Meeting Report: AAPS Workshop on Dissolution Testing and Bioequivalence

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The workshop in La Plata, Argentina, was hosted by the National University of La Plata on March 7 and 8, 2013, with all presentations translated into either English or Spanish. All the sessions were followed by a Q&A panel discussion. The two chairs of the Organizing Committee were Dra. Vivian A. Gray and Dra. María Guillermina Volonté. The members of the Organizing committee were Lic. Pablo Quiroga, Msc; Lic. Arturo Hoyia; Dr. Raimar Löbenberg; and Dra. María Esperanza Ruiz. The Workshop was cosponsored by the AAPS In Vitro Release and Dissolution Testing Focus Group.

Opening remarks were given by María Guillermina Volonté from the National University of La Plata followed by four speakers in the morning session. The first talk, given by Vivian Gray from V. A. Gray Consulting, was titled “Method Development and Setting Clinically Relevant Dissolution Specifications, including Quality by Design.” Her talk gave principles needed to develop a meaningful dissolution test, one that follows the concepts of QbD. The emphasis was on understanding the product release mechanism and knowing the critical quality attributes, leading to clinically relevant dissolution specifications. The role of variability was discussed, and ways to minimize it were explored. Then María Esperanza Ruiz of the National University of La Plata spoke on “Biopharmaceutical Relevance of the Comparison of Dissolution Profiles.” The performance of the main methods proposed for the comparison of percent dissolved versus time curves was analyzed comparatively to propose a more biorelevant combined approach for the comparison of dissolution profiles of multisource drug products. The best correlations were found when the result of the $f_2$ similarity factor was combined with a measure of the dissolution extent (e.g., area under the curve). This combined approach gives a robust and informative result with the most biopharmaceutical relevance.

After the break, Arturo Hoyia of the National University of La Plata discussed “Impact of API Solid-State Properties on Dissolution and Bioavailability.” BCS Class IIa and IIb APIs with absorption limited by dissolution rate and solubility, respectively. Reducing API particle size, selecting crystal habit, and increasing solid wettability can enhance the dissolution/absorption of Class IIa APIs. To increase absorption of very low solubility Class IIb APIs, supersaturated drug delivery system (SDDS) are used, in which a high energy solid form (HESF) (metastable polymorph, unstable amorphous API) can dissolve at a high rate and reach high apparent solubility in gastrointestinal fluid (GIF) during enough time to be absorbed. In these cases, an HESF must be formulated as a solid dispersion containing excipients that stabilize the solid state and inhibit or minimize API precipitation in solution. The session ended with Maria Cruanes from Merck giving a presentation on “Biorelevant In Vitro tools to Guide Dissolution Method Development of Low Solubility Compounds: Critical Excipients and Critical API Attributes.” She stated that the purpose of in vitro tools is to aid in understanding the mechanism of drug release, screen absorption-enhancing excipients, probe API and formulation attributes, save resources, and speed up development.

She described the tool workflow as beginning with in vitro screening, then proceeding to silico simulations, followed by in vivo (animal) studies and lastly in vivo (human) studies. She gave three examples of the efficient use of this tool workflow design.

In the afternoon, Vivian Gray described the American Association of Pharmaceutical Scientists (AAPS), which cosponsored this event. She highlighted the availability of e-membership for Argentinean scientists. The next speaker, Raimar Löbenberg from the University of Alberta, Canada, discussed “Bioequivalence in the Americas Using the WHO Guidelines: An Overview.” He began his presentation by defining bio waivers as based on sponsor bioequivalence tests performed with in vitro dissolution instead of a pharmacokinetic study. The method is used in the approval of generics, approval of products at lower doses, or scale-up and post-approval changes (also known as Variations at EMA). He described how the Biopharmaceutics Classification System (BCS) has changed drug regulations. He showed how BCS is interpreted differently by FDA, EMA, JP, and WHO. He also presented several case studies from South America. The problem with insufficient comparator products was discussed, and he stated that global comparator products are needed. He presented the next talk, “Interchangeability of Multisource Products—How to Use In Vitro Methodology,” which was prepared by Johannes Krämer of PHAST. This talk began with several definitions such as interchangeability, pharmaceutical equivalence, bioavailability, drug product performance, and bioequivalence. The experimental design of dissolution testing as a QC test and for product comparison was provided. An example of in vitro and in vivo performance was discussed. In vivo and in vitro correlations (IVIVC) were defined and referenced. He went on to show that BCS is linked to dissolution and absorption factors $D_n$, $D_o$, and $A_o$. He concluded with the expectations of IVIVC for immediate-release products based on...
The Provision ANMAT Nº 5040/06 establishes the regime of good practices in the implementation of BE studies. This document refers to the guidelines and requirements for information, as well as the documentation to apply for authorization to conduct a study of BA/BE.

