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Highlights from the 2018 Pharm Sci AAPS Annual Meeting in Washington DC

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The American Association of Pharmaceutical Scientists (AAPS) held its Annual Meeting and Exposition at the Convention Center in Washington DC, November 4–7, 2018. Pre-conference workshops and short courses took place November 3–4, 2018. The meeting is a premier gathering of pharmaceutical scientists from around the world.

Pre-Conference Workshop on "Development of Fixed Dose Combination Products: Considerations of Gastrointestinal Physiology and Overall Development Strategy"

Bart Hens (University of Leuwen, Belgium) and **Alexis Aceituno** (Institut de Salud Publica de Chile) organized this workshop, which took place on November 3 and 4 , 2018. A path was paved from mostly academic research on the interaction of drugs and the human gastrointestinal (GI) physiology, with its pronounced inter- and intra-individual variability to regulatory concerns of providing guidance to ascertain intra-lot homogeneity, lot-to-lot-consistency, or bioequivalence (BE) of drug products. Whereas for products containing one defined drug substance the prediction of the in vivo performance may be challenging, the degree of complexity is higher in the case of fixed-dose combination products (FDCPs) containing two or more drug substances. ade.

Basic research

The GI tract's complex nature poses a great challenge for drug product formulators. The proximal part, the stomach, has great influence on the dissolution of drug products. Maura Corsetti (University of Nottingham, UK) and Bart Hens (University of Leuwen, Belgium) discussed the motility, volume, and emptying pattern of the stomach, with the pronounced differences between fasted and postprandial states. They also described a distinctive influence of the water used for intake, sparkling versus still, on the in vivo performance of the acetaminophen product under investigation. The pH level inside the stomach was found to be about 2–3 in the fasted state and 4–5 in the fed state. Under the influence of bile and pancreatic juices, the duodenal pH values range from 4 to 5 in the fasted state and around 6 in the fed state. For the jejunum, the pH level increase due to food intake was less pronounced (pH around 6). The buffer capacity of the physiological fluids is far below the buffer capacity of compendial buffer solutions. Duodenal fluids are composed from bile acids, cholesterol, lipids and phospholipids. In the fasted state mixed micelles prevail, whereas in the fed state lipid droplets are accompanied by multi-lamellar vesicles. Concerning the distal part of the GI tract, other factors need to be considered besides volume, composition, dissolution, and absorption. Dr. Corsetti presented some of her research performed with magnetic resonance imaging (MRI). Mainly diffusion of dissolved drug molecules throughout the thickened and dry chime was observed. Raimar Loebenberg (University of Alberta, Canada), noted that currently there is no universal medium available that can be used to predict every drug substance's solubility or a drug product's in vivo dissolution behavior. He was indirectly addressing the question of clinical relevance, considering the relation of drug release rates to the rate of metabolism via enterocytes. He suggested to set clinically relevant product specifications based on the entire drug absorption and disposition processes governing the bioavailability. Afterwards, Marival Bermejo (University of Elche-Alicante, Spain) presented results generated with the gastrointestinal simulator (GIS) device. The GIS may be described as the extended version of Kostewitz' artificial stomach duodenal device (ASD) (transfer model), and it allows the study of disintegrating dosage forms. Gastric emptying in the fasted state is simulated based on first-order kinetics, and supersaturation phenomena are included. Bermejo stated that the GIS is helpful also for predicting FDCPs' absorption. For the assessment of the formulation performance, several dissolution methods as well as preclinical methods are needed. Formulation changes may affect drug substances differently, and

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hence, risk analysis should include all actives.

The application of the Biopharmaceutical Classification System (BCS) to grant biowaivers for selected FDCP was described by Pablo González (Pontificia Universidad Católica de Chile). In general, BCS-based biowaivers are applicable for BCS class I and III drugs. The prerequisites are that drug substances are not categorized as narrow therapeutic index drugs nor have a critical dose but exhibit linear pharmacokinetics. The BCS-based biowaivers are limited to immediate-release dosage forms with an in vitro dissolution performance similar to the listed reference drug. Dissolution tests must be performed in a comparable way to the latest guidance issued by the United States Food and Drug Administration (FDA).

