Short Course: Development of Fixed Dose Combination Products: Considerations of GI Physiology and Overall Development Strategy

The gastrointestinal (GI) tract is the most popular and used route of drug product administration due to the convenience for better patient compliance. However, its complex nature poses a great challenge for drug product formulators when developing more complex dosage forms such as those combining two or more drugs. Fix dosed combination (FDC) products are two or more single active ingredients combined in a single dosage form representing a contribution to safety and efficacy compared to the co-administration of the mono-products. A complex drug product, to be dosed through a complex route, requires judicious considerations for formulation development. Additionally, it represents a challenge from a regulatory perspective at the time of demonstrating bioequivalence for generic versions of such drug products.

This short course will offer a comprehensive view of the most influential aspects of the GI physiology on the absorption of drugs and current techniques to help understand the fate of orally ingested complex drug products in the complex environment represented by the GI tract. Through case studies on FDC product development and regulatory issues, this course will provide a great opportunity for attendees to explore avenues for successfully developing FDC products and their generic versions.

Learning Objectives:

- Understand the complexities of the GI environment from a biopharmaceutical point of view.
- Understand how each GI segment affects the drug product release and dissolution of drugs.
- Integrate the physiological aspects of the GI that affects drug bioavailability into a more predictive in vitro model.
- Understand the rationale for FDCs development and design.
- Identify ways to demonstrate safety and efficacy for generic versions of FDCs products.
- Identify FDCs current regulations to demonstrate efficacy, similarities, and differences among jurisdictions.

Presentations

All presentations will be available for day one and day two of the workshop no later than 24 hours following the workshop. Presentations will remain online for registered attendees until August 7, 2019.

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Workshop Planning Committee

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Workshop Agenda

Sessions will take place in the Washington Convention Center, room 207 B

Saturday, November 3, 2018	
9:00 am – 9:50 am	**From Stomach to Large Intestine: Part I: What do we need to know from the human stomach?** Bart Hens, PharmD, Ph.D., University of Leuven Maura Corsetti, MD, Ph.D., University of Nottingham
9:50 am – 10:45 am	**From Stomach to Large Intestine: Part II: What do we need to know from the human small intestine?** Bart Hens, PharmD, Ph.D., University of Leuven
10:45 am – 11:00 am	Coffee Break
11:00 am – 11:45 am	**From Stomach to Large Intestine: Part III: What do we need to know from the human large intestine?** Maura Corsetti, MD, Ph.D., University of Nottingham
11:45 am – 12:30 pm	**Integration of GI Physiology into a Predictive Dissolution Device: Part IV: Where to Start?** Raimar Loebenberg, Ph.D., University of Alberta
12:30 pm – 1:30 pm	Lunch Break
1:30 pm – 2:30 pm	**In Vitro Dissolution for a Marketed and Generic FDC Drug Product: Bioequivalent or Not?** Marival Bermejo, Ph.D., Universidad Miguel Hernández de Elche
2:30 pm – 2:45 pm	Coffee Break
2:45 pm – 3:45 pm	**Challenges and Opportunities to Grant BCS and Dose Strength Based Biowaivers for FDC Products** Pablo Gonzales, Ph.D., Universidad Católica de Chile

Sunday, November 4, 2018	
9:00 am – 9:50 am	**Considering the Biopharmaceutical/Physicochemical Aspects of FDC** Amitava Mitra, Ph.D., Sandoz, USA
9:50 am – 10:45 am	**Current Regulatory Requirements to Assess Bioequivalence of FDC Products Worldwide (EU/USA/ Latin America/Japan)** Alexis Aceituno, Ph.D., Public Health Institute of Chile
10:45 am – 11:00 am	Coffee Break
11:00 am – 12:00 pm	**Formulation Design, Challenges, and Development Considerations for Fixed Dose Combination (FDC) of Oral Solid Dosage Forms.** Divyakant Desai, Ph.D., Bristol-Myers Squibb
12:00 pm – 1:00 pm	**Current Regulatory Requirements in the USA to Assess Bioequivalence of FDC Products** Dakshina Chilukuri, Ph.D., U.S. Food and Drug Administration
1:00 pm – 2:00 pm	Lunch Break

Speaker Abstracts and Biographies

From Stomach to Large Intestine: Part I: What do we need to know from the human stomach?