Finally, the Guideline for Good Laboratory Practices in Bioanalytical Centers establishes the requirements to be met by institutions charged for performing the analytical stages of BA/BE studies. They are technically responsible for the truthfulness of the data and information for all processes.

The second speaker, Yanina Rodriguez also from ANMAT, discussed "Standardization of Caco-2 Cell Culture as In Vitro Model for Intestinal Permeability." She introduced the concept of permeability based on the BCS and explained different methods for determining the intestinal permeability of APIs. She explained the Caco-2 cultured system and showed some results obtained in their laboratory. The third speaker was Nikoletta Fotaki from University of Bath, UK. Her topic was "Apparatus 4, Flow-Through Cell, Fundamentals and Applications." She pointed out that in particular, the flow-through cell apparatus is very useful for low solubility drugs, microparticulates, implants, suppositories, and controlled-release formulations. The key features of the apparatus were then described such as the use of an open system for samples that require a high volume of medium and a closed system for samples requiring a low volume of medium (i.e., 27 mL/sample). The key difference between these configurations is that in using an open system, the raw data are obtained in noncumulative form (amounts dissolved at specific time intervals) instead of in the usual cumulative profiles. She explained that the flow-through cell could also be operated under laminar flow conditions where the sample is situated on a bed of glass beads in the cell column or simply placed in the open column under turbulent flow conditions. She discussed several advantages such as the ability to change medium and flow rate within a single run; efficient simulation of intraluminal hydrodynamics; use of long duration test runs without the problem of evaporation; provision for special dosage forms (floating dosage forms, implants, suppositories); avoidance of carry-over effects; facilitation of IVIVC; and correspondence of a single profile to the release in the entire GI lumen. However, there are several disadvantages. A high volume of medium is required when used as an open system and additional training is needed compared with the use of standard USP Apparatus 1 or 2, for example. Using the flow-through cell apparatus is labor-intensive, and filtration efficiency may be an issue when using Apparatus 4 with biorelevant media. She then presented several case studies using Apparatus 4.

After the break, Nikoletta Fotaki presented the next talk, “IVIVC According to USP General Chapter <1088> In Vitro and In Vivo Evaluation of Dosage Forms,” which was prepared by Johannes Krämer. Through practi-
of the mode of drug product administration. His research products becomes controversial for all patients regardless among others. Then, interchangeability of bioequivalent drug administration protocols (day-night/fed-fasting), different T/R ratios under two different (time/condition) opposite T/R ratios, or the same individual could display ratio, and hence different subpopulations could present variability of the test/reference (T/R) drug-exposure profiles do not account for the inter- and intra-individual to the Bioequivalence Study.” Mean drug concentration from the University of the Republic (Uruguay). His presentation was “New Clinical Approaches to the Bioequivalence Study.” Mean drug concentration profiles do not account for the inter- and intra-individual variability of the test/reference (T/R) drug-exposure ratio, and hence different subpopulations could present opposite T/R ratios, or the same individual could display different T/R ratios under two different (time/condition) drug administration protocols (day-night/fed-fasting), among others. Then, interchangeability of bioequivalent products becomes controversial for all patients regardless of the mode of drug product administration. His research group at the Bioavailability and Bioequivalence University Center for Medicines Evaluation (Uruguay) has found different T/R drug plasma concentration ratios when women and men or when fasting and coprandial administration were analyzed. The main reason why two pharmaceutical products were dissimilarly discriminated seems to lie in the gastric residence time. In women and under coprandial administration, there is a delay in gastric emptying, and thus the drug has more time to reach the intestinal absorption site. In men and under fasting administration, rapid gastric emptying does not give enough time for a drug that is delivered at different rates from test and reference dosage to enter the intestine equally. To give accurate information about the best clinical setting to assure both effective and safe interchangeability between bioequivalent drug products, he proposed to extend bioequivalence research assaying in different subpopulations (sex-, age-, genotype-related) and under different administration setting (day-night, fed-fasting, winter-summer, resting-physically active, etc.). Current bioequivalence assessments are rigorous enough to give commercial authorization; however, beyond therapeutic equivalence, biopharmaceutical equivalence should be precluded when two drug products containing the same active ingredient are declared bioequivalent. Vivian Gray closed the workshop with remarks of thanks to the Argentinean organizers and speakers and appreciation for the fine hospitality shown to the AAPS Focus Group speakers. She remarked on the high quality of speakers and audience participation and thanked the translators and organizers for an excellent job.

There were 133 attendees from eight countries: Argentina, Brazil, Canada, Chile, Paraguay, Uruguay, United Kingdom, and United States. There were many student attendees with nine universities in Argentina represented.