Virtual Workshop Report: Approaches, Regulatory Challenges, and Advances in Bioequivalence, Dissolution Testing, and Biowaivers: Manila, Philippines, February 22–24, 2023

James E. Polli[1], Zhao Liu[2], Vivian A. Gray[3], Willison John E. De Luna[4], Andreas Abend[2], Michael Daniel C. Lucagbo[5], Jie Shen[6], Sandra Suarez-Sharp[7], Alicia P. Catabay[8], Leonel Santos,[9] and Bienvenido S. Balotro[10]*

[1]University of Maryland, MD, USA.
[2]Merck Sharp and Dohme, Rahway, NJ, USA.
[3]Dissolution Technologies, Hockessin, DE, USA.
[4]Philippine Food and Drug Administration, Alabang, Muntinlupa City, Manila, Philippines.
[5]School of Statistics, University of the Philippines, Diliman, Quezon City, Philippines.
[6]Northeastern University, Boston, MA, USA.
[7]Simulations Plus, Lancaster, CA, USA.
[8]De La Salle Medical and Health Sciences Institute, Cavite, Philippines.
[9]Eastern Analytical Symposium, Plainsboro, NJ, USA.
[10]College of Pharmacy, University of the Philippines, Ermita, Manila, Philippines.

e-mail: bsbalotro@up.edu.ph

INTRODUCTION

The virtual workshop, "Approaches, Regulatory Challenges, and Advances in Bioequivalence, Dissolution Testing, and Biowaiver," was held February 22–24, 2023, via the Zoom online platform. The conference was co-organized by the University of the Philippines College of Pharmacy (UPCP) and the American Association of Pharmaceutical Sciences-In Vitro Release and Dissolution Testing (AAPS-IVRDT) Community. The webinars were chaired by Vivian Gray (AAPS) and Dr. Bienvenido S. Balotro (UPCP) with Drs. Jie Shen, Nikoletta Fotaki, Imelda G. Pena, and Leonel Santos, and Assistant Profs. Jean Flor Casauay, Ethel Ladignon, Clinton Gomez, and Czarina Dominique R. De los Santos as members of the organizing committee.

The 3-day webinar series consisted of three scientific sessions on basic principles, challenges, and advances in dissolution technologies, bioequivalence (BE), and biowaivers.

Each session was followed by an open forum of the speakers and the participants. Pharmacists who completed the 3-day virtual workshop earned Continuing Pharmacist Education units.

The objectives of the webinars were as follows:

- Learn best practices in developing discriminating methods and increase knowledge of drug product characterization and dissolution testing

- Explore new concepts of modeling to support dissolution specifications

- Develop networking for research collaboration, knowledge sharing, education, and industry exchange in dissolution, biowaiver, and BE topics.

On the first day of the webinar series, there were 909 participants. On the second day, 778 attendees joined the event, and on the third and last day of the webinars, there were 754 participants. The participants included members of industry, regulatory and government agencies, professional organizations in pharmacy practice, academia, and other professionals interested in dissolution, BE, and biowaivers.

Day 1: Basic Principles

Day 1 began with welcome remarks and a program overview given by Vivian Gray and Dr. Bienvenido S. Balotro, respectively. Both served as co-chairs of the organizing committee. The first day of the program was moderated by Dr. Imelda G. Pena, who also presided over the open forum after the presentations. The first talk was by Dr. James E. Polli from the University of Maryland who presented "Biopharmaceutics Classification System (BCS)-Based Biowaivers ICH M9."

Dr. Polli's presentation introduced chemistry, manufacturing, and controls (CMC) activities and discussed some elements of the International Council for Harmonization (ICH) BCS M9 guidance. According to Dr. Polli, the ICH BCS M9 guidance was finalized in 2020 and is recognized worldwide. In M9, immediate-release (IR) oral dosage formulations of BCS Class I and III drug products with the same strength as the reference product may be eligible for a biowaiver. For about half of all drugs, in vitro testing to assess BE is globally acceptable. In vitro studies are sometimes better than conventional in vivo pharmacokinetic studies for assessing BE of IR solid oral dosage formulations. M9 is a notable step forward, as it is the first harmonized allowance of BCS-based regulatory relief, including in Japan.

