

PERSPECTIVE

Quantitative Systems Pharmacology: A Regulatory Perspective on Translation

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Interest in QSP as an approach to mechanistically inform drug development has exploded in recent years. Additionally, both drug development and regulatory scientists have increasingly expressed interest in the potential for QSP to guide regulatory decisions. The extent to which QSP can routinely do either is an open question, and there have been examples of QSP facilitating key decisions and transitions in drug discovery and development.

QSP ON THE REGULATORY HOPE-HYPE CYCLE

QSP is not the first emerging regulatory science touted as potentially transformative across the continuum of drug discovery, development, and regulation. In fact, predecessors have included more traditional, empirical pharmacometric approaches (e.g., exposure/response modeling), pharmacogenomics and precision medicine, and physiologically-based pharmacokinetic PBPK modeling and simulation (arguably a subset of QSP). Much can be learned from the previous 2 decades spent advancing these sciences in the regulatory setting, which might help predict the trajectory of QSP.

All three of these scientific approaches essentially followed the classic hope-hype cycle¹ (Figure 1). First, some triggering event led to exponential growth of enthusiasm around the many possible applications of the new science to drug development and regulatory evaluation. This “event” was actually a convergence of several important factors including (i) a quantum leap forward in science or methodology; (ii) development of enabling tools or technologies (e.g., software); and (iii) an acknowledgement by senior leadership (e.g., within regulatory authorities) of the potential impact of these sciences. This “innovation trigger” was, in some cases, also accompanied by significant interest from the public, most notably in the case of precision medicine, which created broad interest among drug developers, regulators, clinicians, payers, and patients.

Initial expectations were understandably high; however, as proponents began to encounter obstacles to adoption, a disillusionment of sorts set in. In retrospect, these barriers to translation were totally predictable and relevant to QSP as well; they included constraints of the science itself, a steep learning curve among nontechnical experts coupled with very few instructive cases, and high organizational activation energy required to integrate new approaches to

well-established operational frameworks. This “trough of disillusionment” was usually a recognition that expectations needed to be recalibrated considering these facts on the ground. This recalibration was followed by an uptick and steady (albeit sometimes slow) growth in adoption practices.

Importantly, this “slope of enlightenment” itself was often catalyzed by a second convergence of factors driven by continued advances in the science and lessons learned from the previous phases of unrealistic expectation and disillusion. There were some common developments in the fields of pharmacometrics, pharmacogenomics, and PBPK that hallmarked this stage. First, there was increase in and growing championship of these approaches among decision makers and policy makers. This was motivated, in part, by more tangible examples of how the sciences were being brought to bear for the benefit of drug development, regulatory assessment, and therapeutic individualization. Second, there was public engagement that facilitated broad discussion of the contexts in which these scientific approaches could have the highest probability of success and, therefore, the highest return on investment. Third, as we gained more practical experience in the regulatory process of consultation and decision making, we were able to develop business processes and workflows that created more predictable and transparent interactions between drug developers and regulatory scientists. These factors, along with continued institutional support and collaboration among pharmaceutical companies and academic institutions/consortia, allowed for development of best practices and regulatory guidance.

Ultimately, the hope-hype cycle ends with a “plateau of productivity” in which, in the regulatory context, the scientific approach becomes more integrated and mainstream within the broader exercise of regulatory evaluation. Not all emerging sciences reach this aspirational state that balances expectations with realized benefit and risk. In the cases of exposure/response, precision medicine, and PBPK, a critical mass of experience has largely, but not completely, overcome the residual skepticism from earlier eras of outsized promise. Notwithstanding, these approaches have been sufficiently socialized within both the drug development and regulatory environments and have been shown to be enabling in many scenarios, such that a compelling argument can be made that all three are nearing or have reached a plateau of productivity. Of course, there are context-specific caveats and more work needs