This first talk will handle the physiology of the stomach and how physiology can have a major impact on the systemic exposure of the drug. We'll discuss some examples of drug formulations that were tested in the human stomach and were evaluated for their impact on systemic exposure.

Bart Hens, Pharm.D., Ph.D., University of Leuven

During his dissertation research, Bart Hens (Pharm.D., Ph.D.) focused on the behavior of oral drug products in the gastrointestinal tract in humans (KU Leuven, Belgium). Based on the results of these studies, he started to use the data as a reference for optimization and validation of different in vitro/in silico models to increase their predictive power towards the in vivo outcome of an oral drug product. His Ph.D. project was part of a bigger European project between academic institutions and pharmaceutical companies (www.orbitoproject.eu). Since January 2017, Bart started to work as a postdoctoral research fellow in the laboratory of Prof. Dr. Gordon L. Amidon (University of Michigan), where they both explore the impact of gastrointestinal physiology on oral drug behavior by performing clinical studies with a multidisciplinary team. The gathered knowledge will be used as a reference in order to develop a formulation predictive dissolution test for oral drug products. This work is supported by grant # HHSF223201510157C and grant # HHSF223201310144C by the U.S. Food and Drug Administration (FDA). From 2018 on, Bart will be performing research at KU Leuven as a postdoctoral fellow from the Flemish Government (FWO).

Maura Corsetti, M.D., Ph.D., University of Nottingham

Maura Corsetti is Associate Professor of Gastroenterology at the University of Nottingham. She graduated in Medicine and obtained her Specialization (2000) and PhD (2004) at the Universita' degli Studi di Milano in Italy. During her PhD she worked for two years (2001-2002) as a research fellow in the Translational Research Center for Gastrointestinal Disorders (TARGID), University of Leuven, Belgium. For eight years (2004-2012), she was the clinical and scientific referral consultant for functional gastrointestinal (GI) disorders at the San Raffaele University Hospital, Milan, Italy. Then she moved to TARGID, University of Leuven, Belgium where she worked for four years (2012-2016) as Senior Research Supervisor. She is an internationally recognized expert in the study of GI motility and Associate Editor of Neurogastroenterology and Motility, the official journal of the European and American Society of Neurogastroenterology and Motility. She organized the first translational consensus on terminology and definition of colonic motility as studied in humans and animals by means of manometric and non-manometric techniques leading the international experts in the field. She is the leader of Food-Drug Interaction Working Group of the COST Action CA16205: European Network on Understanding Gastrointestinal Absorption-related Processes.

From Stomach to Large Intestine: Part II: What do we need to know from the human small intestine?

The small intestine is the main site of absorption. The physiology of the small intestine can explain the variability in systemic exposure of a drug. Case examples will be discussed with the audience based on in vivo studies that were performed.

Bart Hens, Pharm.D., Ph.D., University of Leuven

Biography listed above.

From Stomach to Large Intestine: Part III: What do we need to know from the human large intestine?

This talk will advance in the understanding of motor and secretory function of the colon as studied in vivo in humans by means of the high-resolution manometry and functional MRI. It will be discussed how the alteration of these colonic function are expected to impact on drugs systemic exposure.

Maura Corsetti, M.D., Ph.D., University of Nottingham

Biography listed above.

Integration of GI Physiology into a Predictive Dissolution Device: Part IV: Where to Start?

The talk will give examples how GI physiology, motility and pharmacokinetics are interconnected and contribute to variability in PK profiles. In vitro data will be presented which will show the importance of physiological relevant conditions to predict the in vivo dissolution of drugs. Different approaches will be discussed on how to design an in vitro predictive dissolution test.