Dr. Polli cited the importance of CMC activities during drug development and product life cycle management for product understanding, quality, and manufacturing. Although typically invisible to prescribers and patients, CMC activities allow ongoing product manufacturing and product quality control while implementing product lifecycle changes, such as excipients, process, and/or manufacturing location.

Dr. Polli also discussed ICH BCS M9 guidance on solubility, permeability, and excipients. Regarding solubility, M9 requires that the highest dose is soluble in 250 mL of aqueous media over the pH range of 1.2–6.8 at 37 ± 1 °C, where the highest dose is not necessarily the highest formulation strength (e.g., a tablet with 250 mg of drug substance) but the highest single therapeutic dose (e.g., two 250-mg tablets). Given that M9 is an alternative to an in vivo human BE study where presumably a single unit of the highest formulation strength is tested, the basis for preferring the highest single therapeutic dose dissolves in 250 mL to be highly soluble is not well described. However, M9 indicates that if the highest dose does not meet this criterion, but the highest strength does, additional data should be submitted to justify the BCS-based biowaiver approach.

With regards to permeability, M9 allows reliance on the Caco-2 monolayer method. Dr. Polli cited a recent workshop report that discussed the importance of global acceptance of permeability methods, opportunities to expand the use of biowaivers (non-Caco-2 cell lines, totality-of-evidence approach to demonstrate high permeability), and the future of permeability testing.

Dr. Polli also discussed the differences of excipients used between test and reference products in M9 related to drug class.

Dr. Zhao Liu (Merck) was the second speaker who presented on method development and setting clinically relevant dissolution specifications including the Quality-by-Design (QbD) approach. Dissolution testing serves as an important tool to guide formulation design and product assessment (and is required for quality control) and surrogate for bioperformance if an in vivo correlation is established. Commonly used compendial dissolution equipment, i.e., United States Pharmacopoeia (USP) apparatus 1–7, which have been harmonized among USP, European Pharmacopoeia (EP), and Japanese Pharmacopoeia (JP), are used for different dosage forms based on their properties and intended use. Different detection methods (spectrometric and chromatographic) were compared, and their advantages and applications were discussed. Spectrometric detection is rapid but needs to demonstrate specificity, whereas the chromatographic method requires more time and expensive equipment but has a wider dynamic range. Automated sampling equipment has been increasingly used for dissolution testing, which also needs to be assessed and compared to manual sampling.

Dr. Liu also discussed a commonly observed dissolution issue known as coning, which is caused by an artifact of the dissolution vessel and hydrodynamics of the dissolution media. The current solution, i.e., apex or peak vessel, can efficiently solve the issue.

Finally, Dr. Liu talked about dissolution as a critical aspect of the QbD approach in drug product and method development. This includes consideration of the properties of the active pharmaceutical ingredient (API), such as BCS class, pKa, solubility, dose range, and whether the product is the salt form. For IR oral dosage forms, particle size distribution, solubility, and diffusion coefficient of the API are critical to the dissolution rate, according to the first principle of API dissolution mechanism (Nernst–Brunner and Noyes-Whitney theories). Formulation of critical quality attributes (CQAs) and manufacturing

critical process parameters (CPPs) can affect drug product dissolution performance, including raw materials (API and excipients), blending and lubrication, compression, and film coating, all of which can be assessed using a fishbone diagram. In addition, analytical method parameters are critical, such as the dissolution apparatus, rotational speed, media, and surfactant selection. In general, the strategy of dissolution method development is based on BCS classes, i.e., for class 1 and 3 are highly soluble compounds, FDA guidance should be used. For class 2 and 4, as well as class 1 and 3 drugs that do not meet FDA guidance, dissolution might be the rate-limiting step for absorption. For amorphous solid dispersion formulations, dissolution can be utilized to detect crystalline API content in the drug product.

