OPENING REMARKS

Kendal Weber, Associate Assistant Deputy Minister, Health Products and Food Branch (HPFB), Health Canada

[No abstract]

About Kendal Weber
Kendal Weber was appointed acting Associate Assistant Deputy Minister of the Health Products and Food Branch (HPFB) in May 2017. This is her second leadership opportunity within HPFB. From 2010 to 2015, she played a key role in advancing legislative and regulatory policy and establishing partnerships for international cooperation as the Director General of the Policy, Planning and International Affairs Directorate.
Most recently, Kendal was the Director General of Strategic Pharmaceutical Initiatives in Health Canada’s Strategic Policy Branch. She collaborated with stakeholders to improve affordability, accessibility and appropriate prescribing of prescription drugs.
Prior to joining Health Canada, Kendal worked at the Privy Council Office, the Treasury Board Secretariat and the former Human Resources Development Canada in various policy roles. Kendal holds a Bachelor of Arts from Western University and a Master of Public Administration from Queen’s University.
INTRODUCTION: Therapeutic Equivalence of Complex Molecules and Formulations

Fakhreddin Jamali, Faculty of Pharmacy & Pharmaceutical Sciences, University of Alberta, Edmonton, Alberta, Canada

Abstract
The implementation of therapeutic equivalence policies have provided public affordability of pharmaceutical products without compromising safety and efficacy. In this context, the most widely used approaches are those involving the principles of bioequivalence. The science behind the bioequivalence approach suggests that, once inside the systemic circulation, identical molecules exert identical effects regardless of their manufacturing source. This simple, yet brilliant concept, emerged, first, in Canada in response to the Compulsory Licensing Act of 1969. However, regulatory policies are dynamic in nature, and as such evolve in response to the emergence of modern products or new scientific or therapeutic findings. Consequently, the initial bioequivalence policies which governed straight-forward formulations such as regular-release oral products are constantly updated to address the need for assessing therapeutic equivalence of products that stand outside of the initial guidelines. This workshop addresses just a few examples of the areas that need more attention. There exist, of course, examples that are outside the scope of this workshop, and need to be discussed in the future. The optical products, the extremely variable drugs, the oral medications for local effects, the quick onset products, and formulations that are affected by changes in the gut micro of macro environment (e.g., pH and gastric dysfunction) are a few examples to discuss in future workshops.

About Fakhreddin Jamali
Dr. Jamali (Doctor of Pharmacy, University of Tehran; MSc, pharmaceutics and PhD, pharmacokinetics, University of British Columbia) is a professor at the Faculty of Pharmacy and Pharmaceutical Sciences, University of Alberta. His research interests include effect of pathophysiological changes on the action and disposition of drugs particularly drug-disease interactions involving inflammation, and the link between arthritis and cardiovascular conditions. He has directly trained 40 PhDs and published 230 refereed articles. For his academic achievements and research, he has been appointed as a Fellow of the Canadian Society for Pharmaceutical Sciences, the American Association of Pharmaceutical Sciences, and the American College of Clinical Pharmacology. He has received many awards including the Killam Professorship and McKeen Cattell Memorial Award of the American College of Clinical Pharmacology. He has been honored with the Alberta Centennial Medal and the Alberta Pharmacy Centennial Award of Distinction. Dr. Jamali has served as consultant and/or a member of the board of directors of many pharmaceutical houses. He has been a member of the Health Canada’s Expert Advisory Committee on Bioavailability and Bioequivalence, and the Expert Advisory Panel on Nonsteroidal Anti-inflammatory Drugs, and Alberta formulary committee. He is the founding editor of J. Pharm. & Pharm. Sci, the first open and free access journal in the field.
SESSION 1: BIOSIMILAR MOLECULES

From Generics to Biosimilars: Clinical and Scientific Considerations

Jian Wang, M.D., Ph.D., Division Manager, Clinical Evaluation Division - Haematology/Oncology, Biologics and Genetic Therapies Directorate, HPFB, Health Canada

Abstract
Biosimilars are biotherapeutic products that enter the market subsequent to a previously authorized biotherapeutic to which they have been proven to be highly similar. Unlike small-molecule generic drugs, biosimilars are large, complex protein molecules that cannot be absolutely identical to the original biological product (reference product). For these biosimilar products, similarity should be rigorously proven from physico-chemical and biological perspectives, and should be supported by clinical pharmacology, clinical efficacy, safety and immunogenicity studies. The purpose of the clinical program is to show that residual uncertainty from quality assessment does not cause clinically meaningful differences in efficacy, safety and/or immunogenicity. Health Canada authorized its first biosimilar, a growth hormone, in 2009, and has since authorized other biosimilars to treat autoimmune disease, diabetes and cancers. Even though regulatory expectations for biosimilar development have been increasingly clarified over the last 10 years, there are still areas of uncertainty when it comes to meeting regulatory expectations. The speaker will discuss the general clinical and scientific principles that Health Canada takes to review and authorize biosimilars, and to compare different regulatory and scientific approaches for market authorization of generics and biosimilars.

