# EDITORIAL

# Pharmacometrics and/or Systems Pharmacology

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When *CPT: Pharmacometrics & Systems Pharmacolgy (PSP)* was launched in 2012, I wrote in my inaugural Editorial[1] about the importance of integration and combination of the disciplines of Pharmacometrics (PMx) and Quantitative Systems Pharmacology (QSP). Over half a decade later, it seems like a good moment to take stock and assess how the journal and the model-informed drug discovery and development (MID3) communities have done in bringing together PMx and QSP.

Several recent papers in *PSP* may serve as "biomarkers" to help us answer this question. Trame *et al.*[2] provided a direct answer in their recent perspective. They assessed the state of PMx and QSP integration by evaluating 228 original research articles published in *PSP* and concluded that 19% could be classified as integrated PMx and systems pharmacology. Mistry[3] presented a view on a more binary choice between the two approaches in the recent perspective "QSP Versus the Rest: Let the Competition Commence!" which was a commentary on the Stein and Looby[4] perspective "Benchmarking QSP Models Against Simple Models: A Path to Improved Comprehension and Predictive Performance." In brief, the discussion revolves around Occam's razor principle that all things being equal, a simple model should be preferred over a complex model. In his recent commentary, Benson[5] attempts to find a common ground and states that "Overall it is apparent that simple or empirical models 'win' in some cases (simplicity, amenability to incorporate statistical parameters, ability to simulate an end point), but complex models in others (richer information content, clearer link to actual biology, potential to gain mechanistic insight)." The main conclusion is that it all depends on the question and that the modeling approach (i.e., PMx or QSP) should be chosen based on the available data, stage of drug development, and answer required. One important distinction that can be made between PMx and QSP models is that the latter can be informative even if they do not predict the data (i.e., it can be argued that Box's aphorism[6] "All models are wrong but some are useful" applies to PMx, but that it should be adapted for QSP to "Wrong models can be useful.") However, Mistry[3] points out that "even for learning about the biological system we would require that the [QSP] model does make accurate predictions at some point, the sooner the better."

An important technical impediment for integration of PMx and QSP is the lack of common scientific and operational standards. For example, best practices exist for PMx model evaluation,[7] whereas in QSP this is an area of ongoing debate.[8]

Both disciplines, but QSP in particular, suffer from the lack of common model tools, languages, and repositories.[9] One of the key editorial policies *PSP* adapted from the start was that model code should be published with every paper. This has been received with great enthusiasm by our authors, reviewers, editorial board, and readers, has distinguished the journal from many of its peers, and is considered to be a great resource for PMx and QSP models. However, a recent analysis of the *PSP* model repository[10] highlighted that more work needs to be done to develop standards for QSP model-code sharing and that current practices do not enable the scientific advancements to be translated into impact in drug discovery and development.

Some final thoughts on where I think the field will/should go next to further integrate PMx and QSP:

- Linking QSP models to clinical end points. This could be the biggest opportunity for linking PMx and QSP. Currently, most QSP model predictions end at the level of biomarkers with no quantitative linkage to actual patient outcome.
- Bringing experimentation back into the remit of QSP. The original National Institutes of Health definition[1] was very clear that QSP "combines computational and experimental methods." In my view, many QSP practitioners seem to have lost sight of this important point and now associate the discipline mainly with the computational aspects. I believe this is not only limiting the wider acceptance of QSP but also its development as a scientific discipline. For example, a combination of high-throughput experiments and control-engineering modeling methods could trigger a shift from the current "inside-out" QSP approach to "outside-in."[11]
- Model reduction. Arguably the most direct technical solution to bring together PMx and QSP is model reduction. Major advancements have been made in this area recently by transferring well-established methods from engineering to the field of quantitative pharmacology,[12] and we should now expect to see applications in drug development and regulatory sciences.

I have no doubt that *PSP* will continue to publish cutting-edge science and applications of these and other topics and facilitate the further integration of PMx and systems pharmacology.

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