The third speaker was Vivian Gray (*Dissolution Technologies*), who presented "Challenges when Developing a Discriminatory Dissolution Method and Aspects of Method Validation." Vivian began with defining a "discriminatory" method and why it is necessary, reiterating that discriminating methods can contribute to specifications that distinguish between bioequivalent and bio-inequivalent batches. She reviewed the necessary characteristics of a discriminatory method and gave resource materials with regulatory and industry expectations. The primary references were European Medicines Agency (EMA) reflection papers and *USP* chapter <1092> The Dissolution Procedure: Development and Validation. Vivian outlined how to develop a discriminatory method. The first step is to identify CQAs related to the drug substance, drug formulation, and drug product manufacturing process. She gave examples in each category. The second step is to identify which of these attributes affect the in vivo release. The third step is to manufacture a drug product that reflects the upper and lower limits (± 20%) of that variable, ideally about two or three variations for each category (drug, drug formulation, manufacturing process). The fourth step is to run these variation products, preferably one variable at a time versus the target product. Lastly, compare the dissolution profiles and determine if there are significant differences among the variables and the target. Hopefully, there will be at least two or three variables that the method can pick up differences for. If not, then go to a backup method that is possibly more complex and may not achieve sink conditions. In addition to a discriminatory method, there should be an in vivo linkage element to the in vitro method data.

Vivian went on to discuss validation aspects related to the sample analysis. This includes the critical validation discriminatory method, which should have an in vivo linkage element to the in vitro discriminatory method parameters of linearity, selectivity, robustness, accuracy, intermediate precision, carryover, filter selection, sinkers, and stability. Robustness and intermediate precision are early indicators of issues that could develop in method transfer. The importance of critical factors in the testing method was emphasized.

Vivian ended her presentation by sharing resources available to the dissolution analyst. This includes websites for the USP Pharmacopeial Forum and USP dissolution compendial tools, the AAPS website with access to several journals, FDA dissolution methods database, and USP dissolution methods database. She also provided the website for *Dissolution Technologies* journal, adding that the website is searchable and open access. She also gave a list of books of interest.

The first day of the program ended with an open forum moderated by Dr. Imelda G. Pena.

Asst. Prof. Jean Flor Casauay gave a synopsis of Day 1 and introduced the opening of Day 2.
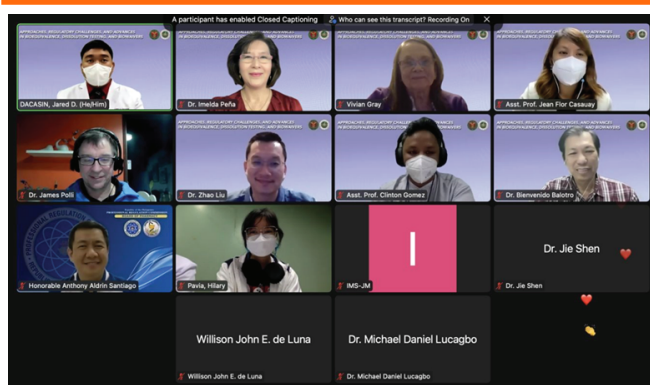
Day 1 virtual workshop attendees and speakers.

Day 2: Challenges
Willison de Luna from the Philippine Food and Drug Administration (FDA) gave the first talk on the second day on "Regulatory Challenges on Dissolution, BA/BE and Biowaivers: The Philippine Experience." Republic Act 9711 and its Implementing Rules and Regulations mandates the FDA to ensure that all drug products comply with the standards of quality, safety, and efficacy. In line with this, Mr. De Luna said that a satisfactory BE study report or biowaiver shall be provided as proof of product interchangeability with the reference or innovator drug product. This is required prior to issuance of a marketing authorization, i.e., Certificate of Product Registration, for a generic drug product in the Philippines. In addition, the FDA conducts inspections of BE testing centers and

clinical laboratories handling the clinical, bioanalytical, and statistical phases of BE studies.

