

Highlights From the 2021 AAPS 360 Annual Meeting

Dorys Argelia Diaz^{1*}, Vivian A. Gray², and Andre Hermans³

¹Global Product Development, Pfizer Inc, Groton, CT, USA.

²V. A. Gray Consulting, Hockessin, DE, USA.

³Merck & Co., Inc., Rahway, NJ, USA.

e-mail: dorys.argelia.diaz@pfizer.com

INTRODUCTION

The American Association of Pharmaceutical Scientists (AAPS) held its annual meeting and exposition event, PharmSci 360, at the Pennsylvania Convention Center in Philadelphia, PA, October 17–20, 2021. This year the PharmSci 360 meeting was both in-person and virtual. The PharmSci 360 annual meeting "hybrid" version was a premier gathering of pharmaceutical scientists from around the world who came together to learn about advances within our field and build connections among scientists globally.

AAPS IN-VITRO RELEASE AND DISSOLUTION TESTING (IVRDT) COMMUNITY MEETING

After 2 years of virtual meetings, the AAPS In-vitro Release and Dissolution Testing (IVRDT) Community was able to get together in person at the AAPS 360 meeting in Philadelphia. Community chair, Ishai Nir, and chair-elect, Andre Hermans presented the 2021 community accomplishments and gave a look ahead to upcoming activities in 2022 in front of an engaged audience.

The IVRDT community co-sponsored five webinars in 2021, which were organized by the Society of Pharmaceutical Dissolution Science (SPDS) US chapter, on topics ranging from the United States Pharmacopeia (USP) apparatus 4 dissolution techniques and modeling applications to dissolution in pediatric drug development.

Beside the highlights report from the 2020 AAPS 360 annual meeting, two additional publications were sponsored by the IVRDT community in 2021 (1–3). "The Case for Apex Vessels," which was a joint effort with the Innovation and Quality (IQ) Consortium, resulted in a USP stimuli article. Also, publication of the book, *In Vitro Drug Release Testing of Special Dosage Forms*, indicates the continued scientific engagement of this community. This engagement will continue in 2022 with additional

webinars and/or workshops on hot topics throughout the year.

Following the success of global outreach in past years, a virtual outreach program with Poland is being prepared for 2022, and a Philippines outreach program is planned for late 2022 or 2023.

During the open community discussion, the group brainstormed additional hot topics for upcoming workshops or online seminars. Dissolution method development challenges for long acting injectable or implantable dosage forms was proposed as a topic for a workshop topic in 2022. Hydrodynamic effects in USP apparatus 1, specifically with respect to mesh size of the basket, was also mentioned as a potential focus point for upcoming webinars.

The meeting was a full success and showed the excitement and scientific engagement of dissolution scientists within AAPS. Everyone within the IVRDT community is looking forward to another successful year in 2022. See photo (Fig. 1) for the meeting attendees.



Figure 1. In-vitro release and dissolution testing (IVRDT) community. Top row left to right: Ashvin Patel, David Kwajewski, Gary Dromgoole. Second row left to right: Vivian Gray, Keith Hamman, Xujin Lu. Third row left to right: Juan Tac, Jennifer Canty, Maria Cruanes, Ishai Nir, Andre Herman, Amos Xxxoye, Patrick Balmer, unidentified guest.

*Corresponding author

PROLOGUE: EVALUATION OF EXCIPIENT VARIABILITY TO SUPPORT QBD FORMULATION DEVELOPMENT

Pauline Janssen, **DFE Pharma – Goch**, gave a talk entitled “Evaluation of excipient variability to support QbD (Quality by Design) formulation development,” that began with a discussion on how excipient suppliers have been asked to manufacture their products to align with QbD principles. The concept of QbD emphasizes that robust formulations and processes should be able to accommodate typical variation seen in active pharmaceutical ingredients, processes, and excipients without compromising manufacturing, stability, or performance factors. QbD has become especially important in the context of continuous manufacturing (CM), which has gained more interest in the pharmaceutical industry.