Industrial applications

Amanita Micra (Sandoz, USA) recommended to analyze the variability of the compounds in order to plan the clinical study design adequately, such as by crossover replicate or multiple doses in steady state. Formulation variables in addition to pharmacokinetic (PK) variables could complicate the BE study design. The results of several dissolution methods should be used to establish relationships with in vivo data. In case of a steep pH solubility curve, the rate of absorption may still be faster than the rate of precipitation in the small intestine. **Divyakant Desai** (Bristol-Myers Squibb [BMS], USA) discussed the BMS strategy in developing FDCPs. The integral part is a decision tree as a useful approach to explore the most suitable formulation and manufacturing process for a fixed-dose combination formulation. Each formulation approach for an FDCP will have its own unique challenges. It is possible to overcome these challenges to develop a rugged formulation and manufacturing process.

Regulatory concerns

Alexis Aceituno summarized his thoughts as a member of a regulatory agency as follows. An equilibrium should be reached between an overcautious registration approach and the potential large public health benefits that would arise from affordable FDCPs of proven efficacy. For FDCPs comprising drugs that are already authorized, efficacy and safety can be obtained from existing large-scale clinical trials. Demonstration of pharmacodynamics and PK efficacy using surrogate markers should be sufficient to not requiring hard endpoints that can be excessively expensive and ethically challenging. Hybrid/generic submission as a regulatory pathway strategy is reasonable for most FDCPs. Attention should be paid to facilitating development of new FDCPs to strengthen product pipelines of generic versions. Recommendations for achieving greater harmonization in the interpretation and application of technical guidelines and requirements for FDCP development and registration are still pending.

Dakshina M. Chilukuri (CDER/FDA, USA) presented his view on clinical pharmacology aspects of FDCP development. In this workshop, the most influential aspects of the GI physiology on the absorption of drugs and current techniques used to understand the fate of orally ingested complex drug products were covered, and international guidelines for FDCPs were presented.

Symposium on "Flexibility in Pharmaceutical Manufacturing - The Path to Achieving Six Sigma"

The symposium organized by **Raymond Skwierczynski** (Skwierczynski Consulting, USA) and **Vishal Nashine** (Celgene, USA) and moderated by Dorys Argelia Diaz and **Arya Jayatilaka**, both of whom are from Pfizer, Inc. (USA) was held on November 7, 2018 (Figure 1). This symposium was part of the "Approaches to Master CMC of the Future – Chemical" theme and discussed the importance of using data-driven changes to allow flexibility in pharmaceutical manufacturing and formulations, improve the quality of product by solving and preventing issues, and streamline regulatory oversight. The Prologue was delivered by **Vishal Nashine** on "Flexibility in Pharmaceutical Manufacturing - The Path to Achieving Six Sigma." He shared advanced manufacturing trends and approaches used in manufacturing of drug products, and he discussed how the increase in performance and reduction of process variation directly contributes to quality of products and improves efficiency and process robustness. He ended his presentation discussing the implementation of new technologies and future paths towards monitoring, optimization, and continuous improvement.

Raymond Skwierczynski's presentation was on "Current State of Pharmaceutical Manufacturing – Two Sigma Manufacturing and Bioprocessing." He compared the practices used in industries that operate at six-sigma to those used in the pharmaceutical industry and shared a path forward for improvement. He provided several examples of how to differentiate special-cause variation from common-cause variation and recognize failure modes that result from each

special-cause variation. He highlighted the opportunity to provide guidance on how pharmaceutical companies can use the "define, measure, analyze, improve, control" (DMAIC) approach to document and execute changes to batch and continuous manufacturing processes to streamline regulatory oversight. He encouraged the participants to actively participate in ongoing discussions of the manufacturing sciences and engineering AAPS Community.

The third presentation was given by **Markus Krumme** (Novartis, USA) on "Adaptive Processes in Pharmaceutical Development and Manufacturing." He provided compelling reasons on why continuous manufacturing is transforming pharmaceutical production by minimizing waste and maximizing efficiency. In this context, production interruptions are a threat that needs attention. A key to success in long-chain continuous manufacturing is to never stop the line and keep the process healthy and running in a state of control for as long as possible. A helpful tool to accomplish that is to dynamically modulate the process (slow down) throughput while maintaining a state of control. The same mechanisms can be used to dynamically respond to different input variables such as material attributes, and compensate for them in adaptive process settings, resulting in constant product quality. Examples of processes that were dynamically manipulated in response to non-ideal conditions while producing products at target quality were given.

