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PERSPECTIVE

Requirements, expectations, challenges and opportunities associated with training the next generation of pharmacometricians

Stephan Schmidt[1] | **Valvanera Vozmediano**[1] | **Rodrigo Cristofoletti**[1] | **Sarah Kim**[1] | **Zhoumeng Lin**[2] | **Natalia de Moraes**[1] | **Francine Azeredo**[1] | **Brian Cicali**[1] | **Hans Leuenberger**[1] | **Joshua D. Brown**[3] | **Jin Y. Jin**[4] | **Cynthia J. Musante**[5] | **Stacey Tannenbaum**[6] | **Yaning Wang**[7]

[1]Department of Pharmaceutics, Center for Pharmacometrics and Systems Pharmacology, College of Pharmacy, University of Florida, Orlando, Florida, USA

[2]Department of Environmental and Global Health, College of Public Health and Health Professions, University of Florida, Gainesville, Florida, USA

[3]Department of Pharmaceutical Outcomes & Policy, Center for Drug Evaluation & Safety, College of Pharmacy, University of Florida, Gainesville, Florida, USA

[4]Clinical Pharmacology, Genentech, Inc., South San Francisco, California, USA

[5]Pfizer Worldwide Research, Development and Medical, Cambridge, Massachusetts, USA

[6]Pharmacometrics US, Astellas Pharma, Northbrook, Illinois, USA

[7]Createrna Science and Technology, Shanghai, China

Correspondence
Stephan Schmidt, Department of Pharmaceutics, Center for Pharmacometrics and Systems Pharmacology, College of Pharmacy, University of Florida, 6550 Sanger Road, Orlando, FL 32827, USA.
Email: sschmidt@cop.ufl.edu

The Center for Pharmacometrics and Systems Pharmacology (CPSP) at the University of Florida has been engaging stakeholders from industry and regulatory agencies in recent years to seek input on the requirements and expectations for next generation pharmacometricians in the workplace. The objective of this article is to share our joint perspective on identified key skills with the broader pharmacometrics community in order to initiate a collective consensus building process on how to best develop them.

PHARMACOMETRICIANS IN A RAPIDLY EVOLVING LANDSCAPE

Pharmacometrics has evolved from a descriptive science to an applied science that is increasingly used in all phases of drug development over the last decades. Today's application for accelerating and streamlining drug development is referred to as model-informed drug development (MIDD) or, more broadly, model-informed drug discovery and development (MID3).[1,2] Due to the increasing application of MID3 approaches, rapid emergence of new data analysis and computational methods as well as increasing

complexity of drug development and regulatory evaluation processes, demands for and toward pharmacometricians have been evolving over the years as well.[3–5] It is no longer sufficient to master a certain tool or technical skill. Instead, these skills need to be applied in a team-based environment to solve a drug development problem. Strong technical skills and the ability to identify when pharmacometrics analyses can be used to answer a particular question are of course the foundation for every pharmacometrician. In addition to these foundational technical skills, it is our firm belief that a successful pharmacometrician should ideally: (1) be an effective communicator, (2) be able to think strategically, and (3) be able to influence team-based decisions, as outlined in Figure 1.

Scientific knowledge and technical skills

A solid foundation of scientific knowledge (e.g., basic pharmacokinetic/pharmacodynamic [PK/PD] and pharmacology concepts) and technical pharmacometrics skills is the basis for being able to successfully apply MID3 approaches.[6] Foundational technical skills include but are not limited to nonlinear mixed effects (NLME) PK/PD modeling, mechanistic PK/PD modeling, including physiologically-based pharmacokinetic (PBPK), quantitative systems pharmacology (QSP) modeling and clinical trial simulations, as shown in Table 1. We believe that a strong technical skill set comprises familiarity with pharmacometric methods, software, and programming language(s), the ability to critically assess the scientific validity of a model and its associated parameter values, as well as knowledge in pathophysiology, PKs, pharmacology, toxicology, statistics, and mathematics. These foundational technical skills are essential to influence decision-making in drug discovery and development as well as during regulatory review. With the increased use of MID3 approaches in drug discovery and early drug development,[1] familiarity with emerging sciences and technologies, such as machine learning, artificial intelligence, and models relating structural properties of chemical compounds to potency/safety/PK, are becoming more important. As a consequence, the spectrum of required technical pharmacometrics skill sets has widened even further and two questions arise. To which extent do pharmacometricians need to cover the entire width of the spectrum? Is there a need for specialization among pharmacometricians?