The U.S. Food and Drug Administration (FDA) released the International Council for Harmonisation (ICH) guideline Q13 in 2020, which is part of their effort to encourage the adoption of CM. An important aspect is that any variation in the product flowing into a CM line will affect final product quality.

The functionality of excipients can be affected by this intrinsic variation, and the impact of this variation on the final dosage form should be understood. To understand the effect and interaction of distinct factors on product performance, input variables should be varied in a purposeful way.

The stretch batch approach is a new technique devised to inform the efficient construction of compliant QbD processes. It can potentially reduce the number of experimental studies required during drug product development. A case study in the stretch batch approach was presented. Multivariate analysis of large datasets to identify major sources of variation was explored.

The topic of excipients continued with Nikoletta Fotaki, **University of Bath**, who presented “Biopharmaceutical implications of excipient variability on drug solubility and dissolution.” The talk began with emphasizing that excipient variability may impact drug product performance and that identification of the biopharmaceutical risks of that variability on oral drug performance is important for facilitating the development of a robust formulation. Specifically, the impact of variability of common excipients (i.e., hydroxypropylmethylcellulose [HPMC], magnesium stearate, and superdisintegrants) on the apparent solubility of drugs was discussed. The effect of excipient variability on a wide range of physicochemical properties and on in vitro dissolution of a highly and a poorly soluble

drug from immediate release formulations was also presented. Roadmaps combining drug and excipient characteristics to identify the cases where excipient variability may present risks in oral drug performance and bioavailability were discussed. She provided references for a more in-depth review of the case studies and concepts presented in this talk (4–7).

HOT TOPIC: DISSOLUTION BEST PRACTICES – MEETING CHINESE PHARMACOPEIA REQUIREMENTS

The first talk of this session was given by Baoming Ning, from the **National Institutes for Food and Drug Control (NIFDC)**, on “Rationale of CHP (Chinese Pharmacopeia) Dissolution.” He gave a brief introduction of the history of CHP and the role of NIFDC in creating monographs and general chapters. He also presented the CHP regulatory science projects on new equipment exploration and technology performed by NIFDC; for example, the reciprocating cylinder, reciprocating holders, and flow through cell apparatus. He went on to describe the history and dynamics of dissolution testing included by CHP since 1985. Baoming provided rationale for CHP acceptance criteria and testing requirements. He presented the differences between dissolution testing as described in CHP and the ICH harmonized text. He reported on the status on implementation of ICH guidelines in China. There is a regulatory science research project to implement ICH Q4B guidelines. Acceptance criteria and requirements on dissolution testing are key points of the ongoing scientific project. He concluded with discussing the potential approaches and roadmap for implementation of ICH harmonized text in China.

The second talk of this session was given by Margareth R. Marques, from the **USP**, on the topic of “Compendial Dissolution Testing.” She discussed how compendial dissolution testing is harmonized among the major pharmacopeias and where the dissolution information can be found in the USP (<711> Dissolution), European Pharmacopoeia (EP, 2.9.3 Dissolution Test for Solid Dosage Forms), and Japanese Pharmacopoeia (JP, 6.10 Dissolution). She shared how ICH Q4 is split into Q4A (Pharmacopeial Harmonization) and Q4B (Evaluation and Recommendation of Pharmacopeial Texts for Use in the ICH Regions). She also noted that Q4B Annex 7 (R2) (Dissolution Test General Chapter) includes country-based implementation status and interchangeability recognition of harmonized pharmacopeial chapters from USP, EP, and JP. She indicated that portions of the USP general chapters that are marked with symbols (♦, ♦♦) to indicate that the text is not harmonized. For instance, for

dissolution testing with gelatin capsules, the USP allows for the use of enzymes but other pharmacopeias do not. She highlighted that in general the tests listed in the USP monograph are the dissolution tests approved by the U.S. FDA for products marketed in the USA, but there are some exceptions (i.e., monographs developed upon request from the World Health Organization for products not approved in the USA).