About Jian Wang
Dr. Jian Wang is the Division Manager of Clinical Evaluation Division – Haematology/Oncology. He manages a team of scientific and clinical evaluators responsible for pre-market risk-benefit assessment. His division has regulatory responsibility for assessing non-clinical, pharmacology and clinical data for biological drugs for the treatment of haematological, oncological, and infectious diseases. At the moment, radiopharmaceuticals, gene therapies and biosimilars (regardless of their indications) are also regulated by the Division. Dr. Wang has broad regulatory experience in pre-market drug regulations for generics, biologics and biosimilars. He joined the Health Canada Pesticide Management Regulatory Agency in 1996. Prior to working at the Biologics and Genetic Therapies Directorate (BGTD), he worked for the Therapeutic Products Directorate (TPD) as an Assessment Officer. He actively participates in various Health Canada, ICH, WHO and DIA working groups and expert committees. He is a member of WHO drafting group for “Guidelines on evaluation of monoclonal antibodies as similar biotherapeutic products” and DIA Biosimilar Conference Program Committee (since 2013).

A ‘Global Reference’ Comparator for Biosimilar Development

Gillian Woollett, Senior Vice President, Avalere Health

Abstract
Major drug regulators have indicated in guidance their flexibility to accept some development data for biosimilars generated with reference product versions licensed outside their own jurisdictions, but most authorities require new bridging studies between these versions and the versions of them licensed locally.
The costs of these studies are not trivial in absolute terms and, due to the multiplier effect of required repetition by each biosimilar sponsor, their collective costs are substantial. Yet versions of biologics licensed in different jurisdictions usually share the same development data, and any manufacturing changes between versions have been justified by a rigorous comparability process. The fact that a biosimilar is usually expected to be licensed in multiple jurisdictions, in each case as similar to the local reference product, confirms that minor analytical differences between versions of reference biologics are typically inconsequential for clinical outcomes and licensing. A greatly simplified basis for selecting a reference comparator, that does not require conducting new bridging studies, is proposed and justified based on the shared data of the reference product versions as well as the proof offered where biosimilars have already been approved. The relevance of this proposal to the interchangeability designation available in the US is discussed.

About Gillian Woollett
Gillian Woollett, Senior Vice President, leads our FDA Practice. She provides the "prequel" of scientific and regulatory strategic policy expertise that supports medicinal products gaining approval at the FDA in a manner that allows them to be successful in the public and private reimbursement world. She is building a bridge for Avalere clients from the FDA space into the traditionally separate Centers for Medicare & Medicaid Services and healthcare policy/business world.

Prior to joining Avalere, Gillian was Chief Scientist at Engel & Novitt, LLP, and was Vice President, Science and Regulatory Affairs, at the Biotechnology Industry Organization (BIO). She joined BIO after being Associate Vice President at the Pharmaceutical Research and Manufacturers of America. She has been an appointee on federal advisory committees to the CDC and the Department of Commerce. Trained as a molecular biologist/immunologist, Gillian publishes in peer-reviewed literature on biotechnology topics and is a frequent speaker on emerging biosciences and their ability to support better and more focused therapies.

Gillian has a DPhil in Immunology from the University of Oxford and an MA and BA in the Natural Sciences Tripos (Biochemistry) from the University of Cambridge.

The Path Forward in Biosimilar Development

Martin Schiestl, Sandoz GmbH

Abstract
Biosimilars represent well-established and safe treatment options for their authorized indications since the first introduction in Canada in 2009. The same holds true for the European Union and the United States where biosimilars are on the market since 2006 (EU) and 2015 (US).

The general concepts in biosimilar regulation are settled but there are still important areas which may greatly affect biosimilar development in the future. As the key concept for development, the comparative analytical studies provide the foundation for determining biosimilarity, which is complemented by confirmatory clinical studies to generate the totality of data required for achieving marketing authorization. The regulatory guidelines in Canada, EU and US are also open to allow dossiers without comparative efficacy trials in certain cases, which opens a path to substantially increase the efficiency in biosimilar development but which require even more robust demonstration of analytical similarity. Consequently the scientific and regulatory debate of analytical similarity gained further attention including its challenges as the ability to analyze all quality attributes which are important or the consideration of the measured variability of quality attributes of the reference biological drugs over time. This variability is important during biosimilar development and for the final evaluation of biosimilarity.
Including recent case studies, the presentation will discuss the challenges above, the contributing elements of the analytical and clinical data for the evaluation of biosimilarity overall, and illustrate a way forward to increase efficiency of biosimilar development.

About Martin Schiestl
Martin Schiestl received his doctoral degree in chemistry with a specialization in bioanalysis from the University of Innsbruck in Austria in 1996. In the same year he started his work on Biosimilar medicines at Sandoz where he built up the analytical and pharmaceutical development departments in charge of the biosimilar pipeline and other biological medicines of Sandoz. He moved into the regulatory and policy field in 2009 and since 2015 he is working as Chief Science Officer for Sandoz Biopharmaceuticals.

