

Meeting Report: Dissolution Testing, Biowaiver, and Bioequivalence

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DAY 1 PART 1

The first joint workshop sponsored by the American Association of Pharmaceutical Scientists (AAPS) and the Peruvian College of Pharmacists “Colegio Quimico Farmaceutico del Peru (CQFPE)” was entitled “Dissolution Testing, Biowaiver, and Bioequivalence” and was held in Lima, Peru on May 3–4, 2019. The meeting was organized by the AAPS In Vitro Release and Dissolution Testing (IVRDT) Community and the Peruvian College of Pharmacists Program Committee Chairs, led by **Susan D'Souza (Tenaya Therapeutics, USA)** and **Luis Moreno Exebio (Instituto Nacional de Salud, Ministry of Health, Peru)**. There were two additional workshops held in Cusco, Peru on May 6–7 and Ayacucho, Peru on May 9–10. The goals and objectives of the workshops are given below.

1. Discuss the use of dissolution as a tool for drug development, biowaiver, and bioequivalence studies.
2. Present Peru research activities and collaborations in dissolution, apparatus calibration, bioequivalence, and drug specification setting topics.
3. Networking for research collaboration, knowledge sharing, education, and industry exchange in dissolution, biowaiver, and bioequivalence topics.
4. Disseminate Peru's new regulatory information for dissolution testing and bioequivalence in Peru and provide information on dissolution method development, current Good Manufacturing Practices (cGMP), and generic product quality.

Marcial Torres (Dean, Peruvian College of Pharmacists) welcomed the workshop's national and international participants and introduced the aims of the workshop. In his opening remarks, Marcial stated that the workshop was part of the Pharmacist/Chemist College of Pharmacists' celebration. In this regard, he set the stage for the first session for which the theme was “**Dissolution, Interchangeability, and Regulation**,” moderated by Luis Moreno Exebio.

Vivian Gray (V. A. Gray Consulting) gave the first talk titled: “The role of dissolution in generic industry.” She discussed the important factors of standardized methodology, linkage to in-patient performance, and use in biowaivers and bridging studies. Methodology issues were explored and setting specification limits were examined. **Dr. David Nicolas Salisrosa (Directorate General of Drug Supplies and Drugs [DIGEMID], Peru)** spoke on “Current regulations of bioequivalence in Peru.” He presented an overview of the legal framework including the new regulations and implementation in alignment with the World Health Organization. He mentioned that the new regulation states that all pharmaceutical products, including multisource products, should be used in a country only after approval by the national or regional authority. He discussed the timelines covered by the patents of the innovator products and highlighted that a multisource pharmaceutical product needs to conform to the same standards of quality, efficacy, and safety as those required of the innovator's product. He also shared in detail the suitable test methods to assess equivalence including in vivo and in vitro studies.

The next speaker was **Vivian Gray**, whose talk was titled “FDA requirements in dissolution testing for evaluation and approval of generic drugs in solid oral dosage forms.”

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She began sharing Abbreviated New Drug Application (ANDA) queries and data requests. The new FDA guidance on highly soluble drugs was presented and similarity factor (f_2) issues were explored. There was a discussion on problems encountered when filing an ANDA. The session ended with the next speaker, **Sandra Suarez Sharp (United States Food and Drug Administration [FDA])**, who spoke on “The role of biopharmaceutics in the regulatory approval of drug products with a focus on modeling and simulation.” She discussed the role of dissolution testing in drug product development and the importance of developing a dissolution method that is not only discriminating but also clinically relevant. She shared the current practices, considerations, and challenges on in-vitro in-vivo correlation (IVIVC) model validation and application. Comprehensive examples of potential applications of a physiologically based biopharmaceutics model (PBBM) in support of drug product quality were provided. Those examples include development of clinically relevance drug product specifications, verification of the design space, and biowaiver request in support of post-approval changes. In her concluding remarks, she noted that building a “clinical safe space” is a stepping-stone toward setting clinically relevant drug product specifications and towards “patient centric” drug product development.

DAY 1 PART 2

The second session theme was “**Modeling, Similarity Factor (f_2), Dissolution Applications.**” The panel discussion was moderated by Susan D’Souza.

