PERSPECTIVE

Pharmacometrics and Systems Pharmacology 2030

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In 2012, a new journal was launched from the ASCPT family, *CPT: Pharmacometrics and Systems Pharmacology* (*PSP*) as both quantitative system pharmacology (QSP) and pharmacometrics were growing fields in pharmacology, drug development, and drug use. In this Perspective, the present editors and associate editors of *PSP* want to share their strategic vision of where these two fields, separately and together, should, would, or could be 10 years from now.

QUANTITATIVE SYSTEM PHARMACOLOGY IN 2030

Progress in science has resulted in a plethora of therapeutic agents, including biologics, multitargeted drugs, rational drug combinations, gene therapies, and cellular therapies. In 2030, we expect there will be many new therapeutic interventions and more applications of precision medicine. The design and use of these new therapeutics will have to include quantitative understanding of pharmacological and biological networks. The continued evolution of systems approaches will lead to the routine use of quantitative models to prospectively predict clinical outcomes, with constant refinement of the system through reverse translation. We can imagine that for a new therapeutic intervention, we use our best understanding of the system to describe what happens when we modulate it, before we initiate clinical trials.

In our future, the integration of systems models, results of clinical assessments, and postmarketing data will be integrated in a dynamic, iterative manner. Thus, integration of systems approaches and pharmacometrics will serve not only as a medium for turning data into knowledge but also as a platform with which we research and develop. By 2030, it might be possible that new drug approval will no longer be on the sole basis of data obtained for the drug in prelaunch clinical trials, but instead on a trial supplemented with our understanding of the system and enhanced ability to predict variability in drug response.

PHARMACOMETRICS IN 2030

Pharmacometrics has demonstrated its impact in supporting drug development and regulatory decisions. Quantitative and computational approaches have become a natural component in most pharmaceutical companies, and regulatory agencies are requesting such analyses to support dosing decisions in product labeling. In the coming decade, we expect pharmacometrics to evolve further in these core activities, but also foster collaborations with adjacent fields. Model-based decision making will become the norm through the drug product life cycle, including biomarker qualification, quantification of associations between adverse and desired effects with exposure to improve benefit–risk assessments, and *in silico*–based extrapolations to different patient groups facilitating study waivers. During the coming decade, we anticipate that there will also be routine incorporation of pharmacometrics in health economic decisions and cost-effectiveness. Similarly, connections to epidemiology will advance, leveraging real-world data to understand different stages of diseases, recurrence patterns, and outbreaks in populations. Models will also include patient-reported outcomes and weight patient requests into population-level treatment decisions.

We also believe the area where pharmacometrics started (i.e., individualizing patient care) will be expanded. Research and entrepreneurial efforts will facilitate the application of pharmacometric models in clinical decisions at the bedside. Labels will include more precision dosing recommendations for different patient populations, and pharmacometrics will be globally applied in developing treatment guidelines postapproval. User-friendly software will enable the direct use of models for

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individualized dosing within routine clinical practice. Data from new measurements and biomarkers for efficacy and adverse events will be integrated. Large studies are needed to demonstrate the effectiveness of model-informed precision dosing and to convince stakeholders of its value.

We foresee the community increasingly interacting with statisticians and overcoming mutual misconceptions. These relationships will develop on both the individual and group levels through organizations such as the joint American Statistical Association–International Society of Pharmacometrics (ASA–ISoP) Statistics & Pharmacometrics Special Interest Group. We anticipate deeper use of statistical frameworks for estimating causal relationships specifying limitations when making inferences, such as confounding and bias in exposure–response relationships. Parameter and model uncertainty will be better acknowledged, frequently through the use of Bayesian methods, including clarification of the elicitation process when incorporating prior information and model averaging. Pharmacometrics can have substantial impact in areas where available information limits traditional statistical tools (e.g., rare diseases). We also expect that by 2030, pharmacometrics experts will become a natural part of investigator-initiated clinical trials to influence study design and evaluation.

Automation is expected to increase; however, expertise in QSP and pharmacometrics will remain essential for evaluating model inputs and outputs and placing results into context. As there will be a continued request for pharmacometric skills by employers, there will be a need for continued education of professionals and workforce development. For global engagement at different levels, white papers, online materials, webinars, fora, and new techniques, in addition to face-to-face courses and conferences, will be crucial to form and disseminate new knowledge. Pharmacometrics should be incorporated into future curricula in pharmacy, statistics, and clinical pharmacology training, and practitioners will likely become specialists in specific disease areas.