In addition to his work at Sandoz, Martin Schiestl has been serving as a member in the expert groups for biological products at the European Pharmacopoeia (2003 - ongoing) and United States Pharmacopoeia (2005-2014). He also joins the ICH process and represented the generic and biosimilar industry in the expert working groups for the ICH Q11 guideline (2007 – 2012) and the ICH Q7 Q&A document (2012 - 2015).

Biosimilars: Opportunities and Challenges for Health Care Professionals and Patients

Scott Edwards, Dr. H. Bliss Murphy Cancer Centre

Abstract
One of the most important advances in modern healthcare has been the development of biologic drugs. Biologic drugs are used to treat many complex diseases and these innovative but expensive medications have improved the quality of life for many patients. Biosimilars have the potential to improve the affordability of some of these expensive biologic medicines. Health care professionals will be faced with numerous challenges associated with biosimilars but there are many opportunities for advancement as well. The practical issues of pharmacovigilance, naming, interchangeability and education needs will be discussed with a focus on the impact of the integration of biosimilars into the Canadian healthcare system.

About Scott Edwards
Scott Edwards is currently the Clinical Oncology Pharmacy Specialist at the Dr. H. Bliss Murphy Cancer Center in St. John’s, Newfoundland. He is also an assistant professor at the School of Pharmacy and the Discipline of Oncology, Faculty of Medicine, Memorial University of Newfoundland. He is active in clinical cancer research in the area of chemotherapy toxicities, supportive care and oral chemotherapy adherence. He graduated from Memorial University of Newfoundland with a B.Sc. (Neuroscience) in 1994 and a B.Sc (Pharmacy) in 1997. In 2005, he graduated with a Doctor of Pharmacy degree from the University of Washington. He completed a Master’s degree in Oncology from Newcastle University in 2015.
SESSION 2: PEPTIDES

Current Thinking on Synthetic Peptides in Abbreviated New Drug Applications

Xiaohui Jiang, Deputy Director of the Division of Therapeutic Performance, Office of Research and Standards, Office of Generic Drugs, FDA

Abstract

Over the years, the US FDA approved a number of peptide drugs in a wide range of therapeutic areas, including metabolic disorders and cancer. Several of the reference listed drug (RLD) products containing longer peptides (30-40 amino acids in length) are produced by recombinant rDNA technology. Over the years, the advances in solid phase peptide synthesis (SPPS) allowed for more efficient and economical synthetic peptide productions. As a result, there is a growing interest from the generic drug industry to submit abbreviated new drug applications (ANDAs) for synthetically produced peptide drug products referencing innovator products of rDNA origin. To address this interest, the Agency has recently published a Draft Guidance for Industry: Submission of Abbreviated New Drug Applications for Certain Highly Purified Synthetic Peptide Drug Products, which applies to five peptide drug products: teriparatide, glucagon, liraglutide, nesiritide and teduglutide. The purpose of this talk is to provide an overview of this guidance, and specifically on the regulatory considerations for pharmaceutical equivalence between the proposed synthetic and the recombinant peptide RLD products.

To reference a drug product of rDNA origin with a synthetic peptide using the 505(j) pathway under FD&C Act, the applicant must demonstrate, among other things, that the synthetic peptide has the same active ingredient and is pharmaceutically equivalent and bioequivalent to the RLD of rDNA origin. Bioequivalence is self-evident when the product is parenteral and contains the same active and inactive ingredients in the same concentration as the RLD. Therefore, the discussion will focus on scientific consideration for establishing pharmaceutical equivalence, which among other things includes active ingredient and impurities. To establish active ingredient sameness, a number of analytical characterization methods may be used to demonstrate sameness in physicochemical properties, as well as primary and secondary structures, oligomers and aggregation states. Biological assays may also be used to as part of the demonstration of API sameness. In terms of peptide-related impurities, due to manufacturing differences, a proposed synthetic peptide may have different impurity profiles when compared to the RLD product. Such difference may have potential safety concerns especially for immunogenicity. With the development of highly efficient purification processes and highly sensitive analytical methods, it is possible to control and monitor the amount of peptide-related impurities in a proposed synthetic peptide product. In addition, as more non-clinical immunogenicity assays become available, the risks of novel peptide impurities can be better assessed. Thus, the impurities in the synthetic peptide drugs can be analyzed and controlled to a level at which the immunogenicity risk is comparable to that of RLD products.

About Xiaohui (Jeff) Jiang

Xiaohui (Jeff) Jiang received his Ph.D. in chemistry from the University of California, San Diego. Currently he is the Deputy Director of the Division of Therapeutic Performance in the Office of Research and Standards, under the Office of Generic Drugs. His work at the FDA is focused on the complex generic products to develop and implement novel scientific approaches in evaluations of active ingredient sameness, pharmaceutical equivalence and bioequivalence. During GDUFA I, he contributed to several complex generic approvals including Glatiramer Acetate injection, Sevelamer and Colesevelam Suspension and Tablets. Prior joining the FDA, Dr. Jiang worked in biopharmaceutical industry and government agencies.
Regulatory Considerations for Complex and Synthetic Peptides – Not Just Another Generic

Karen Hauda, Senior Director Regulatory Policy, Novo Nordisk Inc.