Rahul Kaushik (Nektar Therapeutics, USA) delivered a presentation on "Knowledge Integration - Application of Artificial Intelligence and Machine Learning Tools in Manufacturing." He explained that machine learning has been successfully implemented in various process development, monitoring, and control of clinical and commercial drug manufacturing activities. He said that the next generations of machine learning will focus on improving quality control optimization in manufacturing systems, specifically reducing process variability and predictive capabilities in preventing failures. He shared examples on automation, machine vision capabilities, process monitoring, and use of predictive modeling. On the final note, he highlighted the importance to aim for the use of intelligent systems to enhance key human capabilities throughout the process development and manufacturing of biologics drug substances and drug products.

Brian Carlin (DFE Pharma, USA) closed the symposium with "Flexibility in Formulation." The risk from special-cause variation due to excipient complexity is underestimated, but it can be countered by adaptive formulas, rational excipient specifications, continuous multivariate monitoring, and the fewer process degrees of freedom afforded by continuous manufacturing. Compendial limits may be justified, but for those pharmacopoeial

Figure 1. From left to right: Markus Krumme, Rahul R. Kaushik, Vishal C. Nashine, Dorys Argelia Diaz, Raymond D. Skwierczynski, Brian Carlin, and Arya Jayatilaka.

attributes without acceptance criteria the supplier specifications and methods should be adopted without imposing user-defined limits. Critical material attributes can be used in an algorithm to control the process and/or formula, rather than merely to identify suitable batches. The so-called "non-critical" excipients do not exist, and an alternative Kano-based categorization was proposed. Excipient-related risk and uncertainty during production will not be eliminated but can be mitigated by collaboration with pharmaceutically aligned excipient manufacturers to increase excipient understanding and strengthen the control strategy.

Symposium on "PBPK Modeling and Clinical Pharmacology in Regulatory Applications and Decision Making"

This symposium took place on November 5, 2018, and the moderators were **Shriram Pathak** (Certara UK Limited, Simcyp Division, UK) and **Amit Desai** (Astellas Pharma, USA). The first talk on "Integrating Inter- and Intra-Subjects Variability in PBPK Modelling: Considerations and Knowledge Gaps" was given by **Masoud Jamei** (Certara UK Limited, Simcyp Division, UK). When administering drugs to patients, it is essential to have good understanding of drug safety and efficacy in various subgroups of patients rather than an average person. Expectations of extreme effects, side effects, or lack of therapeutic effects in some subgroups following administration of similar doses requires full understanding of variability and the importance of identifying covariates that determine exposure to drug candidates in each individual. Developing population-based physiologically-based PK (PBPK) models, where such covariates are mechanistically incorporated, can assist with predicting variability between and within subjects. The key element of this approach is the separation of information on the system (i.e., human body) from that of the drug (e.g., physicochemical or metabolism parameters) and the study design (e.g., dose, route and frequency of administration, concomitant drugs and food). Great progress has been made in identifying covariates affecting inter-subject variability; however, the understanding of factors affecting intra-subject variability is still limited. The recent advancements and knowledge gaps in determining inter- and intra-subject variability in PBPK modelling were discussed.

Gordon Amidon (University of Michigan College of Pharmacy) gave a presentation on "Gathering Variability Data in Physiological Parameters for Use in Modelling to Predict BE Outcomes." The focus for the past 5–10 years has been to measure GI variables following a BE protocol (8 oz of water). The goal is to determine the dynamic, time-dependent, initial conditions for a computer prediction of absorption and subsequent plasma levels, assuming the IV PK is known. The approach suggested is via the classical gastroenterological techniques of GI catheter sampling, manometry, and simultaneous plasma level measurement. A non-absorbable drug in solution (in the 8 oz of water) was included. Results of motility studies in the fasted and fed states and surprisingly complex results for gastric emptying were presented. The intestinal luminal samples also provided surprises with regard to the uniqueness of the bicarbonate buffer, as well as the slow in vivo dissolution of ibuprofen and the low intestinal luminal fluid buffer capacity. The GI manometry results further provide insight into the underlying GI basis for plasma level variability. With the heavy emphasis on computational predictions, it is essential that a realistic initial condition (IC) is used in order for the prediction to be realistic of the actual in vivo saturation.