The FDA faces various challenges in implementing the guidelines on product interchangeability. Currently, the number and technical capacity of evaluators handling product dossier review including equivalence studies and inspectors of BE testing centers needs to be augmented. In addition, the coverage of drug products requiring BE studies is limited as the guidelines in the Philippines currently covers oral solid dosage forms only. On the other hand, industry stakeholders encounter difficulties in the conduct and compliance with BE studies, particularly in the costs and expenses related to the BE studies, such as the conduct of clinical trials, procurement of reference drug products (especially for those not registered in the Philippines), and validation of bioanalytical methods. These factors may affect compliance with the requirements and guidelines for registration, leading to delayed availability of generic drug products in the market.

Dr. Andreas Abend presented the second talk entitled, "Challenges with Dissolution Similarity Assessment." He stated that assessing the impact of manufacturing changes on product quality is an important part of pharmaceutical product lifecycle management. Formulations that were used in clinical trials to establish safety and efficacy, or generic drugs that are deemed equivalent to a reference listed drug, all sooner or later experience changes in their composition and or manufacturing process. Thus, it is critical to have reliable tools to ensure that these changes do not negatively impact product quality. A major concern is that such changes may negatively impact drug in vivo performance, resulting in poor efficacy or safety or both. Rather than performing unnecessary clinical studies, industry and regulators rely on dissolution testing to assess potential negative impacts of certain manufacturing changes. The level of testing and the acceptance criteria required to assess the effect of manufacturing changes on in vivo performance is proportional to the risk to the patient. The US FDA's Scale-up and Post approval Change (SUPAC) guidance documents classify changes as minor, moderate, and major. For minor and moderate changes, in vitro dissolution testing is generally accepted to assess the impact of changes; if the required acceptance criteria are met, then the changes are supported. In contrast, major changes, which are likely to impact bio-performance, typically require demonstration of BE before the changes are approved. Changes that are unlikely to impact bio-performance (i.e., minor changes) are supported when the approved quality control dissolution specifications

are met. For moderate changes that could impact bio-performance, comparative dissolution testing is typically required.

The amount of dissolution testing required to support formulation changes for IR products further depends on the physicochemical properties of the API. Drugs with high aqueous solubility belonging to the BCS class 1 and 3 are considered low risk, and if their dissolution rates are not considered very rapid (i.e., 85% dissolved is not released within 15 min), then dissolution profiles generated in a single aqueous medium are usually evaluated for similarity. In case of poorly soluble drugs, further distinctions are made between drugs with high permeability (i.e., more than 85% absorbed after oral administration) and low permeability (those not meeting this criteria). Even moderate formulation changes require BE studies for drugs belonging to BCS class 4. However, for class 2 drugs, dissolution profile comparisons in four aqueous media plus water are required (use of surfactants is not allowed). A differentiation based on the BCS class does not apply for manufacturing changes such as site, process, or scale. Nevertheless, these changes are also categorized as minor, moderate, and major, and the level of data to support these increases with increasing potential to negatively impact product performance. Lastly, Dr Abend stated that BCS-based biowaivers are supported by comparative dissolution testing for class 1 and 3 drugs under certain conditions (per ICH).

The most common approach to assess dissolution profile similarity is the similarity factor, f_2. Introduced by Moore and Flanner in 1996, this mathematical approach is used to decide if two profiles are sufficiently similar in support of manufacturing changes or biowaivers. Similarity factor analysis has since been applied throughout the pharmaceutical industry and regulatory agencies. Unfortunately, health authorities are not aligned on the conditions under which similarity testing is conducted nor the acceptance criteria (albeit usually $f_2 \geq 50$ is typically considered acceptable). In case f_2 cannot be applied due to high variability in the amount of drug dissolved at individual sampling timepoints, agencies offer other mathematical approaches.

