance (e.g., intestinal dilution) or drug product (e.g., increasing viscosity of dissolution fluid).

Plenary Session 3 was dedicated to the utilization of BCS principles in the regulatory environment. Six speakers presented a worldwide overview about BCS-based biowaiver requirements within different jurisdictions. Dr. Mehul Mehta presented the current decision tree that FDA has been using to evaluate BCS-based biowaiver submissions. He said that the Advisory BCS Committee has reviewed sixty three submitted applications so far and 67% of them were granted BCS-based biowaiver approval since they belonged to BCS Class 1. New drug and abbreviated drug applications accounted for 48 and 52% of the submissions, respectively. Dr. Mehta also emphasized that FDA has been reviewing its BCS guidance and they will move towards accepting biowaiver applications for BCS Class 3 drugs in the future, but without changing the dose definition for solubility classification purposes. Prof. Dr. Dressman reviewed WHO, EMA and FDA BCS guidances, pointing out the main differences among them. She discussed the European criteria that allow BCS Class 3 drugs to be biowaived. Although on the one hand the procedure is scientifically robust, on the other hand it is unclear how regulatory authorities will handle the “quantitatively similar” criterion, given that quantities of excipients in the reference formulation are not disclosed, except in some cases in the Netherlands. Even though generic companies can use reverse engineering tools to unveil reference formulations, she pointed out that regulators will have to compare the product composition with the registered formulation. Some legal issues related to confidentiality may arise. Dr. Yanina Rodriguez spoke about the legal framework for generic drugs registration in Argentina. She provide the audience with an overview of the possibilities of biowaivers accepted by the Administración Nacional de Medicamentos, Alimentos y Tecnología Médica (ANMAT) emphasizing biowaivers for lower dosage strengths in case of proportionality of the formulations and based on BCS principles, for some listed BCS Classes 1 and 3 drugs. Dr. Rodriguez mentioned that ANMAT performs some *in vitro* dissolution tests to assess whether the reference listed drugs will fulfill with at least the rapid dissolution criterion before deciding to add a drug into the list. Dr. Gustavo Mendes Lima Santos spoke about the Brazilian legal framework for biowaivers, Resolução RDC n. 37/11. He

presented the three possibilities of biowaiver currently available in Brazil: a) self-evident bioequivalence; b) lower dosage strengths and c) based on BCS. Given that at the time of publication of the Brazilian BCS guideline it was identified that the views about BCS principles were not adequately harmonized through academics, industrial scientists and regulators, the Agência Nacional de Vigilância Sanitária (ANVISA) decided to start off with a stepwise approach, elaborating a dynamic list with some candidates for BCS-based biowaiver decisions. Dr. Santos explained that ANVISA and sponsors share responsibilities on this field. While ANVISA is responsible for the classification of the extent of drug absorbed, risk assessment in terms of drug therapeutic index and evaluating whether there are evidences of non-BE results not detected by *in vitro* dissolution tests for the selected drugs in its internal database (SINEB), sponsors should submit solubility and *in vitro* dissolution results according to the BCS guideline. He also said that the Brazilian BCS guideline is currently under revision and an update is expected by next year. Dr. Alexis Aceituno presented the Chilean legal framework for bioequivalence and biowaiver. He said that at the beginning the Instituto de Salud Publica (ISP) used to require *in vivo* BE studies only for two drugs, but nowadays, the number of drugs has increased to more than one hundred and fifty. He highlighted that BCS-based biowaivers can be granted for some BCS Classes 1, 2 and 3, in a case-by-case approach. The last speaker of this session was Dr. Mariana Pagano who represented the Ministry of Health of Uruguay. She discussed the main points of the legal framework within her jurisdiction, related to interchangeability of generics, mentioning that BCS principles had already been incorporated into the Uruguayan guidelines. At the end of this session it was possible to identify some divergences among the BCS guidelines issued by South American regulatory authorities and also between US-FDA, EMA and WHO. A harmonization of such criteria would facilitate future mutual recognition and information exchange within the regulatory environment, thus, any attempt to harmonize dose definition for solubility classification purposes, cutoff value for classifying drug extent of absorption, experimental *in vitro* dissolution conditions (e.g., for 50 or 75 rpm for paddle apparatus?) and BCS-based biowaiver extensions beyond Class 1 drugs is very welcome.