Abstract
As technology advances, regulatory agencies will be reviewing a broader scope of follow-on products referencing original medicines developed with a full complement of clinical data to demonstrate patient safety and efficacy. Biosimilar pathways are now available in many countries and regions. However, the regulatory approval pathways for follow-on products, especially those made synthetically, that reference complex molecules or recombinant peptides are not clear. Is more data is warranted for these complex peptides than for small molecule generics? This presentation will address regulatory and scientific challenges with complex and synthetic peptides, and opine on whether special considerations beyond generic approval pathways need to be taken into consideration by regulatory authorities.

About Karen Hauda
Karen Hauda is the Senior Director for Regulatory Policy in the Clinical Development, Medical and Regulatory Affairs Division at Novo Nordisk Inc. In this role, she supervises regulatory advocacy and policy, and develops strategies to positively influence the regulatory environment in the United States and globally.

Karen previously held roles at Abbott and AbbVie as Senior Director of Biologics Strategic Development, where she supervised biotherapeutic outreach strategies across all functions globally, and as a Senior Director within the Global Government Affairs and Policy division from 2007 to 2013. Prior to joining AbbVie, Karen served with the U.S. government from 1996 - 2007 as a Patent and Trade Attorney.

Karen has additionally worked as an investigator for cancer gene therapy clinical trials at Johns Hopkins University and her research experience also has encompassed the study of the immune responses to parasitic diseases, including malaria, trichinella and schistosomiasis. Karen has several research publications in prominent peer-reviewed scientific journals. She has taught at universities and community colleges in the areas of intellectual property, trade, public health and emergency medical services and currently teaches in the Department of Global Health at George Washington University, in Washington, D.C.

Karen received a B.S. in Biochemistry and Molecular Biology and a M.S. in Veterinary Science with an emphasis in Immunology from the University of Wisconsin-Madison, and received her J.D. from the Columbus School of Law at the Catholic University of America. Karen is a member of the Virginia State Bar and the Patent Bar.

Recombinant and Synthetic Peptide Drugs – A Generic Pathway is There

Klaus Martin, President, Apobiologix

Abstract
Peptides may form only a small subset of approved drugs, but have proven to provide essential benefits to patients across the globe. Products like insulins, GLP-1 analogs and glucagon in diabetes or teriparatide in osteoporosis are providing significant therapeutic benefits, but are still not universally available for cost reasons. This presentation looks at recent scientific advances enabling a generic approval pathway for synthetic versions of peptide drugs.
About Klaus Martin
Klaus Martin joined Apotex as President, Apobiologix in January 2018. He is a member of Apotex’ Executive Management Committee, leading all global development, operational and commercial activities for its biologics business.

Klaus has extensive experience in all stages of biosimilars strategy and development, including the registration and launch strategies of biosimilar products in Europe, North America and Asia.

Previously, Klaus worked at Polpharma Biologics, where he was Chief Scientific Officer overseeing global late stage development and pipeline selection. Klaus simultaneously held the role of Managing Director, Bioceros BV, a division of the Polpharma Group that specializes in preclinical development of biosimilars and new biologics.

Before joining Polpharma, Klaus had global development and strategy roles of increasing responsibility in Biopharmaceuticals at Sandoz headquarters where his teams supported biosimilar registrations in the EU, US, CA and JP.

From 2016-2017, Klaus was also Chair of the Market Access Committee of Medicines for Europe’s Biosimilars Group, coordinating the industry group’s pricing and reimbursement activities in Europe.

Klaus holds an MSc in Biochemistry from Freie Universität Berlin and a PhD in molecular genetics from Cambridge University.
Consideration for Interchangeability of Controlled Release Formulations of Narrow Therapeutic Index Medications

Nasrullah Undre, Senior Director, Basic Science, Astellas Pharma Europe

Abstract
Narrow Therapeutic Index (NTI) medications, categorised Health Canada Critical Dose Drugs (CDD), are defined as those drugs where comparatively small differences in dose or concentration lead to serious therapeutic failures and/or serious adverse drug reactions.
The following are considered to be NTI medications: Cyclosporine, Digoxin, Flecainide, Lithium, Phenytoin, Sirolimus, Tacrolimus, Theophylline, Warfarin.

Bioequivalence (BE) guidelines for the approval alternative formulations of NTI medications vary across the world e.g. in Canada and Europe, guidelines require CDD or NTI medications to meet tighter bioequivalence acceptance limits of 90.00 to 111.11 for AUC whereas other regulatory agencies allow the 80 – 125% acceptance interval standard. However, even when BE has been established, exposure in individual patients may vary outside of acceptance range. Thus, switching between alternative formulations of Warfarin and Dioxin, is accompanied by clinical evaluation of safety and efficacy or monitoring of exposure e.g. for Warfarin dosage is adjusted according to results of the patients PT/INR (prothrombin time/international normalized ratio, a measure of coagulation).