Xinyuan Zhang (FDA, USA) gave a presentation on the "Role of Virtual Trials Modeling in Product Development, Optimization and Beyond: FDA Perspective." PBPK or mechanistic models have been widely used at various stages of drug product development and regulatory review for different purposes, such as absorption-distribution-metabolism-excretion (ADME) predictions, assessment of potential drug-drug interactions (DDI), providing mechanistic explanation of PK characteristics, and PK predictions in special populations. An overview of the utility of PBPK modeling and simulation in product development, optimization, and regulatory submissions was given. Areas where there is high confidence in model performance and scientific challenges in low-confidence areas were discussed. An update on the PBPK submissions to the Office of Clinical Pharmacology at the US FDA was provided. Case examples of PBPK model applications were discussed to illustrate how PBPK modeling and simulation have been used for decision making from a clinical pharmacology perspective.

The fourth presentation of the symposium was given by **Essam Kerwash** (MHRA, UK) on "Use and Qualification of PBPK Strategies in Regulatory Submissions and Approval – EMA's Perspective." The use of PBPK modeling in drug development and regulatory submissions was described. The biopharmaceutical and drug interaction uses of PBPK modeling were covered, and a special focus was given to the use of PBPK modeling to inform pediatric clinical study design. The regulatory guidance on qualification and reporting of PBPK models from European Medicines Agency (EMA) perspective was provided.

Rapid Fire on "Six Years of Progress in Oral Biopharmaceutics - EU-Project OrBiTo"

This Rapid fire session took place on November 5, 2018 and was moderated by **Sharmila Das** (University of Maryland School of Pharmacy, USA) and **Jong Bong Lee** (Rutgers University, USA). **Bertil Abrahamsson** (Astra Zeneca, Sweden) gave a high level summary of output from OrBiTo (www.orbitoproject.eu). OrBiTo is a project within the European Innovative Medicines Initiative (EU IMI) in the area of oral biopharmaceutics tools that includes partners from nine universities, one regulatory agency, one non-profit research organization, and three small/medium-sized specialist technology companies together with 12 pharmaceutical companies. The OrBiTo project was set up to deliver a framework for rational application of predictive biopharmaceutics tools for oral drug delivery. OrBiTo included novel prospective in vivo studies in human and preclinical models to define new methodologies or refine existing tools. Extensive validation has also been performed of novel and existing biopharmaceutics tools by using historical datasets from industry partners. A combination of high quality in vitro and in silico characterizations of active drugs and formulations was integrated into physiologically based in silico biopharmaceutics models, capturing the full complexity of GI drug absorption.

Anette Müllertz (University of Copenhagen, Denmark), gave a talk on "Progress in Biopharm API Characterization - EU-project OrBiTo." One work package in the EU/IMI project OrBiTo focused on biopharmaceutical characterization of active pharmacological ingredients (APIs) including solubility, dissolution, and permeation assessments. Such characterizations are of crucial importance in understanding and predicting drug absorption of drugs as a basis for API selection and risk assessment in drug discovery as well as input to formulation design and design and interpretation of clinical pharmacology studies. She discussed the development of new tools, the standardization and validation of existing tools, and how this new knowledge has been brought together in a decision-aiding tool to support industrial use of this toolbox.

Afterwards **Maria Vertzoni** (University of Athens, Greece) gave a presentation on "Progress in In Vivo Predictive Dissolution - EU/IMI-Project OrBiTo." One work package has focused on biorelevant product dissolution testing. The use of such methods are critical in product design to reach desired clinical performance and maintain clinical performance in late-stage product development, where manufacturing is scaled-up and processes are optimized. There may also be an increased role in the future of biorelevant dissolution testing in context of regulatory applications. The work within OrBiTo has primarily focused on challenging less-well-understood topics like supersaturating products, extended-release formulations, and influence of gastric motility. This has resulted in some new methods, as well as validation of existing methods ending up in a guidance for rationale industrial usage of such tools.