Plenary Session 4 was dedicated to *in silico* methods. Prof. Dr. Bertil Abrahamson spoke about the Oral Biopharmaceutics Tools (OrBiTo) Project showing the four Work Packages.[9-11] OrBiTo is basically a partnership between pharmaceutical companies, universities and commercial PBPK software developer companies, whose main goal is to improve tools to predict the performance of orally-administered drugs. Prof.

Abrahamson discussed the current situation of the project and the main issues e.g. lack of scientific understanding in areas like intestinal precipitation, gastrointestinal hydrolysis and differences in regional permeability. He also highlighted that conventional quality control dissolution methods often fail to predict *in vivo* outcomes and sometimes they are overdiscriminative to variables that are not relevant *in vivo*. Prof. Dr. Alan Telavi discussed the importance of having in silico models to predict drug intestinal permeability. Prof. Dr. Telavi spoke about some efforts aimed at the integrated prediction of several significant molecular properties in the field of drug discovery, such as pharmacological activity, aqueous solubility, human intestinal permeability and affinity to P-glycoprotein. Dr. Rodrigo Cristofoletti discussed the importance of taking PK/PD relationships into consideration in order to set clinically relevant limits for *in vivo* bioequivalence studies,[12] according to the scientific background provided by the Biopharmaceutics Risk Assessment Roadmap (BIORAM).[13] He also emphasized the importance of *in silico* tools like PBPK/PD models, to explore "what if" scenarios, and sensitivity analysis that may be useful to identify the most relevant variables, which in turn should be more thoroughly investigated using *in vitro* or *in vivo* methods. Dr. Cristofoletti concluded that such approach may help building clinically relevant "safe spaces" which can facilitate continuous improvement of the formulation based on science and risk-based regulatory flexibility. Prof. Dressman came back to the stage one more time to spoke about using *in vitro* results to predict *in vivo* outcomes using PBPK models as convolution techniques. She highlighted the importance of using biorelevant experimental conditions when aiming at predicting *in vivo* dissolution. Prof. Dr. Dressman also provided the audience with some successful examples of *in vitro – in silico – in vivo* extrapolation (IV-IS-IV-E), for poorly soluble drugs like aprepitant and nifedipine.[14-15]

Table 1. Programme

Workshop Implementation of biowaivers based on BCS
Thursday, March 5th
8:00 am Opening Remarks Prof. Pablo Quiroga –National University of La Plata
Dr. Rodrigo Cristofoletti – Therapeutic Equivalence Coordination/ANVISA-FIP Focus Group Member

Prof. Dr. Jennifer Dressman Pharmaceutical Technology at Goethe Universität Frankfurt- Chair of FIP Foucs Group BCS & Biowaiver

Mr Luc Besançon General Secretary & Chief Executive Officer (CEO)-FIP

Session I
BCS and Biowaivers
Chair: Prof. Dr.M. E. Ruiz-National University of La Plata

8:15 – 8:45 am
Introduction to BCS
Speaker: Dr. Vinod Shah- Chair of the FIP Special Interest Group on Regulatory Affairs

8:45 – 9:30 am
Solubility data and requirements for biowaiving
Speaker: Prof. Dr. Jennifer Dressman - Pharmaceutical Technology at Goethe Universität Frankfurt- Chair of FIP Foucs Group BCS & Biowaiver

9:30 – 10:15 am
Permeability measurement and requirements for BCS based Biowaiver
Speaker: Prof. Dr. Peter Langguth- Head Department of Pharmaceutical Technology and Biopharmaceutics, Johannes Gutenberg- University. FIP Focus Group BCS & Biowaiver Member

10:15- 10:45 Break and Exhibition

10:45 – 11-30 am
Risk assessment of extending BCS-based biowaiver decisions to Class 3: potential excipient effects on drug absorption
Speaker: Prof. Dr. James Polli - University of Maryland School of Pharmacy.

11:30 am – 12:15 pm
BCS-based Biowaivers: The Biowaiver Monographs
Speaker: Prof. Dr. Jennifer Dressman

12:15 – 1:00 pm

Intestinal Permeability vs. Metabolism: BCS vs. BDDCS: opposites or complementaries?

Speaker: Prof. Dr. Leslie Benet (video conference) Dept. of Bioengineering & Therapeutic Sciences and - Dept. of Pharmaceutical Chemistry-UCSF

1:00 – 2:00 pm Lunch and Exhibition

Session II

Dissolution aspects of Biowaiving

Chair: Prof. Dr. Silvia Lucangioli- University of Buenos Aires

2.00 - 2:45 pm

Dissolution Profile Comparison Using f2 and Alternative Approaches (bootstrap, multivariate analysis).

