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Dissolution Highlights from the 2014 AAPS Annual Meeting in San Diego

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AAPS held its Annual Meeting and Exposition at the Convention Center in San Diego, California, during the week of November 2–6, 2014. The meeting is a premier gathering of pharmaceutical scientists from around the world and works to address the needs of the attendees, including members of over 40 Focus Groups in nine Sections, or scientific disciplines, including two focused on dissolution testing: the In Vitro Release and Dissolution Testing and QbD and Product Performance groups.

For those with an interest in dissolution testing, there was a roundtable on "Translating Patient Outcomes to Product Quality Attributes" and symposia on "Cloudy with a Chance of Precipitation: Novel In Vitro Screening Tools To Evaluate and Predict In Vivo Performance of Enabled Formulations" and "Exploiting In Vivo Studies To Improve Predictive In Vitro Models for Oral Drug Delivery: Are We Leveraging This New Body of Knowledge?" There were face-to-face meetings of the two focus groups mentioned and the Dissolution Discussion Group. See below for more details about some of these events.

TRANSLATING PATIENT OUTCOMES TO PRODUCT QUALITY ATTRIBUTES

A roundtable on "Translating Patient Outcomes to Product Quality Attributes: Role of Biorelevant Dissolution Specifications" was held on Monday morning. Excellent introductory presentations were made by **Raimar Löbenberg** (University of Alberta) and **Helen Strickland** (Glaxo Smithkline, Zebulon, NC) with **Greg Martin** (Complectors Consulting) as moderator. Dr. Löbenberg's presentation, "In Vitro Methods to Establish IVIVC," reviewed the importance of the in vitro dissolution test in drug development and some of the concepts behind the development of a correlation between in vivo data and data from the dissolution test (i.e., in vitro–in vivo correlation or IVIVC). He cautioned that the in vitro test may be overly discriminating, making it more difficult to establish meaningful IVIVCs. Ms. Strickland's presentation, "Considerations for Translating the Quality Target Product Profile Requirements to Product Specifications to Batch Release and Stability Criteria," focused on statistical evaluation of dissolution data and the effect of batch-to-batch variability on the establishment of specifications. Despite the early hour, the session was well attended, with almost 250 present for the discussion that followed the presentations. The discussion was lively, with several leaders from the field joining in, and probably raised more questions than were settled. It became clear that one size does not fit all, that there are probably some disconnects between data generated using current methodology and the need to correlate laboratory results to critical quality attributes (CQAs) and patient outcomes. The release mechanism and type of dosage form, drug characteristics such as solubility and particle size, and variability batch-to-batch and within batch contribute to the challenge. While today's dissolution procedures may indeed be overdiscriminating, it is likely we will use good science to improve our generation and interpretation of in vitro data, which may be different from the current compendial approaches, perhaps using different apparatus or more sophisticated statistical approaches for data interpretation.

CLOUDY WITH A CHANCE OF PRECIPITATION: NOVEL IN VITRO SCREENING TOOLS TO EVALUATE AND PREDICT IN VIVO PERFORMANCE OF ENABLED FORMULATIONS

This symposium was moderated by **Allen Templeton** (Merck, USA). Enabled formulations such as spray-drying and hot-melt extrusion have joined the arsenal of techniques formulators are using to address absorption challenges with poorly soluble molecules. Important considerations when formulating any poorly soluble compound are evaluating its properties and establishing the correct formulation approach required to solve

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formulation and process development concerns while simultaneously achieving the desire absorption profile for the compound of interest. Developing and applying novel in vitro screening approaches could prove highly beneficial in tuning formulation and process parameters to maximize absorption. **Jesse Kuiper** (Merck, USA) gave a presentation entitled "Dissolution Rate-Limiting AUC: Simple Methodology for Measuring Dissolution Rate of the Entire Dose in Biorelevant Media." At the start of his presentation, he described the absorption process after oral administration of a formulation and emphasized the difference between solubility/permeability-limited exposure and dissolution rate-limited exposure by means of the relationship between the solubilization of the API particles and the absorption. He pointed out that when dissolution is the rate-limiting step in absorption, it is important to understand the effective dissolution rate of the entire dose and introduced the concept of "1X Dissolution" in terms of single particle dissolution modeling. This approach allows quantitative comparisons across formulation types, and an in-depth case study of a low solubility API with amorphous formulations was presented. He concluded by noting that the "1X Biorelevant Dissolution" is a discriminating dissolution method that allows for evaluation of subtle formulation changes and can be used as a simple, powerful tool to predict exposure in animal and human subjects. The second presentation, entitled "Evaluation of Crystallization and Precipitation in Highly Supersaturated Aqueous Solutions," was given by **Lynne Taylor** (Purdue University). Initially, she described the meaning of "supersaturation" and explained the reasons why we are interested in this phenomenon and the factors that can limit it. She pointed out that if the supersaturation generated by a solubility-enhancing formulation is increased, then crystallization is more likely to occur, which is particularly relevant for amorphous solids with a high "solubility advantage." She described variation in crystallization kinetics and crystallization routes of highly supersaturated solutions and the ability of polymers to modify solution crystallization behavior. She pointed out that additive effects are not well understood, and several examples were presented. In the last part of her presentation, she discussed the formation and properties of the droplet phase and crystallization of two-phase systems. The last presentation was given by **Feng Qian** (Tsinghua University, China) and was entitled "Drug–Polymer–Water Interaction and Its Implication to the Dissolution Performance of Amorphous Solid Dispersions." He discussed the risks of amorphous solid dispersions (ASD) stability and posed the questions: What are the key attributes of a well-performing amorphous solid dispersion? and Is there a simple in vitro assay that might be able to predict the in vitro and in vivo performance? He described the dissolution of amorphous solid dispersions and the potential controlling factors by emphasizing the drug–polymer–water interaction as described by determination of the Flory–Huggins interaction parameters. Examples of analyses of drug–polymer interaction by NMR and FTIR for model drugs and polymers were presented, and the ability of polymers to maintain solution drug supersaturation was shown. Finally, he discussed the in vitro dissolution performance of drug and polymer and drew the conclusion that for fast crystallizers that do not interact with polymers, ASD only works if both the drug dose and ASD drug loading are low. A strong drug–polymer interaction may be helpful in maintaining supersaturation, but it does not demonstrate a clear correlation with the dissolution performance of ASDs.