Susan D’Souza gave an “introduction to American Association of Pharmaceutical Scientists (AAPS)”. She shared the IVRDT community mission, community activities, and objectives for 2020 and beyond. She encouraged participants to join the AAPS dissolution community to continue the discussion on dissolution topics and publish their work on dissolution.

Susan D’Souza presented the first talk of the session, “Influence of alcohol on dissolution tests,” where she discussed several in vivo and in vitro studies that have investigated alcohol-induced dose dumping (AIDD) in modified release dosage forms that contain opioids, centrally acting drugs, and drugs with a narrow therapeutic index. The next speaker was **Dorys Argelia Diaz (Pfizer, USA)**. Her talk was “Global scientific considerations for harmonization of comparison of dissolution profiles.” **Dorys Argelia Diaz** gave a second talk on “Complexities of comparisons of dissolution profiles.” She started her presentation explaining the role of dissolution similarity

assessment as a tool for drug development and for regulatory decisions for Biopharmaceutics Classification System (BCS)-based biowaiver requests and post-approval changes. She discussed the global divergent regulatory requirements to meet dissolution similarity requirements and the current complexities to demonstrate product similarity. Through examples, the talk highlighted the importance of early dissolution profile testing design and scientific and regulatory considerations for global comparative dissolution assessments. Dorys advocated for a dialog between industry, academia, trade association, and global regulatory health authorities to foster global harmonization of dissolution similarity requirements.

DAY 2 PART 1

On the second day, the first session theme was “**Generics, Biowaivers, and Peruvian in vitro Studies,**” moderated by Luis Moreno Exebio.

Sandra Suarez Sharp started the session with a presentation entitled “Setting clinically relevant drug product specification (CRDPS): biopharmaceutics perspective on information needed, approaches, and criteria.” She emphasized the importance of establishing CRDPS to guarantee consistent safety and efficacy profiles for the marketed product relative to those achieved by the clinical trial formulation. The challenges and various approaches for establishing a CRDPS were discussed.

Sandra Suarez-Sharp also gave the next talk on “Biowaivers approaches for solid oral dosage forms in new drug applications.” She presented in detail the types of bridging based on the level of risk following formulation or manufacturing changes. Dissolution testing was highlighted as one the key elements in biowaiver approaches (BCS-based biowaiver, IVIVC-based biowaiver, risk assessment, safe space) for solid oral dosage forms.

Luis Moreno Exebio continued the session by presenting “Equivalence studies in vitro: the Peruvian experience.” **Vivian Gray** ended the session by presenting a talk titled “Harmonization of EP and USP, new FDA guidances, proposed USP Chapters.” In this talk, the various dissolution-related chapters in EP and USP were compared for content, all the FDA guidances were summarized, emphasizing the several new guidances, and new USP chapters and monographs on dissolution topics were discussed.

DAY 2 PART 2

The afternoon session theme was “**Emerging Topics in Dissolution and Peruvian in vivo Studies,**” moderated by Miguel Grande Ortiz.

In the first talk, **Miguel Grande Ortiz** discussed the “Equivalence studies in vivo: the Peruvian experience.” **Susan D’Souza** continued the session speaking on the “Drug release from long acting injectables.” At the close of the workshop, **Javier Rodríguez Calzado (CNCC, Instituto Nacional de Salud, Peru)** presented “Statistical considerations of equivalence studies in vivo.” **Susan D’Souza**, past Chair of the IVRDT, closed the workshop with remarks of thanks to the Peruvian 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 thanked the organizers for the excellent job. The participants were very enthusiastic and engaged in the discussion, which indicated that the Workshop was a success.

SUMMARY

The workshop in Lima, Peru was well attended with more than 400 attendees from the industry, academia, and

regulatory members from the United States and Peru. This international workshop provided opportunities to inform and connect scientists in a direct dialog on current challenges in dissolution, biowaivers, and bioequivalence. The workshop also gave participants opportunities to discuss the current implementation of Peru legislation in interchangeability and bioequivalence. The question and answer session was very engaging. Attendees wanted to understand new Peru guidelines on registration requirements to establish interchangeability, familiarize themselves with new in vivo and in vitro assessment tools, and understand the various approaches to submit a biowaiver request.

The two additional workshops in Cusco and Ayacucho had similar programming with additional regional speakers; Vivian Gray, Dorys Argelia Diaz, and Susan D’Souza gave the same talks as they gave at the workshop in Lima.