Keynote Forum

May 14, 2018

Biopharmaceutics 2018

Global Summit on

BIOPHARMA & BIOTHERAPEUTICS

May 14-15, 2018 | Montreal, Canada

David P Elder

GlaxoSmithKline, UK

ICH M9 Biopharmaceutics Classification System-based Biowaivers: Challenges and opportunities

The International Conference on Harmonization (ICH) M9: Biopharmaceutics Classification System-Based Biowaivers was recently adopted. A biowaiver allows for *in vitro* testing to be used in lieu of *in vivo* bioavailability and/or bioequivalence studies to facilitate product approval, where solubility and permeability are not expected to impede bioavailability. ICH M9 should minimize unnecessary *in vivo* studies in man and allow greater public access to medicines. However, this approach is not always universally aligned or recognized. The biggest area of concern is whether solubility should be based on the highest therapeutic dose or on the highest strength of the medicinal product. Different approaches to assessing permeability, i.e. *in vitro* or *in vivo* assessments, will also require harmonization. Thus, far biowaivers have been restricted to pharmaceutical equivalents and primarily to BCS class I compounds. There has been widespread concern regarding the effect of different excipients on the permeability of the drug substance and thereby the bioavailability of different formulations. For example, FDA guidance states, "Unlike for BCS class 1 products, for a biowaiver to be scientifically justified, BCS class 3 test drug product must contain the same excipients as the reference product. This is due to the concern that excipients can have a greater impact on absorption of low permeability drugs." Whilst, it is certainly true that "certain excipients, such as surfactants (e.g., polysorbate 80) and sweeteners (e.g., mannitol or sorbitol) may be problematic", it is by no means true that all excipients can adversely influence absorption. Consequently, ICH M9 faces significant challenges and a target date of 2Q 2019 for step 4 implementation may be difficult to achieve.

Speaker Biography

David P Elder has nearly 40 years of service within the pharmaceutical industry (Sterling, Syntex and for the last two decades with GSK). He is now an independent CMC Consultant and has broad based experience in excipients, biopharmaceutics, drug product and analytical method development. He obtained his PhD in crystallography from the University of Edinburgh. He is a visiting Professor at King's College, London. He is a member of the British Pharmacopoeia. He is the immediate past Chairman of JPAG (Joint Pharmaceutical Analysis Group). He is a member of the Editorial Advisory Board for the *Journal of Pharmaceutical Sciences*. He has published 114 and presented 17 webinars and 133 presentations. He has Co-edited one book on the analytical characterization and separation of oligonucleotides and their impurities (with George Okafo and Mike Webb) and is editing a second book on the ICH quality guidelines (with Andy Teasdale, AZ).

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Michael W Retsky

University College London, UK

Perioperative use of NSAID might prevent early relapses in breast and other cancers

A bimodal pattern of hazard of relapse among early stage breast cancer patients has been identified in multiple databases from US, Europe and Asia. My colleagues and I have been studying these data to determine if this can lead to new ideas on how to prevent relapse in breast cancer. Using computer simulation and access to a very high-quality database from Milan for patients treated with mastectomy only, we proposed that relapses within three years of surgery are stimulated somehow by the surgical procedure. Most relapses in breast cancer are in this early category. Retrospective data from a Brussels anesthesiology group suggests a plausible mechanism. Use of ketorolac, a common NSAID analgesic used in surgery was associated with far superior disease-free survival in the first five years after surgery. The expected prominent early relapse events in months 9-18 are reduced five-fold. Transient systemic inflammation accompanying surgery (identified by IL-6 in serum) could facilitate angiogenesis of dormant micrometastases, proliferation of dormant single cells, and seeding of circulating cancer stem cells resulting in early relapse and could have been effectively blocked by the perioperative anti-inflammatory agent. If this observation holds up to further scrutiny, it could mean that the simple use of this safe, inexpensive and effective anti-inflammatory agent at surgery might eliminate early relapses. We suggest this would be most effective for triple negative breast cancer and be especially valuable in low and middle income countries. Similar bimodal patterns have been identified in other cancers suggesting a general effect. Even if this project works as well as possible, it will not solve the breast cancer problem. We think it will reduce relapse and mortality by 25 to 50% at low cost and toxicity but there will still be a need for treatments to prevent death from metastatic disease. We encourage the excellent work underway to use immunotherapy to curtail tumor growth after relapse..

