

Workshop Report: Implementation of Biowaivers based on the Biopharmaceutics Classification System

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INTRODUCTION

The first Panamerican Workshop on “Implementation of Biowaivers based on the Biopharmaceutics Classification System” (BCS) was held April 26 and 27, 2017 at Pontificia Universidad Católica de Chile, in Santiago, Chile. There were 150 participants representing the Chilean pharmaceutical industry, national regulatory agency, regional bioequivalence centers, and academia. The workshop was sponsored by Pontificia Universidad Católica de Chile, the Ministerio de Salud (MINSAL), the Instituto de Salud Pública de Chile (ISP), the University of Maryland Center of Excellence in Regulatory Science and Innovation (M-CERSI), and the International Pharmaceutical Federation (FIP). The workshop spanned 2 days, involving four sessions and a final roundtable. Co-chairs were Dr. Pablo González, Dr. Peter Langguth, and Dr. James Polli.

The goals of the workshop were for attendees to:

- Understand the scientific bases for the regulatory tests of BCS-based biowaivers (e.g., solubility, permeability, dissolution, excipients)
- Understand how BCS drives science-based regulatory decisions on biowaivers
- Recognize the role of BCS as a scientific framework for quality by design (QbD) drug product development

THE LECTURES

The first session entitled “**Bioequivalence and Biowaivers: Scientific and Regulatory Aspects**” started with a lecture on “**Bioequivalence and Biowaivers: Regulatory considerations for Biowaivers,**” by Dr. Vinod Shah. Dr. Shah discussed bioequivalence requirements and procedures for conducting bioequivalence studies for immediate release (IR) and modified release (MR) dosage forms. It was explained that: (i) drug product safety and efficacy for the generic product is established by it being pharmaceutically equivalent and bioequivalent, and thus therapeutically equivalent; and (ii) the quality of the

product is ensured thru product identity, strength, purity, assay, potency, content uniformity, dissolution (for solid oral dosage forms), and by it being manufactured under FDA’s good manufacturing practices. Biowaiver criteria for lower strengths of IR and MR dosage forms and BCS class I and III drug products were discussed.

The second lecture, “**The Biopharmaceutical Classification System: Theoretical Principles**” by Dr. Pablo González focused on the fundamental principles on which BCS was developed. Bioavailability was defined from a mass balance point of view to differentiate it from fraction dose absorbed (Fa). Factors that modulate Fa that are explicitly considered in the BCS model were presented, with focus on the interplay between drug solubility and permeability in oral absorption. Dr. González discussed dimensionless numbers in detail and exposed their use as parameters to model different drug absorption scenarios (permeability-, solubility-, dissolution-limited cases).

BCS classes were presented and factors that can influence oral absorption for each class were discussed, with a particular emphasis on excipients and class III drugs.

Next, Dr. Alexis Aceituno discussed “**BCS and Strength-based Biowaivers,**” presenting a general description about regulatory requirements for granting BCS- and strength-based biowaivers. The possibility of a BCS biowaiver for orally-disintegrating tablets (ODT) and fixed dose combination products was discussed. In addition, experimental methods to assess dissolution, solubility, and permeability were presented as well as physiological factors affecting these processes. Strength-based biowaivers were described in terms of proportionality criteria, and alternative approaches in case of not strictly proportional formulas across all the strengths or absence of linear pharmacokinetics in the therapeutic range were discussed. Dr. Aceituno discussed discriminative dissolution testing media as well as the need for harmonization among different jurisdictions to decrease the differences among regional regulatory authorities.

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To close this first session, Dr. James Polli addressed “**In vitro-in vivo Correlations (IVIVC),**” which covered biopharmaceutical risk, dissolution profiles, and IVIVC; deconvolution in vitro-in vivo relation (IVIVR) method; and convolution IVIVC. Dr. Polli discussed biopharmaceutical risk and the sometimes limited extent that biopharmaceutical risk is connected with IVIVC/IVIVR analysis. He asked, “*If in vivo dissolution is not-limiting drug absorption, and in vitro dissolution exactly measures in vivo dissolution, what would be the relationship between dissolution and absorption?*” He also presented **Table 1** below, emphasizing that “*successful’ analysis from these varying techniques often relies upon the assumption required by the particular method. For example, the USP level A approach (which is very different than FDA level A approach) requires dissolution to be rate-limiting for such a straight line to result.*”

Table 1. Categories of IVIVC/IVIVR (1)

Name or description of analysis	Abbreviation
Convolution (FDA Level A)	AAA
Deconvolution	AA
Deconvolution (but only linear, e.g. USP Level A)	A
Summary parameters	B
Point estimates	C
Rank order	D

IVIVC, in vitro-in vivo correlation; IVIVR, in vitro-in vivo relation.