The USP does not develop the dissolution, disintegration, or drug release test method. Those methods are developed and provided to them by the manufacturers for an approved marketed product. In several cases, there can be multiple dissolution test conditions due to the manufacturer's formulation strategy, including drug solubility, type of formulation, and manufacturing processes. It was noted that tests are listed in the USP monographs based on the order the methods are received by the pharmaceutical (innovator or generic) companies.

A new dissolution test will be added if there is a difference in any of the following conditions: dissolution medium (composition and or volume), apparatus (type and/or rotation speed or flow rate time), and acceptance criteria. Product-specific conditions are stated in the monographs including any acceptance criteria table different from those in <711> Dissolution. Every time there is any abbreviation, addition, or revision, it will be published in the Pharmacopeial Forum. There is a 90-day period for public comments on any revision to the general chapters, which gives the pharmaceutical industry an opportunity to comment before updates are published in the USP. She provided useful website links in this talk:

- USP Dissolution Method Database: <http://www.usp.org/resources/dissolution-methods-database>
- U.S. FDA Dissolution Method Database: <https://www.accessdata.fda.gov/scripts/cder/dissolution/>
- Dissolution Technologies website: www.dissolutiontech.com

Afterwards, Fasheng Li (**Pfizer**) presented "USP 711 vs CHP (Chinese Pharmacopeia) 0931 Dissolution Acceptance Criteria Comparison - Immediate Release Dosage Forms." He discussed how the operating characteristics (OC) curves generated through Monte Carlo simulations were used to compare the performance of USP <711> and CHP 0931.

He also presented the differences between these

two distinct compendial guidance documents using a product with comparable properties. When comparing USP <711> versus the CHP 0931, there are differences in the acceptance dissolution testing criteria stages. For instance, for stage 1, USP requires that each unit is not less than $Q + 5$, whereas CHP requires that each unit is not less than Q . Another example is the requirements for total number of samples – USP requires up to 24 units whereas CHP may require 6 or 12 dosage units.

In some cases when comparing the three dissolution stages, some divergence in results was reported. For instance, for stage 1, the USP is more stringent than CHP except when the standard deviation is exceedingly small and considering how far the batch mean value is from the specified Q value. For stage 2, the USP <711> is less stringent than CHP 0931 unless the standard deviation is small or relatively large. At the final stage 3, USP is generally less stringent than CHP unless the standard deviation is relatively large.

The speaker encouraged attendees to consider which pharmacopeia they will be testing their products against when designing an effective dissolution strategy and conducting a risk assessment. He also highlighted the importance of the OC in evaluating compendial guidance acceptance criteria. The OC curves can be used to describe the probability of passing the dissolution test criteria for a drug product batch with a given dissolution mean (μ) and standard deviation (σ).

He shared data for 30 batches of the same product with known mean and standard deviation values and similar Q values. Using the USP <711> and CHP 0931 acceptance criteria, different results were obtained (i.e., some passed USP and others failed CHP or vice versa), which illustrates how divergent oral drug acceptance criteria are between USP and CHP.

The last talk was given by Mark Alasandro (**Senhwa Biosciences**) who presented the AAPS Survey on AAPS member awareness of China dissolution requirements and how they have addressed the differences. Around 50% of those surveyed were not aware of the differences between USP and CHP. Around 30% surveyed had problems with these differences, especially with the acceptance criteria differences. The 30% who had a problem with these differences accepted the CHP dissolution requirements. Some persuaded China regulators to accept the sponsor's approach, and the rest had no response. The next step will be a workshop planned in August.

HOT TOPIC: BIOEQUIVALENCE EVALUATION AND USE OF PBPK MODELING IN PEDIATRICS (CLINICAL PHARMACOLOGY - ON DEMAND)

In this session, Fang Wu from the **U.S. FDA** presented "Bioequivalence Evaluation of Pediatric Product using Physiologically-Based Pharmacokinetic Modeling." She introduced the regulatory research on using physiologically based pharmacokinetic (PBPK) modeling to evaluate bioequivalence for pediatric drug products. She discussed the impact of product quality attributes on the bioequivalence of drugs in adults and the pediatric population. She highlighted the importance of implementing biorelevant dissolution, modelling, and simulations to assess risk factors associated with certain drug products that may lead to failed bioequivalence or different relative bioavailability results in the pediatric population.