INFORMATICS FOR CLINICAL PHARMACOLOGY IN 2030

Compared with pharmacometrics, informatics plays an independent and complementary role in driving clinical pharmacology research. On one hand, informatics is a discovery science with excellent interdisciplinary collaborative opportunities based on emerging big data sources and their increased accessibility. These collaborations have led to many novel discoveries and the validation of numerous intrinsic and extrinsic factors that predict drug effects. Some of these discoveries significantly enhanced our understanding of molecular pharmacological mechanisms. Artificial intelligence and new machine-learning algorithms are increasing the potential and impact of big data for discovery in clinical pharmacology research.

On the other hand, informatics is also an implementation science. Clinical informatics is an informatics subdiscipline, which applies information technology to manage healthcare systems, improve the quality of healthcare, and deliver novel healthcare services. Almost all of the existing medication management in both inpatient and outpatient settings are managed through electronic medical record (EMR) systems. Pharmacometrics-based precision dosing requires clinical informatics to assess its added value and facilitate implementation into EMR systems. Learning Health Systems is an anticipated extension of clinical informatics, which promotes the concept that informatics is both a discovery and an implementation science, and will operate in a circular fashion. In this manner, investigators will collect data from patients through the EMR directly and conduct discovery research, but then they will also implement their newly designed clinical decision systems into the EMR for testing and validation.

The popularity and impact of informatics is currently limited by the available tools in the clinical pharmacology community. Although there are some excellent examples (e.g., Pharmacogenetics Knowledge Base (PharmGKB)), many big data and data-mining tools are either unavailable or user unfriendly to pharmacologists with limited informatics skills. We anticipate that by 2030, there will be more informatics tools designed for pharmacologists, which will enable pharmacologists to access and analyze different big data sources, implement their clinical decisions in treating patients, and expand creativity in pharmacological research.

GLOBAL VISION FOR 2030

The coming decade will see more formal links between pharmacometrics, QSP, statistics, and clinical informatics. One form of such synergy will be *hybrid modeling*, in which multiple model types are formally coupled to leverage knowledge from physical processes, statistical properties, data-driven models, and machine-learning algorithms.

As pharmacometrics strives toward more mechanistic models to explore and predict new scenarios, QSP models will be the essential repository of this information. We anticipate that a library of QSP models will be available from which a pharmacometrics modeler could extract a reduced model to describe any input–output relationship that they were exploring. This extracted model would then avoid the need for long model-building processes, especially in circumstances in which the data for modeling often lack the necessary mechanistic information. Model reduction and extraction would become an automated process that could occur simply at the *click of a button* to produce XML code that could be exported to any estimation-based framework. One QSP model could therefore yield tens to hundreds of discrete input–output relationships with thousands of potential uses for differing drugs, drug-targets, and postmarketing analyses. The pharmacometrics framework would then fully embrace both the mechanistic, mathematical, and statistical aspects of model-informed drug development.

In 2030, infrastructure that provides real-time access to data that allows adaptation in trial design, without needing to consider logistical challenges, will be mainstream, along with models that use this real-time data to predict outcomes. Early clinical trials, even in areas outside of oncology, will be conducted in populations of interest. We will design trials with the minimum number of subjects and use quantitative approaches to predict success. During clinical trials, we will integrate biomarker signatures in systems to describe the possibilities with different dosing and combination regimens.

We believe open science will be of particular importance for the expansion of QSP

and pharmacometrics. Sharing model code through open access publications and model repositories allows modelers a kick start when digging into a new area and facilitates expansions beyond previous standards. The availability of models also increases the potential of QSP and pharmacometrics to contribute to improving study design and supporting go/no-go decisions. Open science also stimulates reproducibility, which is essential for the credibility of the field. Further initiatives on open access modeling tools and data repositories are also much welcomed.

With the uptake of QSP and pharmacometrics and the increased number of users, we can expect a greater variety of tools and software. The community should, however, make efforts to harmonize best practices and diagnostic tools for QSP and pharmacometrics across disease areas, and gather best practices on how to evaluate our models.

CONCLUSION

We expect that by 2030, QSP and pharmacometrics will have a profound influence on drug development and use. QSP, physiologically-based pharmacokinetics, and pharmacometrics will be further integrated to better understand and predict variability in patient responses to drug therapy. We expect that our fields will demonstrate impact in the greater society, trusted to influence reimbursement policies and dose decisions at the bedside, and eventually lead to improved global health. We envisage that our journal *PSP* will continue to be at the research front of QSP and pharmacometrics, facilitating global dissemination and implementation, and will be one of the leading forums for discussions on expansion and best practices.

CONFLICT OF INTEREST

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