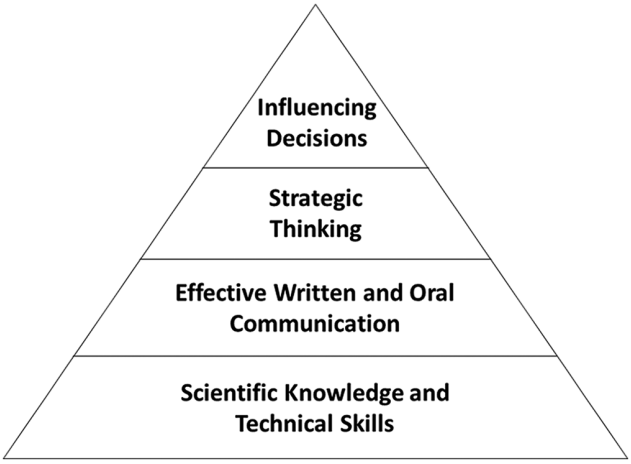

FIGURE 1 Hierarchical skill set for pharmacometricians to successfully apply model-informed drug discovery and development (MID3) approaches.

Effective written and verbal communication

Effective written and verbal communication is a generic skill set that is currently expected from professionals in almost any area. It includes both active communication and active listening. The latter is particularly important in team-based environments, where it helps to anticipate and resolve conflicts, negotiate solutions, and seek compromises. However, effective communication of MID3 approaches and results requires an additional layer of attention.[5,7] Rather than focusing on technical details, pharmacometricians who are effective communicators focus on the context of use, tailor the wording and complexity of their message toward the audience, and help teams that are largely composed of non-pharmacometricians coalesce on answers to some key questions:

- What are the key strategic objectives/questions?
- What information and data need to be collected to be able to answer these questions and how can a modeling approach help?
- What do we know thus far with how much certainty and what assumptions are being made, either in general or by the model?
- What are the decision criteria (both quantitatively and qualitatively) and what is the impact/risk of the decision?
- What do the model-based simulations suggest in terms of efficacy, safety, and potential next steps or future studies?

Strategic thinking

Strategic thinking entails the ability to anticipate both challenges and opportunities and to plan a course of action accordingly.[8] Strategic thinking in the context of

TABLE 1 Summary of the proposed teaching and training activities needed for acquiring technical, strategic, as well as communication and influencing skills.

Skill set	Content	Teaching approach
Technical skills		
ADME principles and NLME modeling	• ADME principles • PK, PK/PD, and disease progression models • Statistical principles of NLME modeling • Model building and selection approaches • Covariate selection approaches • Model evaluation and validation approaches • Categorical PD variables including dropout models • Learn specialized NLME and data management software, such as R	• Series of courses of increasing difficulty in statistics, medicine, biology, pharmacology, and pharmacometrics • Lectures and assignments to acquire software skills facilitated by pharmacometrics faculty • Internships at regulatory agencies and/or pharmaceutical industry
Mechanistic PK and PD models including PBPK and QSP	• Molecular pathophysiology and pharmacology • Mechanistic PK and PD models including PBPK and QSP • Learn specialized PBPK and QSP software	• Series of courses with increasing difficulty • Seminar series in medicine, biology, pharmacology • Lectures and assignments to acquire software skills facilitated by pharmacometrics faculty • Internships at regulatory agencies and/or pharmaceutical industry
Clinical trial simulation	• Statistical principles underpinning various trial designs • Simulating outcomes and operating characteristics (e.g., probability of correct decision) of prospective experiments and clinical trials including variability and uncertainty • Introduction to Bayesian PK/PD modeling • Perform simulation in R with available add-on packages and learn specialized software	• One semester course that builds on NLME and mechanistic modeling teaching blocks • One semester course on design and statistical analysis of clinical trials • Lectures and assignments to acquire software skills facilitated by pharmacometrics faculty • Internships at regulatory agencies or pharmaceutical industry (pharmacometrics or statistics department)
Introduction to emerging sciences and technologies	• Novel treatment modalities • Novel data source and data modalities • Quantitative genetics • Machine learning in drug development	• Seminar series developed in collaboration with associations, industry and other academic institutions
Strategic skills		
Drug discovery and development	• Understand drug discovery and development including novel approaches and regulatory perspectives • Exposure to key regulatory guidance documents (e.g., FIH, PopPK, and DDIs • Preclinical experiments and clinical trial designs • Understand global regulatory landscape (e.g., global regulatory agencies, typical regulatory interaction passes, submission package requirements (high level), and review/approval processes)	• Courses over two semesters. First semester is basic, second semester in more advanced • Crowd-sourced compendium of real-world case studies taught by faculty or guest lectures with experience in pharmaceutical industry or regulatory agency • Include case studies where students take the role of a drug discovery or development team
MID3	• Understand how MID3 can be leveraged to streamline and accelerate drug discovery and development • Special patient populations, such as pediatric drug development and extrapolation approaches	Course that builds upon drug development block and technical blocks. Same teaching as above
Decision making in drug development	• Understand basics of decision making and how it applies to decision making in drug development • Introduction to economic concepts used in decision making	One semester course facilitated by specialized decision making experts in collaboration with guest lecturer from industry that must be closely related to the other two strategic skills courses