For Calcineurin inhibitors (CNI), Tacrolimus and Cyclosporine, effects of over- or under-dosing are not readily monitored, either biochemically or by acute clinical effects. Thus, therapy is optimised by monitoring systemic exposure these drugs.

Oral bioavailability of CNIs is low and highly variable within and between individuals, owing largely to significant pre-systemic metabolism via gastrointestinal (GI) cytochrome P450 3A (CYP3A) enzymes (mainly CYP3A4 and CYP3A5). High intra-patient variability, (IPV), has been shown to be a significant variable associated with poor long-term outcome in transplant patients.

Modifying the delivery of the active ingredient, to a different part of the GI tract, could potentially decrease the variability IPV of CNI exposure. Modified release formulations of CNIs e.g. Cyclosporine micro-emulsion or extended release tacrolimus have been shown to decrease IPV in repeated dose studies in patients.

Consideration of decrease in IPV is an important pharmacokinetic variable for optimal use of such formulations.

About Nasrullah Undre
Nasrullah Undre is based at Astellas Pharma Europe, London, UK, and has been involved in research and development (Clinical Pharmacokinetics and Pharmacology) with Astellas since 1992. Graduate studies at
the University of Hertfordshire, UK followed by postgraduate studies at the Universities of Manchester and London.

During his early career he joined Guy’s Hospital in London, Department of Clinical Physiology, as research associate; his thesis was based on the study of the effects of anaesthetics on myocardial metabolism. He subsequently joined the pharmaceutical industry (GSK), as a principal scientist working extensively in the field of both pre-clinical and clinical pharmacokinetics and drug metabolism. For over three decades, he has been involved in the development of several medicinal products. Areas of research include immunosuppressive agents, topical immunomodulatory agents, NSAIDs, antihypertensive agents, anti-emetics, antidepressants and anti-infectives.

During his career at Astellas, he has been responsible for the development of Tacrolimus containing formulations (Prograf, Advagraf and Modigraf) for prophylaxis of allograft rejection; Protopic for topical treatment of Atopic Dermatitis as well as Micafungin (an antifungal agent of echinocandin class).

He is author or co-author of more than 100 publications in medical journals in the field of pharmacokinetics and pharmacology.

Clinical Perspective of Drugs with Narrow Therapeutic Window: The Case of Tacrolimus in Kidney Transplantation

S. Joseph Kim, Department of Medicine (Nephrology), University of Toronto; Kidney Transplant Program, Toronto General Hospital, University Health Network

Abstract

Drug level variability has been shown to impact patient outcomes and may be a focus for intervention. Tacrolimus is currently the cornerstone for maintenance immunosuppression in kidney transplant recipients. This presentation will review some of the key studies that have linked tacrolimus drug level variability to patient outcomes and will propose some strategies to use these data to improve the care of kidney transplant recipients.

About S. Joseph Kim

Dr. S. Joseph Kim is a staff nephrologist in the Division of Nephrology and Medical Director of the Kidney Transplant Program at the Toronto General Hospital, University Health Network. He is also an Associate Professor in the Department of Medicine and the Institute of Health Policy, Management and Evaluation at the University of Toronto. He is the Past President of the Canadian Organ Replacement Register Board of Directors, former Vice-Chair of the Data Advisory Committee at the U.S. Organ Procurement and Transplantation Network, Chair of the Information System Advisory Committee at Canadian Blood Services, and the Associate Head of the Kidney, Dialysis and Transplantation program at the Institute for Clinical Evaluative Sciences. Dr. Kim completed medical school, internal medicine residency, chief medical residency, and fellowships in nephrology and kidney transplantation at the University of Toronto. In 2008, he completed a PhD in epidemiology and a Masters in biostatistics at the Johns Hopkins Bloomberg School of Public Health. His research interests are in the areas of access to and outcomes of kidney transplantation using data from both centre- and population-based cohorts. His methodological interests include survival analysis and statistical models for causal inference.
Regulatory Approaches to Demonstrate Equivalence of Orally Inhaled Drug Products

Paul A. Wielowieyski, Senior Drug Evaluator, Division of Biopharmaceutics Evaluation, Therapeutic Products Directorate, Health Canada

Abstract
Currently, there is no consensus among regulatory agencies on the equivalence approaches with regards to the approval of subsequent market entry orally inhaled products (OIPs). The European Medicines Agency (EMA) currently approves OIPs based on a “step-wise” approach to establish therapeutic equivalence between the test and reference products, such that the demonstration of therapeutic equivalence via step 1 (in vitro tests), failing that via step 2 (pharmacokinetic (PK) safety studies plus PK pulmonary deposition or lung imaging studies) and failing that via pharmacodynamic (PD) or clinical studies. Several OIPs (including ICS, LABA, LAMA and combinations thereof) have been approved based on a “step-wise” approach.