Patricia Zane (Sanofi, USA) talked on "Progress Regarding In Vivo Understanding - EU-Project OrBiTo," and **Bertil Abrahamsson** (Astra Zeneca, Sweden) covered the "Mechanistic Studies in Man - EU-project OrBiTo". This work package focused on better understanding of the in vivo system, i.e., absorption and prerequisites for absorption in the GI tract. This part has involved more than 10 mechanistic studies in humans for example including studies of drug absorption through local measurements in the GI tract, sampling and novel characterization of GI fluids, in vivo characterizations of GI physiology (e.g., after the FDA standardized breakfast), and extending BCS permeability assessment to the more distal part of the intestines. This work package is also developing guidance for best use of animal models in biopharmaceutics studies based on significant industry experience.

Amin Rostami (Certara USA Inc) covered the "Validation of PBPK tools - EU-Project OrBiTo." In this work package the focus was on in silico tools for prediction of oral absorption, often referred to as PBPK tools. These tools have during the last years become a "working horse" in pharmaceutical product development, and there is a great interest also in regulatory applications in the biopharmaceutics area. The OrBiTo work included building a new database with in vivo data as well as biopharmaceutical and other characteristics, to a large extent with unpublished data from the industry. This database was used for an initial gap analysis of available PBPK tools in a unique blinded study design. This gap analysis was followed by a new validation study after implementation of improvements of tools, approaches and data sets.

The "Industrial Impact of EU-Project OrBiTo" was given by **Kerstin Schaefer** (Boehringer Ingelheim, Germany). OrBiTo is a project within the EU IMI (www.imi.europa.eu/). IMI is the biggest public-private partnership in the area of medical research and is an innovative collaboration between the European Commission and European pharma industry (EFPIA). The objective is to make the drug discovery and development process more efficient

to bring better medicines faster to patients. Therefore, it has been of crucial importance for OrBiTo not only to produce new science but also support applications in the industry.

Finally, **Gordon Amidon** discussed the "Remaining Challenges and New Initiatives in Oral Biopharmaceutics." As a short answer to the question of the remaining challenges, he noted: gastric emptying and intestinal transit and probability distributions of administered dosage form/drug, based on direct measurement of GI variables, usually with simultaneous plasma measurement of drug. The next challenge will be to provide an in vitro apparatus that captures these physical and physiological variables in a device that realistically represents the in vivo process. A device that captures the in vivo GI variables and processes is the biggest need in pharmaceutical product development today. He highlighted that there is a need to measure these variables, under typical BE protocol conditions, fasted and fed, in order to develop a realistic device representing the in vivo processes. Further, for the next generation, a new stochastic mathematical modeling approach to GI processes to represent the physiological GI processes in a realistic manner is needed.

Symposium on "Rapid and Cost-Effective Delivery of New Drugs to Patients - Clinical Pharmacology"

This symposium took place on November 6, 2018, and the moderators were **Ross Walenga** (FDA, USA) and **Maha Mehanna** (i3 Pharmaceuticals, LLC, USA), The first talk was given by **James Mann** (AstraZeneca, UK). His presentation was on "Calquence: A Case Study in the use of Biopharmaceutic Tools to Expedite the Drug Development Process." Calquence was recently approved in the US after a rapid development program. The role of biopharmaceutical tools that helped build a mechanistic understanding of the drug dissolution and absorption process for the drug, which ultimately aided in the rapid development and setting of clinically relevant specifications, were discussed. He covered the use of in vivo smartpill studies, TIM-1, novel methods for understanding mechanistic dissolution, integration of in vitro data into PBPK modelling, and how it culminated in an approved product.