(Continues)

TABLE 1 (Continued)

Skill set	Content	Teaching approach
Communication and influencing skills		
Scientific communication that engages audiences	• Obtain skills that are needed to write concise documents that excite management and are technically correct • Obtain presentation skills, tailored to the audience and convincing stakeholders • Special considerations for regulatory interactions (written and verbal)	• Specialized faculty or guest lecturer • Interactive course where students would work toward a presentation to a panel of MID3 experts from academia, industry, and regulators. Ideally, the panel should include non-technical decision makers so that students can practice telling convincing stories to non-pharmacometrics experts • Conference attendance to sharpen scientific presentation skills and establish/expand scientific network • Toastmasters
Negotiation and influencing skills and leading drug development teams to consensus	• Become aware of your presence and the impact of your presence with focus on drug development teams • Learn to "speak the language" of collaborators in interdisciplinary teams	• Specialized faculty or guest lecturer in a multiple day workshop • Virtual internship/fellowships with regulatory agencies or pharmaceutical industry

Note: The individual starting point for each activity may differ between students/trainees based on their prior training and experience. At the same time, some training activities will require joint teaching efforts from stakeholders from academia, industry, and regulatory agencies.

Abbreviations: ADME, Absorption, Distribution, Metabolism, Elimination; DDIs, drug-drug interactions; FIH, first-in-human; MID3, model-informed drug discovery and development; NLME, nonlinear mixed effects; PBPK, physiologically-based pharmacokinetic; PD, pharmacodynamic; PK, pharmacokinetic; PopPK, population pharmacokinetic; QSP, quantitative and systems pharmacology.

drug development requires a thorough understanding of the drug development process, applicable regulations and guidelines, and appreciation of organizational constraints (cost, time, value/risk). Obtaining this understanding requires time and is often the reason why junior pharmacometricians have difficulty leveraging MID3 approaches to streamline and accelerate drug development. Exposing junior pharmacometricians to drug development problems already during their training program (e.g., during internships in industry/regulatory agencies or joint research projects with industry/regulatory agencies) is consequently important. On the other hand, MID3 approaches provide an opportunity to facilitate strategic thinking because they allow for the integration of complex knowledge from multiple sources, explore different scenarios by quantifying assumptions, and prospectively choose the one that best meets the organization's goal (e.g., most pragmatic or has the highest probability of success).

Influencing decision making

The combination of technical and strategic skills ensures that pharmacometricians can identify critical questions in drug development programs that may be answered using MID3 approaches. Strategic skills as well as the ability to influence and negotiate are essential for identifying critical questions within and across project teams, provide teams with an option for decision making based on modeling and simulation, and conveying the solutions in a manner that engages the audience. The ability to systematically integrate information and extrapolate beyond what has already been studied holds great potential for influencing decisions in drug development and regulatory approval.