The US FDA’s bioequivalence recommendations for generic locally acting OIPs are based on the aggregated weight-of-evidence approach, which incorporates in vitro studies, pharmacokinetic studies, and pharmacodynamic (or clinical efficacy) studies. During the last five years since the authorization of the Generic Drug User Fee Amendments (GDUFA) in 2012, the US-FDA has developed several product-specific guidance document for complex orally inhaled drug products and provided a roadmap towards ANDA approval. In the next five years one overarching goal for OIDPs “will be to build on the research of the first five years of GDUFA to create clear pathways to establish BE, without the need for comparative clinical endpoint studies.”

Health Canada’s approach for evaluating BE for OIPs is based on the aggregated weight-of-evidence approach which utilizes appropriate in vitro studies, pharmacokinetic studies, and pharmacodynamics (clinical endpoint) studies to demonstrate equivalence of OIPs to the CRP. The aggregated weight-of-evidence approach is similar to that taken by the US Food and Drug Administration (FDA) and differs from the step-wise approach taken by the European Medicines Agency (EMA) with regard to Step 2 (use of pulmonary bioavailability studies as pivotal indicator of comparative efficacy).

The presentation will discuss the regulatory approaches to demonstrate equivalence of OIPs.

About Paul A. Wielowieyski
Paul A. Wielowieyski is a senior drug evaluator in the Division of Biopharmaceutics Evaluation. His division has regulatory responsibility for assessing comparative bioavailability studies provided in support of generic products, line extensions of innovator products, bridging studies of formulations used in early clinical development through commercialization and post-approval changes. He joined the Health Canada in 1999. He actively participates in Health Canada and ICH working groups. He is a Health Canada’s representative on the ICH M9 expert working group.
Health Canada’s Regulatory Approaches to Demonstrating Equivalence of Orally Inhaled Products (OIPs) – The Clinical Perspective

Violina Thomas, Assessment Officer, Therapeutics Products Directorate, Health Canada

Abstract
Subsequent Market Entry orally inhaled products (OIPs) in Canada can be submitted as an Abbreviated New Drug Submission (ANDS), or as a New Drug Submission (NDS).

At this point in time, if an OIP product is submitted as an ANDS Health Canada will evaluate bioequivalence (BE) of the product compared to the Canadian reference product (CRP) based on the aggregated weight-of-evidence. The following requirements need to be fulfilled:

- Both products need to be qualitatively and quantitatively (Q&Q) similar
- Both products must have similar in vitro characteristics
- Both products must have equivalent systemic exposure, as demonstrated through PK studies
- Both products must be equivalent as shown in a clinical end-point study
- “Sameness” of device

This presentation will outline the regulatory advice provided to potential Sponsors with regards to specific requirements for the clinical end-point studies to demonstrate equivalence of OIPs. More specifically, the current requirements for inhaled corticosteroids (ICS) and long-acting bronchodilators will be discussed.

About Violina Thomas
Dr. Violina Thomas is an assessment officer with the Therapeutic Products Directorate at Health Canada. She has over 11 years of experience as a clinical reviewer in the Allergy and Respiratory Drugs Division. Through the years, Dr. Thomas has provided regulatory advice to potential sponsors of ANDS submissions for OIPs with regards to the design and conduct of clinical end-point trials for short-acting beta agonists, inhaled corticosteroids, long-acting bronchodilators, and combinations thereof.

Dr. Violina Thomas is an international medical graduate who obtained her medical degree from the Medical University of Varna, Bulgaria and subsequently completed postgraduate training, including a fellowship in medical and clinical pharmacology. Dr. Thomas completed her PhD at the University of Kuopio (currently part of the University of East Finland), in Finland and continued with her post-doctoral research at Université de Montréal, Neuroscience Research Unit, Hôpital Saint-Luc, Montréal, Canada.

Clinical Development of Generic Versions of Inhaled Long Acting Bronchodilators

Richard Allan, Senior Director, Senior Clinical Scientist, Mylan Global Respiratory Group, Mylan Pharma UK

Abstract
The clinical development of generic orally inhaled products (OIPs) is challenging:

- OIPs exert their effect directly in the lung so unlike oral products the systemic exposure does not drive efficacy.
- Direct measurement of a drug at the site of action is not feasible.
- Variability of products within the approved specification can lead to PK bioequivalence not being achieved even for Reference vs., Reference.
- Regional guidance (EU, US, Canada) differ with regards to requirements for clinical development, leading to additional or different work required for each regional submission.
- Therapeutic equivalence may require large patient based studies with clinical endpoints as well as PK bioequivalence.
The presentation will discuss these points and highlight the current requirements for the clinical development of a generic OIP for Canada.

**About Richard Allan**
Richard Allan is a graduate of The University of Birmingham in UK with almost 20 years Clinical Development experience spanning a range of different therapeutic areas. He began his career at Pfizer, focusing on early Clinical Development, including extensive Translational Medicine activities as well as leading Clinical Projects into Phase 2. He has developed a wealth of experience of developing drugs in the allergy and respiratory area. He joined Mylan in 2011 as one of the founding members of a specialist group formed to develop respiratory products at the company. Whilst at Mylan he has developed both novel orally inhaled products as well as generic orally inhaled products.

