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PERSPECTIVE

Iberoamerican Pharmacometrics Network Congress 2018 Report: Fostering Modeling and Simulation Approaches for Drug Development and Regulatory and Clinical Applications in Latin America

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This report provides a brief description of the 2018 Red Iberoamericana de Farmacometría (RedIF) Congress that took place in Guadalajara (Mexico) on November 7–9, 2018. The meeting aimed to foster modeling and simulation (M&S) approaches for drug development, regulatory sciences, and clinical application in Latin America. The organizations that cosponsored the meeting were the following: University of Guadalajara, International Society of Pharmacometrics (ISoP), International Pharmaceutical Federation (FIP), Clinic of Chronic Diseases and Special Procedures (CECyPE), Zurich Pharma, Pharmet (Pharmometrica), Lixoft, and ICON.

IBEROAMERICAN PHARMACOMETRICS NETWORK

Pharmacometrics and systems pharmacology have emerged in the developed world and were established as new paradigms in drug discovery and development. Model-informed decisions are proved to reduce economic costs and favor ethics, focusing on optimizing clinical trial designs as well as on extracting the meaningful and relevant information from the data, far beyond statistically significant *P* values.[1–4] The application of this quantitative framework for dose optimization and therapeutic innovation is on its way to change the rationale in which drugs are used in the clinical setting. As stated before by Pillai *et al*.,[5] for the developing world these approaches represent an "opportunity to bring modern methods into play" and thus push forward the development of drugs, therapeutic strategies, and basic research in pharmacology and pharmaceutical innovation in our countries. The implementation, standardization, and acceptance of these disciplines entail an effort that should be concertedly performed by means of scientific exchange and collaboration between all stakeholders.

In this context, the RedIF was founded in 2017 as the natural association of research groups from Argentina, Brazil, Chile, Colombia, Cuba, Mexico, Panama, Spain, and Uruguay. The main interest of this network is the promotion and advancement of pharmacometrics in Latin America, creating a multidisciplinary framework aimed to (i) support the learning process about the development of mechanistic population pharmacokinetic/pharmacodynamic (PK/PD) models, (ii) promote and spread the use of pharmacometrics in Latin America, (iii) promote multicenter population-based PK/PD and disease progression studies in Latin America and the interchange of scientists across country members, (iv) create a database about the Latin American population to help researchers in meta-analysis studies and therapeutic drug monitoring, and (v) harmonize nonclinical and clinical practices to facilitate the exchange of information to fulfill registration requirements of new medications in Latin America.

THE PRESENTATIONS

The Chairs of the meeting, Mr Jaime Gutiérrez Chávez (Mexico) and Dr Iñaki F. Trocóniz (Universidad de Navarra, Spain) welcomed the audience and speakers and opened the meeting. A total of 125 scientists from academia, industry, and regulatory agencies from 12 countries attended the meeting.

The first keynote lecture was delivered by Dr Iñaki F. Trocóniz (Universidad de Navarra, Spain), who addressed the role of quantitative systems pharmacology to understand and hit the target of complex diseases. He focused on the Model-Informed Drug Discovery and Development (MID3) approach to guide dosage optimization, emphasizing the importance of moving from simply operating

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in silico tools toward comprehensive data analysis and interpretation.

The Plenary Session 1 was dedicated to "Therapeutic Drug Monitoring." Dr Paula Schaiquevich (Hosptial de Pediatría JP Garrahan, Argentina) highlighted the importance of considering not only PK but also PD variability when applying therapeutic drug monitoring in pediatrics. The key role of prior knowledge, in terms of quality and abundance, was also addressed. Dr Michael Neely (Children's Hospital Los Angeles, United States (US)) presented a nonparametric approach for individualized therapy and several examples providing the routine monitoring of patients using this tool. He also provided the basis for multiple-model optimal as a new sampling strategy that requires minimal computation while having distinct advantages when compared with existing approaches. Dr Silvia Romano (Universidad Autónoma de San Luis Potosí, Mexico) spoke about several local initiatives on therapy individualization. She pointed out the relevance of clinical testing for constitutional pharmacogenetic variants implicated in interindividual drug response variability as an important guide for dosing adjustments.