To broaden the impact that pharmacometricians can have on a final decision, it is important for her/him to be involved in all phases of drug discovery and development, including prospective study design, execution of the study, analyzing the data, and performing simulations for the next trial(s) along with making go/no-go decisions. Establishing this mindset early on in focused teaching and research curricula that integrate drug discovery and development with pharmacometrics is consequently beneficial. At the same time, it is important to remember that decision making is a complex process, which is affected by evidence, beliefs, assumptions and bias, a combination recurrent in common judgments. Biases in judgments reveal heuristics in our thinking under uncertainty, which can lead to severe and systematic errors.

Decision making is also impacted by the way a scenario is framed. For example, a 90% chance of success would likely be perceived more favorably than a 10% risk of failure, although they are mathematically the same.[9] We believe that pharmacometricians must understand this interplay

and continuously educate themselves on how to maximize the impact of MID3 with the overall goal in mind (i.e., to accelerate and streamline drug development and ultimately improve patient care). At the same time, they must be willing to make trade-offs, when necessary (i.e., be adaptive and pragmatic to achieve consensus amongst team members).

CURRENT CHALLENGES AND FUTURE OPPORTUNITIES

On top of the general increase in demand for pharmacometricians, there is an imbalance among supply, demand, and professional working opportunities between different regions of the world, resulting in geographic and academic brain drain.[10] Particularly the latter poses an imminent threat to the pharmacometrics community because if this trend continues, we will soon reach a point where we will no longer have a sufficient number of academicians, particularly at the Associate and Full Professor level, that are able to train next generation pharmacometricians.

To overcome these challenges, a general rethinking of traditional, siloed "business models" toward joint efforts between academia, industry, and regulatory agencies will be required. These efforts can be established at various levels, ranging from loose affiliations, such as adjunct appointments or internship opportunities for students and trainees, to structured partnerships with a dedicated logistic, financial, educational, and research infrastructure support. The latter would allow to overcome limitations of individual stakeholders (e.g., limited time for developing concepts or platform models outside the direct drug development pipeline or teaching drug development without having worked in the industry) and provide planning security (e.g., proactive workforce pipeline development, PhD and postdoctoral support for the duration of the training program, or increased utilization of large-scale databases for disease platform model development) for all parties involved. These joint efforts would also allow for the development of applied training modules, where stakeholders bring their individual strengths to the table (i.e., concepts and hands-on software training [academia], drug development context and possibly data [industry], regulatory context [regulators]). Combining forces would also allow us to stay abreast with the rapidly evolving drug development and regulatory evaluation landscape and offer training for new modalities, concepts, and analysis approaches in a timely fashion. Ideally, these partnerships would be interdisciplinary in nature to enable a broader vision to problems and ultimately spark innovation by crossing traditional knowledge boundaries. A transdisciplinary approach that integrates, for example, PBPK, machine learning, and artificial intelligence or pharmacometrics and pharmacoepidemiology, would also further a mindset of constant learning and collaboration, which is key to success in team-based environments.

To facilitate the interactions, we collectively composed a list of proposed teaching and training activities needed for developing technical, strategic, as well as communication and influencing skills (Table 1). We recognize that this list, although too lengthy for any single PhD or postdoctoral fellowship program, is not all-encompassing and that the outlined activities should be tailored toward the individual trainee's educational background and working experience. We also recognize that training activities in academia may have to be complemented by downstream activities. For example, two-way sabbaticals may allow working professionals from industry or regulatory agencies to retool in academia, whereas academicians could stay abreast with latest advances in drug discovery, development, and regulatory evaluation while spending time in the industry or at the agency.

Finally, we do not intend to infringe on individual faculty's freedom to train their students as they see fit, dismiss previous curricula proposal,[6] or suggest that academia should take sole responsibility for the proposed teaching and training activities. We rather intend to use this proposal to spark a broader conversation among stakeholders in the pharmacometrics arena to collectively build consensus on key skills and outline viable avenues for how to best develop them. As such, we invite all stakeholders to join this conversation and welcome any constructive feedback on our proposal.

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ORCID

Stephan Schmidt https://orcid.org/0000-0002-4998-1167
Valvanera Vozmediano https://orcid.org/0000-0002-2636-1889
Sarah Kim https://orcid.org/0000-0002-9179-0735
Natalia de Moraes https://orcid.org/0000-0002-4389-058X
Jin Y. Jin https://orcid.org/0000-0002-3627-0323
Cynthia J. Musante https://orcid.org/0000-0002-3003-0169

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