Dr. Polli presented three examples of deconvolution IVIVR analysis, as well as an example of convolution IVIVC analysis. The three examples of deconvolution IVIVR analysis are described in the literature and are for metoprolol, piroxicam, and ranitidine. (1-4) Metoprolol is a BCS class I drug. Piroxicam is a BCS class II drug. Ranitidine is a BCS class III drug. Their IVIVR analysis results reflect drug solubility and permeability, including the role of dissolution and biopharmaceutical risk. A convolution example highlighted pharmacokinetic profiles, with less emphasis on drug absorption mechanistic interpretation.

Plenary sessions 2 and 3 focused on **Evaluation of Drug and Product Performance**. First, Dr. Gustavo Mendes gave a lecture on “**API Solubility: Methods and Regulatory Requirements.**” Dr. Mendes discussed how proof of high solubility is one of the fundamental aspects for the classification of drugs by the BCS system. For that, pharmacopoeial methods, such as shake-flask, are recommended and methods for drug quantification should be sensitive enough to detect possible degradation. A drug will be considered highly soluble if its highest dose or highest strength administered orally as an

IR formulation is completely solubilized in up to 250 mL of each buffer solution used within the physiological pH range (1.2–6.8) at $37 \pm 1^\circ\text{C}$. Such experimental conditions are related to standard physiological conditions and also to the volume of liquid usually used for administration of oral medications. Dr. Mendes commented that a necessary issue for harmonization is the definition of the dose to be considered for the classification of drug solubility, given that regulatory agencies have different requirements. “*The debate between the highest dose in a single intake (as described in label) or the highest strength per unit is still pending resolution, and the creation of the ICH biowaiver working group represents a positive perspective in this regard,*” said Dr. Mendes.

The following lecture was on “**Refinement of in vitro Disintegration Methods for Solid Dosage Forms**” by Dr. Peter Langguth. Dr. Langguth discussed complexity of the solid oral dosage form disintegration process in detail, emphasizing phenomena such as viscosity of the dissolution fluid, its pH and buffer strength, the fluid diffusivity into the dosage form, fluid flow (hydrodynamics), and mechanical stress in the stomach following tablet administration. Generally, in pharmacopoeial-type equipment, the disintegration is tested in a basket-rack assembly, where the dosage form is moved vertically in a 1 L beaker filled with disintegration medium over a specified distance at a given frequency. Dr. Langguth showed that computational fluid dynamic simulations suggest that these conditions are far from representing the actual situation in the stomach and improved methodologies are required to simulate in vivo dosage form disintegration. A particular situation exists for highly viscous media, e.g., the stomach conditions after administration of a solid meal, such as the standardized FDA breakfast. It has been shown that disintegration times of solid dosage forms may increase dramatically in such situations, which may decrease drug dissolution and absorption. Dr. Langguth mentioned that current and future work is targeted towards improving the disintegration equipment and introducing standardized viscous media with improved in vivo predictability as well as formulation development of more robust dosage forms.

Next, Dr. Vinod Shah addressed the topic of “**Dissolution Method Development and Regulatory Requirements.**” The importance of dissolution testing was identified, and the development of dissolution methods for IR, MR, poorly soluble drug products, and gelatin capsules were discussed. Regulatory requirements for setting dissolution specifications were explained. A methodology

for dissolution profile comparison and its value was presented, and dissolution-based biowaivers discussed.