By the end of this session, Dr Manuel Ibarra (Universidad de la República, Uruguay) presented the mission ("to promote the advancement of pharmacometrics in Latin America through its application in pharmacological research, enhancing drug development and introduction of therapeutic strategies as well as in the clinical setting supporting dose optimization and rational use of medicines. Additionally, we aim to create a multidisciplinary framework for education and training of scientists getting into this discipline") and vision ("to become a recognized Iberoamerican network in the field of pharmacometrics by the promotion of education and training of personnel in this area and the encouragement of its application in the fields of development, registration, and use of medicines, while integrating academia, industry, regulatory, and clinic sectors") of the RedIF, which contains, so far, representatives from nine countries.

The Plenary Session 2 was about "PK/PD Modeling." Dr Stephan Schmidt (University of Florida, US), who briefly reviewed the evolution of M&S, also discussed the importance of moving toward concrete applications of the learn-confirm paradigm. He presented two successful case studies in which integrative M&S approaches guided clinical (dosing adjustment) and regulatory decision making (investigation of purported therapeutic inequivalence after replacing brand name by generic formulations). Dr Marc Lavielle (Inria and Ecole Polytechnique, France) presented new methods, algorithms, and tools for model building and model assessment included in the R package Rslmx ("R speaks Monolix").[6] He ran real-time modeling for warfarin PK to illustrate the advantages of using an automatic iterative procedure to accelerate and optimize the process of model building (Stochastic Approximation for Model Building Algorithm). Lastly, Dr Bibiana Araujo (Universidade Federal do Rio Grande do Sul, Brazil) exemplified the influence of disease states on drug tissue distribution. She explained the basis of microdialysis and the use of it to assess the impact of cryptococcal meningitis on drug penetration through the blood–brain barrier, emphasizing the need to consider disease progression when investigating the necessity of dosage optimization.

The second keynote lecture was delivered by Dr Hartmut Derendorf (Distinguished Professor, University of Florida, US), who spoke about applying M&S for dose optimization on Earth and in space. He started his presentation showing the economic issues surrounding drug development and the potential for applying quantitative modeling approaches. He reviewed the development of microdialysis to assess drug tissue distribution, highlighting the scientific contribution of Iberoamerican scientists. He also highlighted the limitations of static metrics for PD (e.g., minimum inhibitory concentration) for antimicrobials and the usefulness of metrics characterizing the time course of PD response (e.g., kill curves). Finally, he discussed how simulated microgravity does not seem to affect disposition of antimicrobial drugs using ciprofloxacin as a case study.

The Plenary Session 3 was titled "Virtual Bioequivalence (BE)." Dr Rodrigo Cristofoletti (Anvisa, Brazil) reviewed the average BE paradigm, highlighting that it is not a scientific fact *per se* but a judgment (i.e., relying on facts, beliefs, and assumptions but also prone to biases). He spoke about the importance of predictive *in vitro* dissolution tests to generate reliable inputs for the mechanistic absorption models; otherwise, virtual BE trials may lead to false negative or false positive results. He also noted that commercially available, physiologically based pharmacokinetic (PBPK) software do not account for interoccasion variability, and further developments are still needed to create a virtual BE platform. Dr José Trinidad Urízar (Universidad Autónoma de San Luis Potosí, Mexico) pointed out the lack of a clear and harmonized definition of virtual BE. He also stressed the requirement of high-quality information to parameterize the system component of the PBPK model and highlighted some critical knowledge gaps. He also spoke about other applications of PBPK models in drug development, including drug–drug interactions. Dr Elba Romero Tejeda (Universidad de Guadalajara, Mexico) discussed formulation-related issues leading to failures in the demonstration of BE among brand names and generics. She raised a thought-provoking question (i.e., are we ready for virtual BE?), contrasting the rapid scientific progress and the slow regulatory process. She mentioned the relevance of RedIF as an independent and neutral board to moderate the dialogue among different stakeholders involved in drug development in Latin America.

The Plenary Session 4 was dedicated to "Translational PBPK/PD." Dr Mirjam Trame (Novartis, US) briefly reviewed the historical development of PBPK models since the pioneer work of Torsten Theorel to today, highlighting its main applications. She presented a successful case study using global metabolomics biomarkers to guide interspecies scaling. She also discussed the importance of verifying whether the model is able to predict prior clinical knowledge before exploring what if scenarios. Dr Leyanis Rodríguez Vera (Universidad de Havana, Cuba) applied population PK to optimize nimotuzumab dosage regimens in patients with advanced breast cancer. Further investigations about the PK/PD relationships should be considered to decide whether PK changes are indeed clinically

relevant. Dr Teresa Dalla Costa (Universidade Federal do Rio Grande do Sul, Brazil) was the last speaker of this session. She presented a translational study to determine the efficacious cefazolin prophylactic dose for bariatric surgery using free subcutaneous concentrations accessed by microdialysis. She reinforced the necessity of considering tissue-free concentrations as well as PD biomarkers, e.g., minimum inhibitory concentration, to investigate potential prophylactic effective doses.