Speaker: Prof. Dr. Vinod Shah

2:45 - 3:30 pm

Clinical Relevance of Dissolution Testing in Quality by Design.

Speaker: Dr. Bertil Abrahamson- Astra Zeneca (Sweden) FIP Focus Group Member.

3:30 - 4:00 pm Break and Exhibition

4:00 - 4:45 pm

BCS based biowaiver for weak acid Class 2 drugs – what are the risks?

Speaker: Prof. MSc. Pablo Quiroga-National University of La Plata and Bago Laboratories

4:45 - 5:30 pm

Improving understanding and prediction of food effects on oral drug product performance

Speaker: Prof. Dr. Peter Langguth- Head Department of Pharmaceutical Technology and Biopharmaceutics, Johannes Gutenberg- University. FIP Focus Group BCS & Biowaiver Member

5:30 – 6:00 pm

Q & A

Moderator: Dr. Dr. Silvia Lucangioli- University of Buenos Aires

Friday, March 6th

Session III

BCS and Legal Framework

Chair: Rodrigo Cristofoletti

8:15 – 09:00 am

'Implementation of BCS based biowaivers - FDA experience'

Speaker: Dr. Mehul Mehta - Director, DCP I (Division of Clinical Pharmacology I), OCP (Office of Clinical Pharmacology), in CDER (Center for Drug Evaluation and Research), FDA - FIP Focus Group BCS & Biowaiver Member.

09:00 - 09:45 am

BCS and Biowaivers Regulations in EMA and WHO

Speaker: Prof. Jennifer Dressman

09:45 – 10:30 am

Regulatory Aspects of Biowaivers in Argentina

Speaker: Dra. Yanina Rodriguez - Pharmacology Department -INAME-ANMAT

10:30 – 11:00 am Break and Exhibition

11:00 am – 11:45 am

BCS and Biowaivers Regulations in Brazil

Speaker: Dr. Gustavo Mendes Lima Santos - Therapeutic Equivalence Coordination/ANVISA

11:45 - 12:30 am

Current and future aspects of biowaiver applications in the bioequivalance regulatory framework in Chile.

Speaker: Dr. Alexis Aceituno - Chief Biopharmacy and Bioequivalence Department.

Agencia Nacional de Medicamentos ISP Chile

12:30 am - 1:15 pm
Medicines Interchangeability: regulatory aspects related to Biowaivers in Uruguay
Speaker: Dra. Mariana Pagano - Ministerio de Salud Pública de la R.O.U.

1:15 – 2:30 pm Lunch and Exhibition

Session IV
Innovative and in silico methods
Chair: Prof. Arturo Hoya – National University of La Plata

2:30 - 3:15 pm
The OrBiTo Project
Speaker: Dr. Bertil Abrahamsson

3:15 – 4:00 pm
In silico Models for the prediction of permeability of drugs
Speaker: Prof. Dr. Alan Talevi - University of La Plata

4:00 – 4:45 pm
Connecting oral formulation performance to therapeutic effect using PBPK/PD modeling and simulation: ibuprofen as an example
Speaker: Dr. Rodrigo Cristofoletti

4:45 – 5:15 pm Break and Exhibition

5:15 – 6:00 pm
Coupling Dissolution with PBPK for predicting in vivo behavior of poorly soluble drugs
Speaker: Prof. Jennifer Dressman

6:00 – 6:15 pm
Q & A
Moderator: Prof. Arturo Hoya – National University of La Plata

6:00 pm

Closing Remarks

Prof. Jennifer Dressman

Figure 1. Speakers and Moderators of the International Workshop on Implementation of Biowaivers based on the Biopharmaceutics Classification System (BCS)

From left to right, a) rear row: Prof. Dr. Peter Langguth, Prof. Dr. Bertil Abrahamson, Dr.Mehul Mehta, Dr. Rodrigo Cristofoletti, Dr. Gustavo Mendes Lima Santos, Prof. Pablo Quiroga, Prof. Dr. Alan Telavi, Dr. Mariana Pagano and Prof. Arturo Hoya; b) front row: Prof. Dr. James Polli, Dr. Vinod Shah, Prof. Dr. Jennifer Dressman, Prof. Dr. Maria Esperanza Ruiz, Dr. Yanina Rodriguez and Prof. Dr. Silvia Lucangioli.

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