She discussed the importance of a PBPK absorption model and how it is used to predict the effect of changes in critical process parameters (CPP), critical material attributes (CMA), and critical quality attributes (CQA) on in vivo performance. The CPPs (e.g., compression force), CMAs (e.g., solubility, particle size, polymorphism forms, and excipients) and CQAs (e.g., dissolution) are used to establish, validate, and refine the model. Describing these factors is essential to establish an in vitro-in vivo relationship, which can then be used to set clinically relevant drug product specifications and parameters for bioequivalence evaluation.

The use of new tools and approaches for linking pharmaceutical quality to clinical performance is encouraged by the recent FDA draft guidance document, "The Use of Physiologically Based Pharmacokinetic Analyses – Biopharmaceutics Applications for Oral Drug Product Development, Manufacturing Changes, and Controls Guidance for Industry." (8) The development of modeling and simulation has advanced by integrating the physicochemical properties of the active pharmaceutical ingredient, dissolution data, and physiology of the gastrointestinal tract activity.

Another draft guidance document mentioned was "Evaluation of Gastric pH-Dependent Drug Interactions with Acid-Reducing Agents: Study Design, Data Analysis and Clinical Implications Guidance for Industry." (9) This states that PBPK simulations can sometimes be used to further assess potential interactions between acid-reducing agents and drugs. PBPK applications are evolving, so sponsors should consult the appropriate FDA

review division if needed before applying a PBPK model in the drug development process.

The discussion of pediatric products that failed bioequivalence or had different PK parameters in relative bioavailability studies in pediatrics compared to data from adults was interesting. One challenge is how dissolution rates can vary among people based on age-related absorption effects, which have been shown as a common putative risk factor associated with differences in relative bioavailability (DRBA) between pediatrics and adults.

A case study was presented in which a PBPK model was developed for a putative class 1 or 3 (Biopharmaceutics Classification System) drug, oseltamivir phosphate (OP), and its pro-drug of the active metabolite, oseltamivir carboxylate (OC), in both adults and pediatrics. The steps involved in developing this model include acquiring physicochemical and ADME (absorption, distribution, metabolism, excretion) information about both OP and OC compounds; in vitro dissolution profile of OP; in vivo PK profiles following intravenous and oral administration of OP and OC; then the development of a base PBPK model of OP and OC. Subsequently, the model was validated using in vitro data as well as in vivo PK profiles for OP and OC following administration of different dosing regimens and generic drugs in adults and pediatrics. Finally, the model was used to conduct a virtual bioequivalence simulation and analysis on both the reference and test OP products in adults and pediatrics to determine a dissolution safe space for OP.

The development and application of PBPK modeling to pediatric populations provides a quantitative basis for setting clinically relevant specifications that can be used in both adults as well as children. This model aids in mitigating the risk associated with the bioequivalence and relative bioavailability of pediatric drug products.

PARTNER PRESENTATION: ACHIEVING VIRTUAL BIOEQUIVALENCE WITH PBPK IN LIEU OF CLINICAL STUDIES

Nikunj Kumar Patel and Ellen Leinfuss (**Certara**), presented "Achieving Virtual Bioequivalence with PBPK in Lieu of Clinical Studies." The speakers shared case studies that show how model-integrated evidence has been utilized to optimize formulations, justify dissolution specifications, support SUPAC, support biowaivers based on scientific evidence, and confirm equivalence.

They also shared how quantitative methods and computational modeling are used to support science-based decisions. Best practices for PBPK modeling,

including model development and performance assessment in virtual bioequivalence studies, was also presented.

Several case studies were provided to highlight the many advantages associated with having a verified, scientifically sound model development and simulation process. Cases included the use of PBPK in support of a manufacturing site changes and formulation changes for pediatrics from tablet to suspension.