The third keynote lecture was delivered by Dr Mats Karlsson (Uppsala University, Sweden), who spoke about extensive model assessment through model–proxy analyses. His talk focused on a diagnostic tool to quantitatively identify model misspecifications and rectifying actions. He showed how model-based postprocessing of routinely used diagnostics such as conditional weighted residuals may be valuable for residual unexplained variability model identification during model development and evaluation.[7]

The Plenary Session 5 was dedicated to "Drug Disease Modeling." Dr María García-Cremades Mira (University of California San Francisco, US) presented a case study using a disease progression model to investigate the efficacy of tenofovir in HIV prophylaxis and the risk factors associated with HIV transmission. She emphasized that disease progression may affect both PK and PD components and thus should be considered when addressing drug efficacy and safety. Dr José Rodrigo González Martínez (Centro de Investigación y de Estudios Avanzados del Instituto Politécnico Nacional, Mexico) spoke about compensatory homeostatic mechanisms in hypertension therapy and how the clinical outcome may not directly relate to the plasma drug concentration. He also pointed out the challenges related to dosing adjustment in case of critically ill patients. In this case, it would be relevant to consider covariates related to pathophysiologic status and therapeutic measures using a Bayesian-like approach.

In addition, three poster sessions, including 38 presentations and six oral communications were held during the meeting. Furthermore, prior to the meeting, 2-day hands-on workshops on Monolix (presented by Dr Marc Levielle) and NONMEM (presented by Dr Iñaki Trocóniz and Dr Manuel Ibarra) as well as a postcongress workshop on nlmixr (presented by Dr Mirjam Trame) completed the scientific program that altogether consisted of 64 attendees, among PhD students, senior academics, regulators, and industrial scientists. Following the RedIF educational philosophy, the precongress workshops were given in Spanish.

Altogether, **Figure 1** summarizes the topics covered during the congress.

Pharmacometrics and Quantitative Systems Pharmacology concepts are still emerging in Latin America. Just a few experienced research groups, whose academic training was done in traditional M&S centers abroad, have been struggling to spread state-of-the-art concepts and applications of M&S in their countries. No formalized M&S curricula have been implemented nor has guidance on PBPK or population PK modeling been issued by regulatory authorities in Latin America yet. In this context, the 2018 RedIF Congress created a platform for academicians, industrial scientists, and regulators to exchange their latest research, discuss challenges, set new collaborations, and foster M&S-based approaches for drug development, including regulatory and clinical applications throughout Latin America.

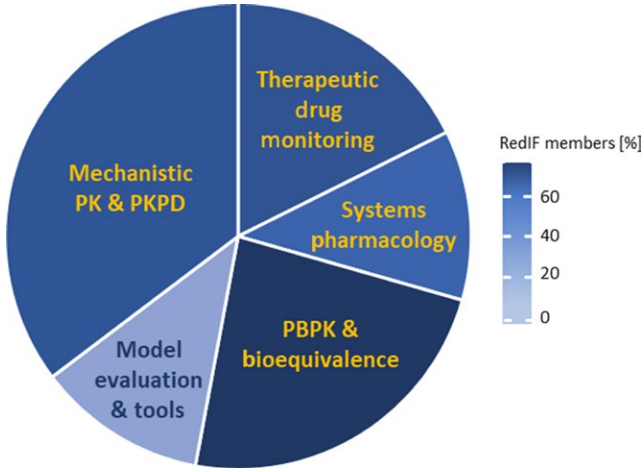

Figure 1 Different topics under the umbrella of the Pharmacometrics discipline covered during the 2018 Red Iberoamericana de Farmacometría (RedIF) Congress in Guadalajara (México). The graphic also shows the distribution the distribution per topic of speakers who are RedIF members. PBPK, Physiologically Based Pharmacokinetic; PK, Pharmacokinetic; PKPD, Pharmacokinetic and Pharmacodynamic.

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