Interestingly, f_2 does not allow for type 1 error control (i.e., the risk of declaring profile similarity when profiles are dissimilar), and the use of superior statistical methods is not allowed. The fundamental problem with any profile similarity assessment is not the mathematical treatment of the data, but the discretionary power of the in vitro dissolution method to accurately assess how product

changes impact the in vivo performance. Without a clear link to in vivo performance, a dissolution test has unknown clinical relevance, and one cannot be certain that two profiles that are similar based on mathematical evaluations are equivalent in vivo. Likewise, two product variants with dissimilar in vitro profiles according to f_2 or other statistical tests may have similar in vivo performance. To overcome these fundamental challenges, a group of scientists (Abend, Hoffelder et al) developed a decision tree and best practices when dissolution data are used to assess the impact of manufacturing changes on product quality. The question at the core of the decision tree is whether or not an in vivo link between dissolution and pharmacokinetic point estimates exists. When this link has been established, then the dissolution method is clinically relevant, and decisions can be made based on comparing new dissolution profiles (after manufacturing changes) with the profiles used to establish the dissolution specification. If the dissolution profile representing a new manufacturing process falls within an acceptable dissolution safe space, then products made under these conditions are unlikely to negatively influence in vivo performance. However, if a safe space does not exist, then appropriate statistical methods with type 1 error control should be used.

Next, Dr. Michael Daniel Lucagbo gave a talk about statistical assessment of dissolution similarity. Dissolution profile comparisons are important in evaluating postapproval changes. Such comparisons should be based less on subjective assessments and more on scientific evidence and rigorous statistical procedures. Dr. Lucagbo presented some statistical approaches to assess dissolution similarity. Let μ_1=(μ_11,…,μ_1p)' and μ_2=(μ_21,…,μ_2p)' denote the population (p) mean values of the dissolution profiles of the test and reference products. When comparing these two dissolution profiles, regulatory guidance emphasizes f_2, given below.

$$f_2 = 50 \log_{10} \left(\frac{100}{\sqrt{1 + \frac{1}{p} \sum_{t=1}^{p} \left(\mu_{1t} - \mu_{2t} \right)^2}} \right)$$

The similarity factor is a monotone function of the so-called Euclidean distance (ED), whose formula is shown below. Consequently, f_2 essentially provides the same information as the ED.

$$ED = \sqrt{\sum_{t=1}^{p} \left(\mu_{1t} - \mu_{2t} \right)^2}$$

Dr. Lucagbo also cited other methods to compare dissolution profiles besides f_2 that are available. For example, another method that depends on the ED is the quadratic mean difference (QMD), which is computed as $QMD = \sqrt{(1/p)\, ED^2}$. Hoffelder et al. provide in-depth discussion of model-independent statistical methods to evaluate similarity.

Instead of the ED as a measure of distance, many statisticians prefer the (squared) Mahalanobis distance (MD), which is computed as shown below:

$$MD = \left(\boldsymbol{\mu}_1 - \boldsymbol{\mu}_2 \right)' \boldsymbol{\Sigma}^{-1} \left(\boldsymbol{\mu}_1 - \boldsymbol{\mu}_2 \right)$$

where Σ is the common covariance matrix. Dr. Lucagbo provided references for the statistical tests for dissolution profile similarity using MD (e.g., Tsong et al.). For this test, rejection of the null hypothesis is an indication of similarity of dissolution profiles. Another reference is Wellek, who also provides an exact MD-based statistical test for similarity under a multivariate normal framework.

Dr. Liu moderated the panel discussion at the end of the second day.
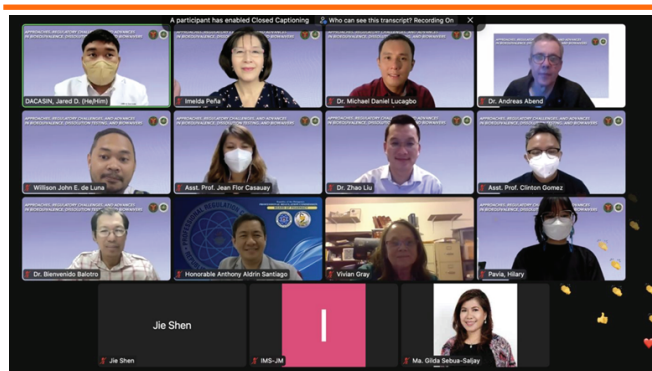
Day 2 virtual workshop attendees and speakers.