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**Weight of Evidence Approach (in vitro, PK, PD & Human Factor Studies) for Establishing Therapeutic Equivalence of Orally Inhaled Drug Products in Patients**

**Ashish Sharma, Executive Director, Clinical PK/PD group, Translational Medicine & Clinical Pharmacology, Boehringer Ingelheim Pharmaceuticals, Inc.**

**Abstract**
Numerous factors (drug, formulation, device and disease) can influence the delivery, efficacy and safety of orally inhaled drug products. Establishing therapeutic equivalence of these products can be a tricky task. In the presentation, the author presents his arguments on why the weight of evidence approach is the most robust for adequately establishing the therapeutic equivalence of an orally inhaled drug product and ensuring efficacy and safety in patients.

**About Ashish Sharma**
Ashish Sharma is a Pharmacist by training (registered pharmacist in Manitoba). He holds a Masters degree in Pharmaceutics from Memorial University of Newfoundland (1999) and a PhD in Clinical Pharmacology from University Laval (2003). He has worked in clinical pharmacology over the past 14 years with the last 12 years at Boehringer Ingelheim Pharmaceuticals. He currently heads the Clinical Pharmacokinetics/Pharmacodynamics group at Boehringer Ingelheim Inc. in Ridgefield, Connecticut.
Health Canada Perspective

Bruce Randall, Director, Bureau of Pharmaceutical Sciences, TPD, Health Canada

[Abstract and Bios not currently available]

Need for Bioequivalence Standards that Reflect the Clinical Importance of the Complex Pharmacokinetics (PK) of Paliperidone Palmitate Long-acting Injectable Suspension (Paliperidone Palmitate LAI)

Stephen Sherman, Director, Risk Management, Janssen Inc.

Abstract

Paliperidone palmitate LAI dissolves slowly after intramuscular (IM) injection before being hydrolyzed to paliperidone and absorbed into the systemic circulation. The resulting PK profile is biphasic, comprised of an initial relatively fast zero-order input, which allows rapid attainment of therapeutic concentrations without oral supplementation; and a subsequent slower first-order input, which is sufficiently sustained to allow once monthly administration.

Changes to the manufacturing process can substantially alter the release characteristics of paliperidone palmitate LAI and consequently its PK profile. As an example, larger or smaller particle sizes can result in delayed or accelerated release of paliperidone, respectively. Such changes are clinically relevant, as even transient excursions above therapeutic blood levels can be associated with adverse effects, including tachycardia, hypotension, QT prolongation, and extrapyramidal symptoms (EPS). Conversely, even a short delay in attaining therapeutic levels of paliperidone on initiation of treatment, or a return to trough levels before the end of a dosing interval during repeated dosing, increases the risk of relapse and return of symptoms schizophrenia.

Given the integral relationship of the PK profile to the product’s clinical effects, it is important to have bioequivalence standards that reflect the complexity of the paliperidone palmitate LAI PK profile. Although both the US FDA and EMA have product-specific guidelines, their requirements differ substantially. In Canada, no product-specific guidance exists for LAIs, and the recently revised Comparative Bioavailability Standards guidance applies only to oral and non-injectable formulations. In the absence of international consensus on bioequivalence requirements for paliperidone palmitate LAIs, the current presentation reviews the PK properties in the context of FDA and EMA requirements, and proposes possible bioequivalence standards that could be adopted in Canada.

About Stephen Sherman

Dr. Stephen Sherman is Director of Regulatory Risk Management at Janssen Inc. Canada, with responsibility for overseeing the preparation of Risk Management Plans and risk mitigation strategies across all therapeutic areas. He has 20 years of pharmaceutical experience, working with several companies in a variety of roles in Regulatory Affairs. His educational background includes an M.Sc. in Pharmacology, a Ph.D. in Neuroscience, an M.B.A. in Marketing and post-doctoral experience in Neurophysiology. Dr. Sherman has diverse research experience including work on mechanisms of chronic pain and allodynia, spinal analgesia, diabetes, ADHD, and schizophrenia.
Long Acting Injectables: Generic Development Complexity and Regulatory Landscape

Mihir Shanbhag, Director, Co-Development, Apotex Inc.

Abstract
Generic development of high barrier to entry products requires significant investment in terms of time and capital due to the high complexity of the formulation, manufacturing process, and bioequivalence criteria. These development complexities will be outlined for specific types of long acting injectables and their niche manufacturing process will be discussed in order to elucidate the truly complex nature of these products. In addition to the development intricacies, the regulatory landscape is quite unclear for complex products in Canada. Significant differences in regulatory guidance in different markets adds to the difficulty of bringing complex generic drugs to market. Therefore, development approaches will be proposed with a focus on convergence of regulatory agency requirements in order to provide customers with faster access to these medications.