Speaker Biography

Michael W Retsky has completed his PhD in Physics from University of Chicago and made a career change to cancer research 30 years ago. He was on Judah Folkman's Staff at Harvard Medical School for 12 years. He is Editor and Romano Demicheli is Co-Editor of a Springer/Nature book on breast cancer published in July 2017. He is the Founder and on the Board of Directors of the Colon Cancer Alliance and has published more than 60 papers in physics and Cancer.

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Karen Mulkijanyan

Tbilisi State Medical University, Georgia

Comfrey based remedies: Past, present and future

History of Comfrey *(Symphytum L.)* remedies clearly illustrates that despite plant extracts are still among most attractive sources for drug development as they are considered relatively safe for use in humans, many of their chemical constituents represent serious risks to the human health and it is important to justify biological effects that the vegetal products obtained from medicinal plants can present. For ages, folk remedies on the basis of extracts of various comfrey species were used both internally and externally to treat different disorders, but nowadays internal usage is banned due to the presence of hepatotoxic and carcinogenic pyrrolizidine alcaloids (PAs) - symphytine, echimidine and lasiocarpine. When determining principal constituents responsible for diverse curative properties of comfrey, a novel biopolymer poly[3-(3.4-dihydroxyphenyl) glyceric acid] (PDGA) was isolated from PAs- and allantoin-free high molecular fractions from *S. asperum, S. caucasicum* and its monomer 3-(3,4-dihydroxyphenyl) glyceric acid (MDGA) was synthesized at I Kutateladze Institute of Pharmacochemistry. Pharmacological properties of PDGA and MDGA were studied both *in vitro* and *in vivo* experiments. The obtained results revealed: *in vitro* i) abrogation of melanoma cells adhesion to tumor-conditioned medium- and VEGF-activated endothelial cells as well as ii) strong inhibition of human prostate cancer (PCA) cells growth. Consistent with *in vitro* results, *in vivo* study showed iii) efficacy against PCA 22Rv1 tumors; iv) anti-inflammatory activity in formalin- and carrageenan induced edemas; v) rapid burn and wound healing (fourfold superior to that of allantoin – substance claimed to be comfrey's most active ingredient) due to the shortening of the second phase of wound healing - the inflammatory response; vi) significant stimulation of leucopoiesis in mice drug-induced leukopenia; vii) promising results in prevention of ethanol- and NSAID-induced gastric ulcers. Importantly, all observed effects were accompanied with no or minor side effects, suggesting high therapeutic potential of novel API from comfrey.

Speaker Biography

Karen Mulkijanyan is the Head of the Department of Preclinical Pharmacological Research at Tbilisi State Medical University Institute of Pharmacochemistry. He has obtained his MS in Biochemistry in 1981 and PhD in Pharmacy in 2005. His research areas include pharmacology of anti-inflammatory, ulcer preventing, wound healing and vasoactive drugs; analysis of SAR and prediction of bioactivity of natural, modified and synthesized compounds. He is also an expert in IP protection and technology commercialization. He was the Manager/Key Investigator of fundamental and applied research projects funded by CRDF Global/GRDF (2007-2014), STCU (2011), GNSF/SRSNF (2009-2016). As Organizing Committee Member, he arranged about 10 international congresses and conferences on Pharmacology and Pharmacy. He is the author and co-author of more than 100 papers in peer-reviewed journals, about 40 presentations at national and international scientific meetings

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Jay Babu Ramapuram

Auburn University, USA

Ceramides based liposomes for melanoma treatment

Ceramides are composed of a sphingoid base attached to a fatty acid via an amide bond. These lipids serve both a structural role in membranes and an intracellular signaling role within a cell. Ceramide is a natural molecule that targets discrete kinases and signaling pathways linked to proliferation and/or survival. Due to its potent regulation of cell growth, differentiation, and death, ceramide has been identified as a putative therapeutic agent in cancer and cardiovascular disease. The use of ceramide to inhibit Akt signaling is a novel approach under preclinical evaluation. Ceramide targets the PI3K/Akt pathway through dephosphorylation of Akt, leading to increased cytotoxicity and cell apoptosis when in combination with another chemotherapeutics, can enhance cell death. An obstacle that has limited clinical use of ceramide is its hydrophobicity, which can be overcome by packaging it into a nanoliposomal formulation for systemic delivery. Hydrophilic drugs can be entrapped in the aqueous compartment, while the lipid bilayer can be utilized to incorporate hydrophobic drugs. Associating a drug with liposome markedly changes its pharmacokinetic properties and lowers systemic toxicity; furthermore, the drug is prevented form early degradation and/or inactivation in circulation. This presentation discusses the role of ceramides in the formulation of liposomes for the delivery of model anti-cancer drugs such as doxorubicin and daunorubicin. The synergistic function of ceramide based liposomal formulations in melanoma, breast and prostate cancers will be discussed