Afterwards, **Sandra Suarez** (FDA, USA) gave a presentation on "Accelerating Development through Application of Quantitative Mechanistic Modelling Techniques." Drug product development is a particularly costly and lengthy process. The growing availability of quantitative methods, coupled with advances in instrumentation, bioinformatics tools, and software are shifting the ways drug discovery and drug development are accomplished. The application of mechanistic models such as physiologically based biopharmaceutics modeling (PBBM) is growing rapidly and is becoming an essential part for streamlining drug discovery and development. She discussed the FDA position on how mechanistic modeling and simulation (e.g., PBBM, PB-IVIVC/IVIVR) can be applied to accelerate drug product development, focusing on the strategies for building a safe space towards regulatory flexibility in support of drug product quality.

Daniele Ouellet (Janssen, USA) talked about the "Pharmacometrics to Support Regulatory Questions and Approval." Efforts on multiple fronts are ongoing to accelerate drug development and ensure that new drugs targeting unmet medical needs are provided to patients in the most efficient manner. Pharmacometric approaches can help leverage knowledge acquired at each stage of development to inform the next step and optimize the development strategy. Key questions that can be addressed include go/no-go decision, selection of optimal dose and dosing regimen, support of the to-be-marketed formulation, and characterization of clinical pharmacology to support regulatory approval. Dr. Quellet gave several examples of pharmacometric applications that helped accelerate drug development and support regulatory approval of oncology compounds.

The final talk on "Novel Clinical Trial Designs to Accelerate Drug Development" was given by R**obert Schmouder** (Novartis, USA). The capability of conducting exploratory clinical trials is being squeezed from almost every direction, and there is a need to decompress this situation. Some new methods, including increasing patient engagement, conducting trials remotely, use of platform trial approaches and real time data analysis, may help to smooth the way to more efficient clinical trial operation.

Symposium on "Quality and Characterization Considerations for Formulation Development – Chemical"

This symposium took place on November 6, 2018, and the moderators were **Yongchao Su** (Merck & Co., USA) and **Jon de Vlieger** (Lygature, Netherlands - NBCD Working Group). The first presentation of the symposium was given by **Katherine Tyner** (FDA, USA) on "Regulatory Perspective on Critical Quality Attributes for Complex Drug Products." Complex systems are distinguished by having multiple interactive variables, structures, and relationships. In the realm of drug products, complexity may arise from the active ingredient, formulation, dosage form, route of delivery, device combinations, and various combinations thereof. The complexity of drug products has been increasing over the years, in part, to enhance the

delivery of poorly soluble drugs, increase drug delivery to traditionally un-druggable sites, and meet the demands of increased focus on personalized and precision medicine. Historically, complex products have involved robust scientific and industry discussion throughout all aspects of the review process to ensure quality of these products for the US market. She discussed the interplay of critical quality attributes as they relate the review process of complex drug products, applicable regulatory guidance, and current regulatory programs.

Andreas Abend (Merck, USA) gave a presentation on "Predictive Dissolution Methods." Predicting in vivo performance of pharmaceutical products is a key a challenge for scientists working in the pharmaceutical sciences field. Currently, there are no in vitro or in silico tools available that can accurately predict the PK behavior of a new drug substance due to complex in vivo steps the drug substance encounters once ingested and finally eliminated. Applying in vitro dissolution testing combined with dissolution modeling can be used to anticipate differences in PK performance, which can be used to guide formulation candidate selection and bioperformance risk assessment throughout product development. To be truly predictive, one must measure PK performance and then establish a link to in vitro data. Different in vitro approaches to guide formulation candidate selection and to predict in vitro dissolution performance were presented along with current challenges to develop predictive dissolution models for immediate-release products.

A presentation on "High-Resolution Characterization of Structure, Interaction, and Miscibility of Drug Products" was given by **Eric Munson** (University of Kentucky, USA). The local interactions between a drug and its surrounding environment are critical in both small and large molecule formulations. For small molecules, the drug-polymer interaction is needed to ensure that the drug does not crystallize in an amorphous solid dispersion. For proteins, phase separation in lyophilized formulations will lead to reduced stability and the potential for aggregation. He showed the ability to probe these local structures and interactions in both small and large molecule systems. Case studies demonstrating how structural properties (e.g., degrees of interaction, changes in conformation) can impact functional properties such as crystallization and aggregation were presented.