Raimar Löebenberg, Ph.D., University of Alberta

Raimar Löbenberg holds a BS in pharmacy from the Johannes Gutenberg-University in Mainz, Germany. He received his PhD in pharmaceutics from the Johann Wolfgang Goethe-University in Frankfurt in 1996 for his work in drug delivery using nanoparticles. He then joined Dr. Dressman's lab and investigated the dissolution behavior in Biorelevant dissolution media. After that he joined Dr. Amidon's lab in Ann Arbor where he investigated different aspects of oral drug administration including computer simulations. He joined the University of Alberta in 2000. His research interests are in Biopharmaceutics to predict the oral performance of drugs and botanicals and inhalable nanoparticles to treat lung diseases like cancer and tuberculosis. He is founder and director of the Drug Development and Innovation Centre at the University of Alberta, which holds an NHP site license. He was president of the Canadian Society for Pharmaceutical Sciences 2014/15 He is member of the United States Pharmacopeia Dietary Supplement Expert Committee. He is vice chair of the Specialty Committee of Traditional Chinese Medicine in Pharmaceutics of the World Foundation of Chinese Medicine Science. He is member of the Health Canada Scientific Advisory Committee on Pharmaceutical Sciences and Clinical Pharmacology.

In Vitro Dissolution for a Marketed and Generic FDC Drug Product: Bioequivalent or Not?

Development of Fixed-Dose Drug Combination Products (FDCP) could be challenging when both drugs do not belong to the same BCS class i.e when the limiting factors for their absorption are different.
In the lecture, the concept of using BCS as a risk assessment tool of Bioequivalence issues will be illustrated with the aid of a case study of a FDCP.

A generic company attempted to develop a FDCP of two drugs belonging to class 3 and class 2 from BCS. They failed two show BE in two Human BE studies, in each one failing for one of the drugs while succeeding for the second.

The application of a biopredictive dissolution test using the Gastrointestinal simulator GIS will be shown as a method to explore the causes of failure in BE for the Class 2 compound.
Potential methods to assess the risk associated with the class 3 drugs will be discussed.

Marival Bermejo, Ph.D., Universidad Miguel Hernández de Elche

Marival Bermejo, Pharm.D. PhD. Has been Full Professor at the University Miguel Hernández, Spain since 2008. She became Assistant Professor at the University of Valencia in 1994 and promoted to Associate Professor in 1998. She performed two post-doctoral research stages at ITODYS in Paris VII University, with Prof. Christiane Mercier and at the University of Michigan, with Prof. Gordon Amidon. Her research is centered on in vitro models of biological barriers and predictive dissolution methods. She coordinated the Alpha-III-project “Red Biofarma”, funded by the European Commission to promote education in South-American universities and regulatory agencies about drug product development tools. She has co-authored 100 papers, 10 books chapters and is co-author with Gordon Amidon of the English/Spanish versions of Modern Biopharmaceutics, a CD-Rom teaching tool. She is member of the Board of the Drug Delivery Foundation and external assessor of the Spanish Agency of Medicines and EMA. Dr. Bermejo is foreign member of the Chilean Academy of Sciences for her contribution to Pharmaceutical Scientists education. In 2015 she received a Fulbright scholarship for a sabbatical period at the University of Michigan working on in vivo predictive dissolution and has been appointed as visiting research scholar in 2016-17-18 summer periods.

Challenges and Opportunities to Grant BCS and Dose Strength Based Biowaivers for FDC Products

Fixed-dose combination (FDC) products combine two or more active pharmaceutical ingredients (API) in one finished pharmaceutical product (FPP), offering greater patient compliance, better therapeutic efficacy, and attractive new product development opportunities.
The World Health Organization (WHO) recognizes four possible scenarios for FDC product registration, each of them posing different requirements to the manufacturer. Scenarios 1 and 2 are FDC products that must demonstrate bioequivalence either relative to an existing FDC-FPP or to the single entity products.
The Food and Drug Administration (FDA) and the European Medicines Agency (EMA) allow Dose Strength based Biowaivers of FDC products that are proportionally similar to the strength of the single entity products (the most sensitive) that demonstrated bioequivalence. FDA and EMA have different proportionality criteria based on the number of compartments in the FDC product (monolithic, bilayer).
Currently, both FDA and EMA allow Biopharmaceutics Classification System (BCS)-based biowaivers of FDC-FPP provided all active pharmaceutical ingredient belong to either class I or III of the BCS.
Regulatory agencies have defined criteria regarding allowable differences in excipients between multisource FDC and reference product(s).
The FDA and EMA different proportionality criteria will be exposed and discussed since they present a challenge to biowaiver of FDC products in different regions. Also, different requirement regarding compositional differences for BCS-I only FDC products between FDA and EMA will be discussed.