Day 3: Advances
Dr. Imelda G. Pena gave a synopsis of the second day and opened the third day of the event.

Dr. Shen gave the first presentation, "In Vitro-In Vivo Correlation (IVIVC) of Complex Dosage Forms." She introduced the IVIVC and its categories, history, and current landscape. She discussed IVIVC development and validation in detail, highlighting considerations for formulation selection, in vitro dissolution method development and modelling, and in vivo study design and deconvolution techniques. Dr. Shen shared two case studies: 1) an extended-release formulation (upadacitinib, a BCS class I compound for rheumatoid arthritis) and 2) a long-acting suspension product (INVEGA SUSTENNA, a schizophrenia treatment), exemplifying the key steps of IVIVC development and validation. Dr. Shen ended her talk with recent exciting advances in demonstrating a level A

IVIVC for complex long-acting polymeric parenterals with an example of risperidone poly(lactic-co-glycolic acid) (PLGA) microspheres in a rabbit model.

Dr. Sandra Suarez-Sharp (Simulations Plus) gave the next presentation on "Mechanistic modeling as an In Vivo Linkage to In Vitro Dissolution Methods." Incorporating QbD principles into the pharmaceutical industry has broadened the scope of dissolution testing beyond its traditional role of supporting biowaivers after significant CMC changes, as outlined in the SUPAC guidance. The significance of whether an attribute, parameter, or in-process control is deemed critical to a drug product performance is contingent upon meeting dissolution criteria, irrespective of wide variations in those specific attributes/parameters. Consequently, dissolution testing assumes a pivotal role that cannot and should not be replaced solely by controlling critical material attributes (CMAs) and CPPs. This necessity arises because dissolution testing stands as the sole in vitro assessment capable of probing the extent and rate of in vivo drug release.

Despite the well-established value of dissolution testing in drug product development, its recognition as a key facilitator of "enhanced" drug product understanding often encounters obstacles due to uncertainties surrounding predictive ability and clinical relevance. This challenge is particularly pronounced for drug products containing BCS class 2 and 4 compounds and modified-release formulations. Dr. Suarez's presentation addresses the transition from discriminative to bio-predictive dissolution methods, acknowledging the need to establish relationships between critical attributes/process parameters, dissolution, and systemic exposure. Failure to comprehend these relationships can lead to overly broad, excessively stringent, or entirely irrelevant drug dissolution acceptance criteria, hindering our ability to determine whether the method is overdiscriminating, thereby imposing hurdles on companies, or under discriminating, thereby posing risks to patients.

A recommended approach involves initiating or considering the implementation of risk assessment and prior knowledge to identify potential CMAs, CPPs, and critical formulation variables (CFVs) that are likely to impact both in vitro and in vivo drug product performance. This approach ideally includes design of experiments (DoE) studies to confirm the level of risk and, more crucially, employing dissolution as an endpoint in these studies to identify formulation variants with extreme dissolution profiles. These variants can then be evaluated in relative BA/BE studies to establish the essential in vivo link and determine the level of rank order (over/under discriminating method), crucial for constructing an in vitro-in vivo relationship (IVIVR) or IVIVC and ultimately defining a safe space.

Although IVIVCs have been considered the gold standard for establishing the essential link to bolstered dissolution testing, the adoption of physiologically based biopharmaceutics modeling (PBBM) has gained traction within the scientific and regulatory communities for such roles. The strength of PBBM lies in its ability to leverage extensive data generated across the product development process, including biopharmaceutics, in vitro, and clinical pharmacokinetic data, to create a physiologically meaningful connection between in vitro and in vivo aspects. Coupled with virtual BE, this approach results in the establishment of a safe space. Consequently, this approach facilitates the construction of the crucial in vitro-in vivo link and empowers dissolution testing to set its boundaries, permitting the rejection of batches falling beyond this safe space. Ultimately, this leads to clinically relevant and bio-predictive dissolution testing, and thus manufacturing flexibility.