To close the first day of lectures, Dr. Langguth gave a talk on **“Product Design from a Biopharmaceutical Perspective,”** addressing how acceptable biopharmaceutical performance of oral drug products requires a formulation design that relates to the BCS class of the active ingredient. Dr. Langguth emphasized that BCS class I and III compounds in IR dosage forms generally do not require sophisticated formulation designs from a biopharmaceutics perspective, as long as rapid disintegration and dissolution in fasted and fed states can be assured. Particularly in the fed state, rapid disintegration/dissolution may be compromised, which may lead to “negative food effects” in case of BCS class III compounds. Dr. Langguth mentioned that current development work is targeted towards improving the robustness of IR tablets in this regard. Formulation strategies to improve dissolution and solubility of low soluble BCS class II and IV compounds were presented, such as salt formation, micronization, solid dispersions, nanosuspensions, cyclodextrin complexes, microemulsions, and the like. It was emphasized that formulation strategies depend on acid-base properties of the drug (e.g., BCS class IIa, IIb, or IIc) and on physicochemical drug parameters such as logP, melting point, solubility in oil, and the dose to be administered. Dr. Langguth commented on the challenge of counting with strong in vitro tools to predict in vivo absorption of formulated products. *“Although a number of mainly non-pharmacopoeial in vitro tools are available, their validation still needs to be improved to be utilized in formulation selection and bioequivalence prediction,”* said Dr. Langguth.

The second day of lectures resumed with **Dr. Ismael Hidalgo** addressing the topic of **“In situ and in vitro (Cell-based) Permeability Methods.”** Dr. Hidalgo commented on bioequivalence being the most useful criterion to ensure the safety, quality, and therapeutic efficacy of generic drug products and how bioequivalence can be ascertained by comparing the pharmacokinetic profile in humans of the generic product with that of the innovator, or reference-listed drug. However, these studies are costly, time-consuming, and have raised ethical concerns. BCS allows demonstration of bioequivalence for over 60% of oral drug products (BCS class I and class III), using in vitro dissolution data. However, to determine whether a product is eligible for the in vitro BE approach, the active pharmaceutical ingredient (API) must be classified in terms of solubility and permeability. The permeability

classification can be done using in vitro models such as cultured cells or in situ perfused rat intestine, provided they are validated. *“In Latin America, in vitro models are the only feasible strategy to implement bioequivalence requirements in a reasonable time,”* said Dr. Hidalgo.

Lectures continued with Dr. James Polli addressing the **“Excipient Effects: in vivo and in vitro.”** Dr. Polli discussed results of a series of human bioequivalence (BE) studies to elucidate the effect of large quantities of common excipients on BCS class III drugs. The results are described in the literature, including a reply to a letter to the editor from scientists from Spain, Canada, and Germany. (5, 6) The studies presented measured the impact of 14 commonly used excipients on BCS class 3 drug absorption in humans. Cimetidine and acyclovir were used as model class 3 drugs across three separate BE studies in healthy human volunteers, denoted as study 1A, 1B, and 2. In study 1A and 1B, three capsule formulations of each drug were manufactured, collectively involving 14 common excipients. Capsules with hydroxypropyl methylcellulose (HPMC) or magnesium stearate exhibited lower absorption. The cimetidine commercial solution contained sorbitol and also resulted in lower absorption. In study 2, two capsule formulations with lower amounts of HPMC and magnesium stearate, the sorbitol-containing commercial solution, and a sorbitol-free solution were assessed for BE. Overall, 12 common excipients in large amounts did not impact BCS class 3 drug absorption in humans; these excipients need not be qualitatively the same nor quantitatively very similar to reference, but they cannot exceed the quantities studied. Meanwhile, BCS class 3 biowaivers require HPMC and microcrystalline cellulose be qualitatively the same and quantitatively very similar to the reference product.

Next, Dr. Pablo González discussed the role of **“Intestinal Transporters”** on oral drug absorption. Current data on intestinal expression level and subcellular distribution patterns were presented for most relevant subfamilies of transporters. In particular, topological models, tissue expression, and substrates and inhibitors (including excipients) were presented for both ATP-binding cassette transporters (P-gp, BCRP, and MRP2) and solute carrier transporters (Pept-1, OCTs, and OATPs) with the highest intestinal expression levels. Cell-based in vitro models to study transporter-mediated drug permeability such as Caco-2 and MDCK were presented with emphasis on the role of efflux transporters and the efflux ratio parameter as a means to describe active drug efflux in over-expression cellular systems.