It was recommended that both innovator and generic pharmaceutical companies implement computational modeling in the early and late development stages to enhance the drug development process and to make evidence-based recommendations with confidence. A PBPK model provides a means for predicting clinical outcomes with greater accuracy than traditional methods.

SUMMARY

Attendees of this year's conference were left with an unforgettable experience. The hybrid format allowed for both virtual and in-person attendance, which made it possible to cover several topics relevant to dissolution testing. These topics included the impact of excipient variability on dissolution and the application of modeling and simulation tools to assess product performance during early and late drug development. Finally, there was an emphasis on continuous knowledge sharing and collaboration for implementation of the various in vivo predictive methodologies to facilitate consistent application and timely decision-making in the drug development process.

CONFLICT OF INTEREST

The authors disclosed no conflicts of interest related to this article.

REFERENCES

1. Gray, V. A.; Diaz, D. A.; Dressman, J.; Tsume, Y.; Fotaki, N. Highlights from the 2020 AAPS 360 Annual Meeting. *Dissolut. Technol.* **2021**, 28 (2): 36–40. DOI: 10.14227/DT280221P36.
2. Mann, J.; Cohen, M.; Abend, A.; Coutant, C.; Ashworth, L.;

Shaw, R.; Reynolds, G.; Nir, I.; Shah, V.; Shaw, S.; Patel, A.; Lu, X.; Cicale, V.; McCallum, M.; Patel, S.; Topolski, J.; Prüfer, S.; Tomaszewska, I.; Kourentas, A.; Mueller-Zsigmondy, M.; Williams, J.; Ainge, M.; Berben, P.; Bouquellé, A.; Abrahamsson, B.; Karlsson, A.; Varghese, R.; Li, F.; Orce, A.; Nickerson, B.; Shao, X. Stimuli to the revision process: The case for apex vessels. *Dissolut. Technol.* **2021**, 28 (4), 6–23. DOI: 10.14227/DT280421P6.

3. Fotaki, N.; Klein, S.; Eds. *In Vitro Drug Release Testing of Special Dosage Forms*. Wiley, 2019.
4. Zampieri, P.; Flanagan, T.; Meehan, E.; Mann, J.; Fotaki, N. Biopharmaceutical understanding of excipient variability on drug apparent solubility based on drug physicochemical properties: case study—hypromellose (HPMC). *AAPS J.* **2020**, 22, 49. DOI: 10.1208/s12248-019-0411-1.
5. Zampieri, P.; Flanagan, T.; Meehan, E.; Mann, J.; Fotaki, N. Biopharmaceutical understanding of excipient variability on drug apparent solubility based on drug physicochemical properties. Case study: superdisintegrants. *AAPS J.* **2020**, 22, 46. DOI: 10.1208/s12248-019-0406-y.
6. Zampieri, P.; Flanagan, T.; Meehan, E.; Mann, J.; Fotaki, N. Impact of magnesium stearate presence and variability on drug apparent solubility based on drug physicochemical properties. *AAPS J.* **2020**, 22, 75. DOI: 10.1208/s12248-020-00449-w.
7. Zampieri, P.; Flanagan, T.; Meehan, E.; Mann, J.; Øestergaard, J.; Fotaki, N. Biopharmaceutical implications of excipient variability on drug dissolution from immediate release products. *Eur. J. Pharm. Biopharm.* **2020**, 154, 195–209. DOI: 10.1016/j.ejpb.2020.07.014.
8. *The Use of Physiologically Based Pharmacokinetic Analyses—Biopharmaceutics Applications for Oral Drug Product Development, Manufacturing Changes, and Controls Guidance for Industry*; Draft Guidance for Industry; U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), October 2020.
9. *Evaluation of Gastric pH-Dependent Drug Interactions with Acid-Reducing Agents: Study Design, Data Analysis, and Clinical Implications Guidance for Industry*; Draft Guidance for Industry; U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), November 2020.