PBBM serves as a catalyst in solidifying the essential in vitro-in vivo link by seamlessly integrating formulation and manufacturing factors with dissolution to forecast their impact on systemic exposure. PBBM fosters a mechanistic understanding of in vivo drug release and its interaction with physiology, culminating in the development of IVIVRs. This approach offers a simplified route to biowaivers, particularly for IR drug products, where the success rate of IVIVCs has historically been limited. Dr. Suarez-Sharp's presentation underscores the importance of a fundamental shift in the pharmaceutical industry, promoting an approach to drug development that prioritizes early bio-predictive measures, with PBBM taking on a pivotal role in this transformation.

The final presentation was given by Dr. Alicia P. Catabay (De La Salle Medical and Health Sciences Institute [DLSMHSI]), "BA/BE Studies for Drug Development and In Vivo Drug Product Performance Evaluation." Dr. Catabay talked about the Center for Biopharmaceutical Research (CBR) at DLSMHSI. The CBR was established primarily to support the Philippine government's National Drug Policy and, in particular, to provide quality assurance by proving BE testing of locally manufactured pharmaceutical products in comparison with innovator drugs or those drugs already available in the market. Instituted in 1997, the CBR was originally a tripartite project of the Department of Pharmacology of the DLSMHSI College of Medicine, Novartis Inc., and the Bureau of Food and Drugs (now known as the Philippine FDA).

Dr. Catabay emphasized the role played by the CBR in ensuring the quality and efficacy of generic medicines. Currently, the BA/BE unit is the only fully independent academic-based BE testing laboratory in the Philippines, operating under Good Clinical Practices (GCP) and Good Laboratory Procedures (GCP). It was the first of five centers to be accredited by the Philippine FDA for BE studies, and it has garnered the Center of Excellence award given by the United States Pharmacopeia. The BA/BE unit conducts six to eight studies per year and boasts a 24-bed testing facility, recently upgraded in July 2019. Due to the pandemic, operation of the CBR was put on hold until it reopened in 2022, when partner laboratories started sending in requests for BA/BE testing. Today, the CBR is a primary center for establishing the BE of locally made drugs, ensuring the safety, efficacy, and quality of these drugs that are more accessible to the Filipino public.

The bioanalytical component of BA/BE testing is outsourced because there is no accredited bioanalytical laboratory in the Philippines. Samples are sent to Indonesia, Singapore, and Malaysia. The CBR is exploring partnerships with different funding agencies to establish a bioanalytical laboratory.

Asst. Prof. Ethel Andrea C. Ladignon facilitated the open forum and gave a synopsis of the webinars.

Dr. Leonel Santos gave the closing remarks and thanked all the presenters and participants who joined the 3-day virtual workshop.
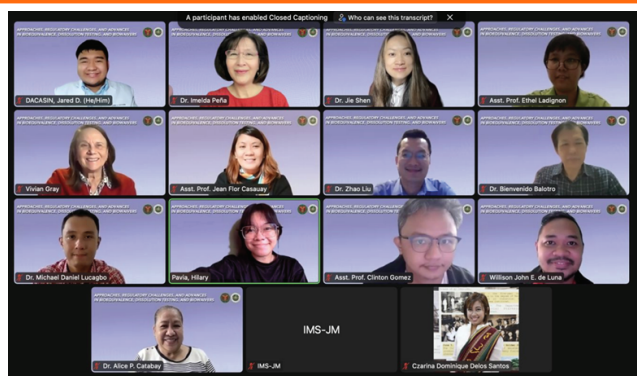
Day 3 virtual workshop attendees and speakers.

ACKNOWLEDGEMENTS

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