Joe Lubach (Genentech, USA) talked about "Current Technical Challenges of High-res Characterization of Drug Products and Insights of Impacts of Molecular Information on Drug Development." High-resolution characterization of solid dosage forms represents an ever-challenging problem facing pharmaceutical scientists. Detailed solid-state analysis of a drug product should include the active ingredient of course, but also the excipients as well as potential interactions between the drug and excipients. He presented applications of solid-state NMR spectroscopy to gain bulk and molecular-level insights into complex solid dosage forms, including crystalline and amorphous materials, drugs and excipients, and ubiquitous water. NMR has proven to be a critical tool in the characterization and understanding of drug product behavior in recent years. High-resolution and exquisite selectivity can be obtained through a variety of experiments to probe nuclei, such as 13C, 15N, 19F, 23Na, 31P, and even 1H. Applications such as quantitation of solid forms, drug-excipient interactions in amorphous formulations, and water distribution throughout a formulation were discussed.

Symposium on "Rapid and Cost-Effective Delivery of New Drugs to Patients - Formulation & Quality"

This symposium took place on November 7, 2018 and was moderated by **Xiaofei Liu** (FDA, USA). **Steven Baertschi** (Baertschi Consulting, LLC, USA) gave a presentation on "Strategic Approaches to Development of Phase-Appropriate Specifications including Organic Impurities Control." Development and implementation of impurity control strategies is a complicated yet critical process necessary to ensure overall pharmaceutical product quality and patient safety. There are well-established guidelines for control of new impurities in drug substances and new drug products (ICH Q3A/Q3B, USP Chapters <476> and <1086>). These guidances only apply to commercial products or products in late-stage clinical development (Phase 3). There is also guidance for mutagenic impurities (ICH M7), which covers early clinical development through commercialization; however, it is a relatively new guideline and questions regarding its implementation remain. Thus, there is a lack of regulatory guidance regarding impurity controls at early stages of clinical development (prior to Phase 3), Dr. Baertschi covered best practices and case studies regarding development and implementation of organic impurity control strategies at early stages of small molecule clinical development.

Talia Flanagan (AstraZeneca, UK) gave a presentation on "The Use of Biopharmaceutics Risk Assessment to Guide Product Development." Biopharmaceutics provides the link between chemistry, manufacturing, and control (CMC) activities and product performance in the

patient (i.e., achievement of the intended therapeutic outcomes). Biopharmaceutics risk assessment is a key element of drug product development, influencing formulation approach, manufacturing strategy, and clinical study design, and underpinning a clinically relevant control strategy at registration. She presented the application of the biopharmaceutics risk assessment roadmap (BioRAM) approach, an innovative strategy and framework for patient-centric drug development. BioRAM is a systems approach, which brings together scientists from pharmaceutics, manufacturing, and clinical and preclinical disciplines to perform an integrated biopharmaceutics risk assessment. This can be used to drive product development activities, with the goal of optimizing product performance for patient benefit.

Ken Waterman (FreeThink Technologies, Inc., USA) talk about "Stability Modeling for Highly Accelerated Determination of Drug Product Shelf-Life." Dr. Waterman presented "ASAP," which employs isoconversion (time to hit the specification limit at each condition) with designed temperature and relative humidity (RH) conditions (based on a humidity-corrected Arrhenius equation) to build a model for degradant formation or potency loss for drug products and drug substances. Once the model is built, the shelf-life inside packaging can be determined based on the calculated RH inside the packaging. ASAPprime employs this science in combination with statistical tools to enable accurate estimations of shelf-life with several factors determined computationally (e.g., packaging, storage conditions, storage excursions).

The final talk of the symposium was on "3D Printing for Drug Delivery Applications," given by **Xiaofei Liu**. 3D printing has seen rapidly expanding medical applications in the last several years. The complex drug delivery system is an evolving area that has benefited from 3D printing tools, which provide customized and optimized drug delivery solutions. For drug-devices combination products, e. g., inhalation and transdermal drug delivery systems, 3D printing can be especially helpful for novel designs of the device constituent part and to ensure product quality and performance. For generic combination products, 3D printing of drug delivery devices will potentially impact the current device sameness recommendations for the generic products from a product performance perspective. He discussed updates on the latest 3D printing applications in drug delivery to promote product quality and bioequivalence assessment.