Pablo Gonzales, Ph.D., Universidad Católica de Chile

Pablo González is a Pharmacist from Pontificia Universidad Católica de Chile (UC, 2002) and received his Ph.D. degree from the University of Maryland (2008). Currently Dr. González is Assistant Professor at the Department of Pharmacy of the Faculty of Chemistry UC where he teaches Pharmaceutical Technology. The main research area of Dr. González is oral drug absorption with focus on intestinal transporters and their potential role as targets for drugs and pro-drugs, structure-permeability relationships of small molecules, drug absorption mechanisms, and the impact of both excipients and components of intestinal fluids on drug permeability. Dr. González has published several papers on high-impact journals and mentored over 30 thesis students. Currently, Dr. González is the Principal Investigator of a FONDEF IDea Grant form Chilean government (CONICYT) on development and validation of in vitro and in situ methodologies to study drug permeability and the potential impact of excipients commonly used in solid dosage forms on drug absorption (2017-2018). Dr. González is a member of the Bioequivalence Unit of the Center for Clinical Investigation at UC (CICUC) and Principal Investigator of the Biowaivers Unit of the Center of External Studies and Assays of the Faculty of Chemistry at UC (CEQUC).

Considering the Biopharmaceutical/Physicochemical Aspects of FDC

Fixed dose combination (FDC) products are becoming a popular treatment option because of increased patient compliance and convenience, improved clinical effectiveness and reduced cost to the patient, among several other reasons. A commonly applied approach for approval of a FDC product is demonstrating bioequivalence between the FDC and co-administration of individual mono-products, provided that there is adequate safety and efficacy data for co-administration of the individual agents. However, achieving bioequivalence between the FDC and individual mono-products can be very challenging, and sometimes not possible since combining multiple active ingredients, especially insoluble molecules, in a single drug product could complicate its biopharmaceutical and pharmacokinetic behavior. In this presentation, some of the major challenges often encountered while assessing bioequivalence during FDC development will be discussed along with discussion of future opportunities to facilitate FDC development and approval.

Amitava Mitra, Ph.D., Sandoz, USA

Amitava Mitra currently works in Clinical Development at Sandoz, he has previously worked in the Biopharmaceutics group at Merck & Co. Amitava graduated with a PhD in Pharmaceutical Sciences from University of Maryland, Baltimore. Amitava's main research interests include pharmacokinetics, biopharmaceutics, PBPK modeling & simulation of oral and alternate drug delivery systems and IVIVC. He has interacted with global regulatory authorities (FDA, EMA & PMDA) on these topics. Amitava has published more than 30 research and review articles in peer-reviewed journals and has also authored book chapters on the topics of modeling & simulation, oral and alternate drug delivery, fixed dose combinations, and general biopharmaceutics. He has more than 20 podium presentations in national & international conferences. Amitava has been involved in cross-organization (industry, academia and regulatory) consortium such as OrBiTo & IQ.

Current Regulatory Requirements to Assess Bioequivalence of FDC Products Worldwide (EU/USA/ Latin America/Japan)

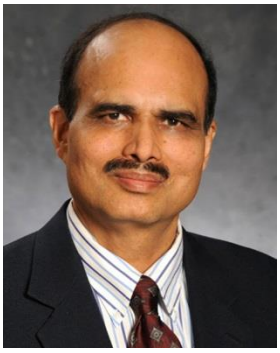
Fixed dose combination (FDC) products represent a great opportunity for formulation development and innovation as they combine at fixed ratios two or more pharmaceutical ingredients in a single dosage form resulting in better patient compliance and therapeutic management. However, their complex nature compared to mono-drug products pose several challenges from a regulatory perspective because safety and efficacy of individual ingredients may change. Therefore, a comparison of regulatory requirements to assess bioequivalence of FDC products under different jurisdictions worldwide seems necessary and it will be presented and discussed.

Alexis Aceituno, Ph.D., Public Health Institute of Chile

Alex R Aceituno, PhD, pharmacist, regulator, Public Health Institute of Chile. Alexis possesses a broad regulatory and academic experience in the biopharmaceutical field, with more than 20 years as academic staff and 10 years in the National Drug Regulatory Agency of Chile. As regulator, he has been heading the implementation process of bioequivalence requirements both for registered and seeking registration products. He has participated in a series of scientific and regulatory initiatives such as the Biofarma Red (Europe and Latin America). In addition, he participated and concluded a program on International Health leadership by PAHO aimed at help implementing bioequivalence requirements for Central American and Caribbean countries. He is currently collaborator for a project directed at studying the correlation between drug permeability and the potential effect of different types of excipients.