About Mihir Shanbhag
As Senior Director, Co-Development, Global R&D, Mihir is responsible for leading the R&D function focused on delivering high barrier complex products for global markets. His primary focus is on developing and commercializing complex injectables, opthalmics and inhalation products. Mihir joined Apotex in June of 2016, bringing with him 10+ years of rich and varied R&D experience with a focus on complex product development. Prior to Apotex, he has held positions of increasing responsibility at Mylan, Sandoz and Actavis. He holds a Bachelors of Science in Biological Engineering from Cornell University, a Doctorate in Biomedical Engineering from Drexel University, as well as a Master of Business Administration (MBA) from Rutgers University.

Bioequivalence and Interchangeability for Modified-Release Formulations with Multiphasic Concentration Profiles

Laszlo Endrenyi, PhD, DSc, Professor Emeritus, University of Toronto

Abstract
The most usual regulatory expectation for the determination of bioequivalence (BE) is that the 90% confidence interval around the ratio of geometric means of primary parameters (AUC and Cmax) of two drug products should be between 0.80 and 1.25. However, the approach does not always indicate the therapeutic equivalence of the formulations. For example, with some modified-release (MR) formulations having complicated concentration profiles, it is not sufficient to satisfy the BE expectations only for the primary parameters. FDA and EMA recommended BE requirements for an additional parameter, the partial AUC (pAUC). However, it is not clear how the cut-off time limiting pAUC should be set. FDA expects clearly defined time-points whereas EMA suggests that the cut-offs be evaluated on a case-by-case basis. FDA established science-based cut-offs, for instance, for MR zolpidem and methylphenidate (MPH). The latter were more recently empirically tightened. Generic MR-MPH formulations have very differing concentration profiles each of which is bioequivalent with that of the reference product. Consequently, the case-by-case approach of regulation may have merit. Furthermore, interchangeability among the diverse generic products could be questioned.
About Laszlo Endrenyi

Laszlo Endrenyi is Professor Emeritus of pharmacology and biostatistics in the University of Toronto. He has served the university in various positions including on its Governing Council and as Associate Dean of Graduate Studies. He sat on the Board of Directors of the American Statistical Association and the Canadian Society for Pharmaceutical Scientists; he was a president of the latter. Externally, he has served on grant review committees and editorial boards of research journals including the Amer. J. Physiol, J. Pharmacokin. Pharmacodynam., J. Pharm. Pharmac. Sci., Biosimilar, and J. Pharm. Sci. He has received several recognitions, including an honorary doctorate from the Semmelweis University of Medicine. He is a Fellow of the Canadian Society for Pharmaceutical Sciences and of the American Association of Pharmaceutical Scientists and received the Lifetime Achievement Award of the latter.

Dr. Endrenyi published books on Kinetic Data Analysis and on Biosimilar Drug Product Development, and over 200 research papers. Several of these established principles for the design and analysis of enzyme and pharmacokinetic investigations. They included principles and applications of optimal study designs. More recently, he extensively developed principles and applications for the evaluation of bioavailability, bioequivalence and biosimilarity. He developed various sensitive measures characterizing the rate of drug absorption. He extensively investigated issues of drug interchangeability.

Dr. Endrenyi's studies were instrumental in the adoption of some regulations and the withdrawals of others. He has consulted with the Food and Drug Administration and Health Canada and served on their advisory committees. He has consulted also with industry in the areas of pharmacokinetics, biostatistics, the design and evaluation of experiments, clinical trials, and the analysis of bioavailability, bioequivalence and biosimilarity studies.
CONCLUDING REMARKS

Patrick Stewart, Director General, Therapeutic Products Directorate, Health Canada
[No abstract]

About Patrick Stewart
Dr. J. Patrick Stewart is the Director General of the Therapeutic Products Directorate in the Health Products and Food Branch (HPFB) of Health Canada. He is responsible for overseeing the review and for the approval of drug and medical devices submissions seeking authorization to be sold on the Canadian market or in the context of clinical trials. He is also responsible for managing the strategic vision, focus and priorities of the directorate and ensuring they align with those of the branch, department, and federal government.

Prior to this role Dr. Stewart was the Director General of the Marketed Health Products Directorate in the HPFB for 2.5 years where he was responsible for the oversight of the vigilance of marketed health products in Canada including ensuring that Canadians and health professionals are informed of important issues impacting the safety and effectiveness of health products in a timely manner.

Dr. Stewart holds a Bachelor and Master of Science Degree as well as a Medical Doctor Degree from McMaster University. His residency training includes Canadian College of Family Physicians Certification and CCFP Emergency Medicine certification. Over the course of his career, he worked for over 20 years as full-time emergency physician both in a tertiary care teaching hospital as well as an Urgent Care Clinic. In a former role as an Assistant Professor with the Faculty of Medicine at the University of Ottawa, he was responsible for coordination undergraduate medical student education in the Emergency Departments in Ottawa and was actively involved in the Ottawa Civic Hospital Emergency Department’s research program.

Dr. Stewart joined Health Canada in August of 2005 and since then has filled several roles in the Therapeutic Products Directorate including directing the Office of Clinical Trials for five years and filling the role of Executive Medical Director for TPD for 3 years.