EXPLOITING IN VIVO STUDIES TO IMPROVE PREDICTIVE IN VITRO MODELS FOR ORAL DRUG DELIVERY: ARE WE LEVERAGING THIS NEW BODY OF KNOWLEDGE?

This symposium was moderated by **Maria Cruanes** (Merck, Puerto Rico). Recent and current studies in humans are revealing new information about GI tract physiology and providing an untapped source of inspiration for in vitro models of drug release and absorption. This new knowledge has the potential to translate into better in vitro and in silico models and advance the science of oral formulation design and development in a more fundamental way. The first presentation given by **Patrick Augustijns** (University of Leuven, Belgium) was entitled "Drug and Formulation Behavior in the Upper Small Intestine." He emphasized that the configuration of supersaturating drug delivery systems is a promising concept to obtain adequate oral bioavailability of poorly soluble compounds. Various in vitro tools are available to assess drug supersaturation of poorly soluble drugs during dosage formulation development and formulation screening. However, whether formulations indeed create and maintain supersaturation in the small intestine has never been demonstrated. Recent studies have illustrated that intubation using multilumen catheters allows exploring the complex and dynamic gastrointestinal environment by characterizing the aspirated fluids. Determining concentrations and

solubility in aspirated intestinal fluids allows direct assessment of supersaturation in the upper small intestine. The research group of Reppas has recently used this technique to demonstrate intestinal supersaturation after applying a drug solution directly into the stomach. He demonstrated that supersaturation takes place in the upper small intestine after oral administration of a dosage form. Three case studies were presented in which supersaturation was created (1) through the use of a solid dispersion (itraconazole capsules), (2) through the use of a cyclodextrin-based solution (itraconazole), or (3) by enzymatic conversion of a prodrug (abiraterone acetate). He concluded that these in vivo results could serve as unique reference data for validation, optimization, or both of different in vitro/in silico tools. Afterwards **Christos Reppas** (National and Kapodistrian University of Athens, Greece) talked about "Simulating the Lower Intestine Based on In Vivo Data." In the first part of this presentation, the environmental conditions in the lumen of the lower intestine were summarized with emphasis on the physicochemical characteristics of the liquid portion in health and inflammatory bowel disease. Recent data on the colloidal structures in the liquid portion of ascending colon contents were presented and their impact on drug solubility was discussed. In the second part of his presentation, he described and evaluated the usefulness of currently applied in vitro methodologies in the evaluation of orally administered extended-release products and prodrugs for action in the lower intestine. The importance of the environment in the lower intestine on luminal behavior of highly dosed active pharmaceutical ingredients (APIs) (i.e., APIs belonging to Development Classification System Class IIb or IV) based on recent in vitro and in silico data was highlighted. He concluded his presentation by summarizing the difficulties in simulating certain aspects of the environment in the lower intestine and identifying the key reasons. The last presentation, given by **Manish Gupta** (GlaxoSmithKline, USA), was entitled "Novel In Vivo Tools to Better Understand Drug Product Design and Testing." He started with an integrated in vivo–in vitro–in silico approach toward improved formulation design. A novel in vivo tool, the "stable isotope approach," applied toward generating meaningful in vivo knowledge in a cost-, time-, and resource-effective manner, was discussed in detail. The advantages and the limitations of this approach were described. Examples of application of this approach and useful imaging options were shown. Case studies on the impact of gelatin versus HPMC capsule shell and micronized versus non-micronized drug substance on pharmacokinetics demonstrating integration of in vivo knowledge with biorelevant in vitro testing were presented. He concluded by discussing options toward a risk-based dissolution strategy.

IVRDT FOCUS GROUP FACE-TO-FACE MEETING

The annual face-to-face meeting of the focus group was held at midday on Monday, November 3. The current chair, **Xujin Lu** (BMS, USA), reviewed the accomplishments of the focus group, the focus group website, and described the objectives set for 2015. The student outreach activities were presented by **Trinh Phuong Vo** (Mercer University, USA). Three hot topics were discussed: "Enzyme Proposal and Semisolids, Significant Revisions to Chapters <711> and <1724>" (**Vivian Gray**, *Dissolution Technologies*, USA), "Measurement of Vibration in Dissolution Baths Across Laboratories" (**Erika Stippler**, USP, USA), and "USP Toolkit, Mechanical Calibration, and *Dissolution Technologies* Journal" (**Vivian Gray**, *Dissolution Technologies*, USA). A lively discussion by all attendees followed. Ideas and points to consider for future activities of the focus group were proposed. Finally, programming ideas for the 2015 AAPS Annual Meeting and the sessions of interest for the focus group at the 2014 AAPS Annual Meeting were presented (**Nikoletta Fotaki**, University of Bath, UK).