Formulation Design, Challenges, and Development Considerations for Fixed Dose Combination (FDC) of Oral Solid Dosage Forms.

Formulations for fixed dose combination (FDC) oral solid dosage forms are very challenging. In a FDC formulation, quantity and qualitative aspects of impurity/degradant profiles of both actives need to be maintained. It is also essential to preserve drug absorption/pharmacokinetics profiles of both actives. Moreover, the size of the dosage form should be appropriate for ease of swallowing. To address some of these challenges, decision trees for formulation design and manufacturing process selection will be presented. Formulation considerations for routinely used formulation techniques for the FDC formulation design such as monolithic system, bi-layer, and active coating will be discussed using relevant case studies.



Divyakant Desai, Ph.D., Bristol-Myers Squibb

Divyakant Desai is a Research Fellow in the Bristol-Myers Squibb Company. He obtained his undergraduate degree in pharmacy (B. Pharm.) from University of Bombay, India and his M.S. in Pharmacy from the University of Rhode Island. After getting his Ph. D. from Rutgers in pharmaceutics, he joined Bristol-Myers Squibb. He has been working in the area of oral dosage form for the last 30 years. He was the lead formulator for nine commercial products. He has more than 45 research articles in peer-reviewed journals and many formulation and technology related patents. He won many prestigious awards at Bristol-Myers Squibb for the formulation design of some key commercial products. He was presented the James Palmer Product Development Award for Onglyza™ tablet formulation in 2009 and the Ondetti and Cushman Innovation Award for developing Abilify Discmelt™ tablet formulation in 2006. He was declared as the winner for the 2012 Edison Patent Award in the pharmaceutical category for the formulation patent of saxagliptin and its fixed dose formulation with metformin for the treatment of type 2 diabetes by the Research and Development Council of New Jersey. He has been elected to Fellowship status in AAPS in 2013.

Current Regulatory Requirements in the USA to Assess Bioequivalence of FDC Products

This presentation will provide an overview of the clinical pharmacology aspects of FDC development. Specific examples of FDC-related regulatory issues will be presented. This will give attendees a flavor of the thinking behind the successful application of the combination rule and bioavailability principles.

Dakshina Chilukuri, Ph.D., U.S. Food and Drug Administration

Dakshina Chilukuri, Ph.D., is a clinical pharmacology reviewer at the FDA. Dr. Chilukuri has been involved with the drug development of anti-infective agents for the past 16 years. At the FDA, he is responsible for the review of clinical pharmacology information submitted in INDs and NDAs. Dr. Chilukuri has written several reviews for various anti-infective agents including several pediatric applications. He has delivered presentations at Advisory Committee meetings and several other scientific and regulatory meetings. He is the project lead of the BA Guidance revision committee responsible for the revision of the BA/BA guidance. His expertise is in the areas of BA studies, biopharmaceutics and anti-infective drug development.

Organizing Committee Biographies

Bart Hens, Pharm.D., Ph.D., University of Leuven

During his dissertation research, Bart Hens (Pharm.D., Ph.D.) focused on the behavior of oral drug products in the gastrointestinal tract in humans (KU Leuven, Belgium). Based on the results of these studies, he started to use the data as a reference for optimization and validation of different in vitro/in silico models to increase their predictive power towards the in vivo outcome of an oral drug product. His Ph.D. project was part of a bigger European project between academic institutions and pharmaceutical companies (www.orbitoproject.eu). Since January 2017, Bart started to work as a postdoctoral research fellow in the laboratory of Prof. Dr. Gordon L. Amidon (University of Michigan), where they both explore the impact of gastrointestinal physiology on oral drug behavior by performing clinical studies with a multidisciplinary team. The gathered knowledge will be used as a reference in order to develop a formulation predictive dissolution test for oral drug products. This work is supported by grant # HHSF223201510157C and grant # HHSF223201310144C by the U.S. Food and Drug Administration (FDA). From 2018 on, Bart will be performing research at KU Leuven as a postdoctoral fellow from the Flemish Government (FWO).

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