The final session entitled “**BCS-based quality-by-design (QbD)**” started with a lecture on “**Dissolution to Predict Product Performance through QbD**” by Dr. Bertil Abrahamsson. Dr. Abrahamsson emphasized how product dissolution is the link between pharmaceutical factors and clinical performance for oral products. Thus, dissolution is a critical aspect in product development and quality control given that it reflects or predicts the in vivo situation. Dr. Abrahamsson presented how recent progress in understanding of the absorption process and characterization of gastrointestinal fluids has provided a toolbox for in vivo predictive dissolution testing (7). This has allowed for a rational approach of using dissolution testing in the context of quality-by-design (8) including: definition of target properties, screening of prototypes to meet targets, identification of critical process formulation variables to maintain target properties, definition of biorelevant test that discriminates for critical variables, confirming of in vivo relevance of test method and acceptance criteria by in vivo data (if BCS class II and IV drugs or controlled-release product), and application of dissolution criteria in control strategy.

Next, Dr. Alexis Aceituno addressed the topic of “**Drug Product Formulations and Biowaivers: A Regulatory Point of View,**” discussing the need for looking at excipients in the compositional formulas as active ingredients in terms of biopharmaceutical properties. This is linked to the known effects of certain excipients on oral drug absorption, which is considered critical for class 3 drugs. The need for compliance of Q1 and Q2 levels at the moment of comparing a test product with the innovator if a biowaiver request is to be granted was presented. A brief description of typical critical excipients affecting drug intestinal permeability and proposed mechanisms, the way this has been acknowledged by international jurisdictions in biowaiver guidance, and the need for evaluating the real in vitro or in vivo impact that critical excipients may have on the intestinal permeability of model drugs was also discussed. Dr. Aceituno concluded that a better and more complete understanding of excipient effects on drug permeability is essential to extend experimental results to other drugs.

To close this fourth session, Dr. Bertil Abrahamsson gave the lecture, “**Recent Progress in Understanding and Predicting Oral Absorption with Focus on the IMI project OrBiTo.**” OrBiTo is a project in the area of oral biopharmaceuticals tools that includes 27 academic or industrial partner organizations.(9) The OrBiTo project aim is to deliver a framework for rational application of predictive biopharmaceuticals tools for oral drug delivery.

This is being achieved through novel prospective investigations to define new methodologies or refinement of existing tools. Extensive validation has been performed of novel and existing biopharmaceutical tools by using historical datasets from industry partners. A combination of high quality in vitro or in silico characterizations of API and formulations are integrated into physiologically based in silico biopharmaceuticals models, capturing the full complexity of gastrointestinal drug absorption. “*This approach gives an unparalleled opportunity to deliver transformational change in European industrial research and development towards model-based pharmaceutical product development,*” said Abrahamsson. So far, more than 60 papers have been published. (10)

Finally, a roundtable on the subject of “**Bioequivalence and Drug Product Interchangeability**” was held. Participants represented different sectors related to pharmaceutical products including Dr. Enrique Paris (President of the Chilean Association of Physicians), Mr. José Luis Cárdenas (President of PROLMED), Mr. Jean Jacques Duhart (Executive Vice-President of the Chamber of Pharmaceutical Innovation), Mr. Mauricio Huberman (President of the Chilean Association of Pharmacists and Biochemists), and Dr. Alexis Aceituno (National Institute of Health, Chile). There was a consensus among representatives that only by strengthening the interchangeability standard, with emphasis on biowaivers, drug product quality can be assured.

Chile and South America are regions with increasing public interests in public standards for medication quality. Local companies and universities have implemented biopharmaceutical tools to predict drug product performance and quality. Regional regulatory authorities have increasingly harmonized requirements. Overall, the workshop was an excellent opportunity for pharmaceutical scientists in Chile and South America to exchange approaches in oral drug development and learn of new biopharmaceutical approaches from North America and Europe.

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CONFLICT OF INTEREST

No conflict of interest has been declared by the author(s).

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Speakers at the First Panamerican Workshop on “Implementation of Biowaivers based on the Biopharmaceutics Classification System”. From left to right: Pablo M. González, Vinod Shah, Claudio Paulos (organizing committee UC), Alexis Aceituno, Bertil Abrahamsson, James E. Polli, Ismael Hidalgo, Peter Langguth.