Speaker Biography

Jay Babu Ramapuram has completed his PhD from Indian Institute of Technology, Varanasi, India. He is the Professor in the Dept. of Drug Discovery and Development at Auburn University, USA. He has over 80 publications that have been cited over 1300 times, and his publication H-index is 21 and has been serving as an Editorial Board Member of reputed Journals in his research area.

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Teruo Murakami

Hiroshima International University, Japan

Modulation of absorption sites and bio-availabilities of orally administered drugs depending on the solubility *in vivo*

In pharmacotherapy, most drugs are taken orally to be absorbed systemically from the small intestine, and some drugs are known to have preferential absorption sites in the small intestine. For example, many substrate drugs for P-glycoprotein (P-gp) are absorbed mostly in the proximal intestine, because of the lower P-gp expression and higher luminal drug concentrations. High luminal concentration of dissolved P-gp substrate drugs can saturate P-gp-mediated efflux transports. In contrast, the fraction of unabsorbed P-gp substrate drugs in the proximal intestine can cause P-gp-mediated drug interactions in the middle and distal small intestine, where P-gp is abundantly expressed. Most of P-gp substrate drugs are categorized as BCS Class 1 and 2 compounds, and BCS Class 2 compounds are low solubility and high permeability. By increasing the solubility of such BCS Class 2 drugs, especially the solubility in the stomach, the absorption rate and bioavailability of P-gp substrate drugs are improved. In the presentation, I introduce the absorption sites of orally administered drugs, as well as, influencing factors and experimental techniques, according to the reported data collected by PubMed. Also, I will show some examples regarding the effect of solubilization on absorption site and bioavailability of orally administered P-gp substrate drugs. Securing the solubility and stability of drugs prior to reaching to the main absorption sites and appropriate delivery rates of drugs at absorption sites are important goals for the development of effective pharmacological products for pharmacotherapy

Speaker Biography

Teruo Murakami has completed his graduation from Osaka University of Pharmaceutical Sciences and his PhD from Graduated School of Pharmaceutical Sciences, Osaka University, Japan. He has worked for Institute of Pharmaceutical Sciences and Graduate School of Biomedical Sciences, Hiroshima University for 25 years, and he is now the Professor of Hiroshima International University, Japan. His research interests are tissue distribution of weakly basic drugs, and intestinal absorption including intestinal ABC and SLC transporters. He has over 160 publications that have been cited over 3200 times, and his publication H-index is 30 and has been serving as an Editorial Board Member of four international journals

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David P Elder

GlaxoSmithKline, United Kingdom

Stability, storage and cold chain supply of biologics

The presentation will look at a comparison of biologicals vs. small molecules, highlighting some of the key challenges inherent with biological molecules. Before looking at the main degradation pathways for therapeutic proteins (taken as an exemplar of complex biological molecules) and reviewing the stability challenges facing biological development organizations. The presentation will then focus on the "Cold Chain" challenge, highlighting that over half of the top 50 biological drugs in the world require cold chain, i.e. refrigerated storage and distribution due to stability concerns. Cold chain storage and transportation, and some of the challenges and regulatory considerations will then be reviewed, focusing on global good distribution practice (GDP) requirements before providing concluding remarks to complete the presentation.

Speaker Biography

Dr. Elder has 40 years of service within the pharmaceutical industry, with Sterling, Syntex and for the last 23 years with GSK. He is now an independent CMC consultant with broad based experience in formulation and analytical method development. Dr. Elder obtained his PhD in crystallography from the University of Edinburgh. Dr. Elder is a visiting professor at King's College, London. He is a Fellow of the RSC and chartered chemist and scientist. He is a member of the British Pharmacopoeia. He is the immediate past chairman of JPAG (Joint Pharmaceutical Analysis Group). He is a member of the Editorial Advisory Board for the Journal of Pharmaceutical Sciences. He has published over 131 papers in international journals and has given 17 webinars and over 138 presentations at international symposia. He has co-edited a book on the Analytical Characterization and Separation of Oligonucleotides and their Impurities and on ICH Quality Guidelines.

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