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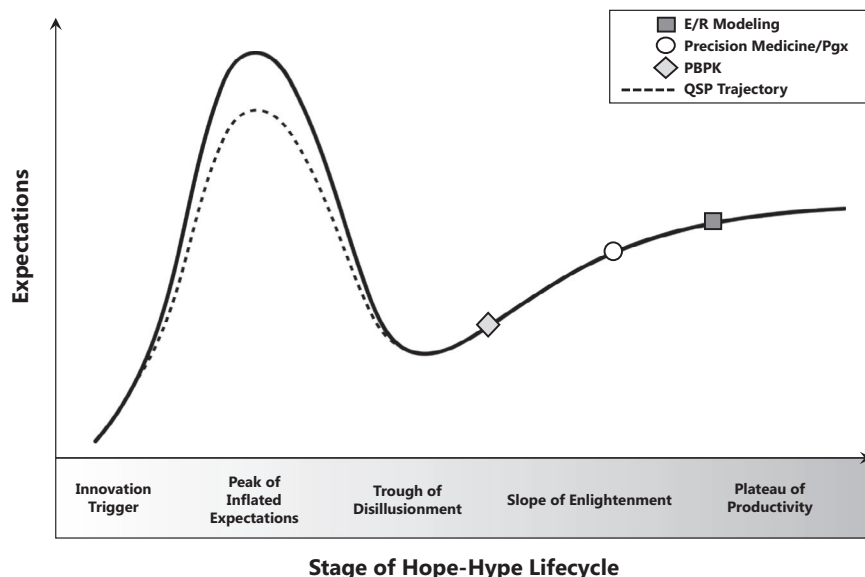


Figure 1 Conceptualizing emerging regulatory science on the hope-hype continuum. Quantitative systems pharmacology (QSP) is one of several regulatory sciences that have followed a hope-hype lifecycle. Other regulatory sciences, such as exposure/response (E/R) modeling and simulation, precision medicine/pharmacogenomics (Pgx), and physiologically-based pharmacokinetic (PBPK) modeling and simulation are at various stages on this continuum. The significant investment by the scientific community in defining the opportunities, challenges, uses, and best practices in QSP should, at minimum, lower the peak of inflated expectations and may facilitate more integration of QSP in drug discovery, development, and regulatory evaluation. Note: The point estimates are for conceptual purposes only; it could be argued that placement of these points on the hope-hype curve are context-dependent and highly subjective. All representations are for the science in a regulatory context (e.g., as opposed to in clinical practice).

to be done. Nonetheless, major developments, including the incorporation of both precision medicine and model-informed drug development (MIDD) provisions, in the last two reauthorizations of the Prescription Drug User Fee Act, respectively, strongly signal widespread recognition of the value of these approaches.

Interestingly, scientists in the field have also recently remarked that QSP seems to be progressing on a hope-hype path.² QSP is arguably on an expedited pathway because of the very thoughtful work being conducted by drug development, regulatory, and academic scientists (further discussed in the next section).

SETTING EXPECTATIONS

QSP's trajectory has shared many similarities with the above sciences. Because of advances in science and technology, quantitative systems approaches have been heralded as potentially transformative in facilitating drug development and reducing attrition.³ Challenges and barriers to adoption and implementation have been identified, resulting in identification of new opportunities and level setting.⁴ Finally, efforts are underway to integrate routine quantitative systems approaches where appropriate.^{2,5,6}

QSP may be on track to progress through the hope-hype cycle more expeditiously than the previously discussed sciences largely because of a frontloaded effort to identify the specific applications of QSP that have the greatest value proposition. This, of course, depends on when one considers the promise of QSP to have been first articulated; at minimum, there has been a concerted effort to "contextualize

the current status of QSP based on its multidisciplinary roots and its historical successes and challenges in order to establish its next direction."⁷

There is an increasing number of examples of QSP's role in guiding drug development. Although there are fewer examples of QSP being leveraged to guide regulatory decisions (e.g., labeling, postapproval requirements, and waiving clinical trials), it can be credibly argued that the real impact of QSP is to de-risk a drug development program as it progresses.^{4,6,8} It is not surprising, then, that most case examples of QSP center around key drug development considerations, such as hypothesis generation, compound selection/prioritization, translational biomarker development, and nonclinical and clinical trial design⁴ (*vis-à-vis* application of QSP for distal regulatory purposes).

The QSP community has done a laudable job in landscape analysis and communication of current state. These kinds of rigorous analyses of industry (and regulatory) practices were critical to advancing the fields of pharmacometrics, precision medicine, and PBPK modeling/simulation. These assessments of QSP may mitigate the potential for overinflated expectations (**Figure 1**) and lead to a more rapid transition to steady-state adoption of QSP approaches in drug development.

Several important insights can be gleaned from these examinations of the state of QSP. Nijsen *et al.*,⁴ for example, describe foundational issues around "challenges, barriers, and opportunities" for QSP modeling within research and development, with emphasis on preclinical QSP. We learned of the wide range of QSP modeling definitions and resource investments, the stage at which QSP modeling is initiated,

model size and complexity, perceived and actual impact of QSP modeling along with success/failure determinants, and perhaps most importantly the contexts of use for QSP. Ermakov *et al.*² performed additional survey work wherein they provided useful insights into the platform capabilities needed to robustly develop and apply QSP models. In a consortium effort, Cucurull-Sanchez *et al.*⁵ identified the translational barrier caused by lack of standardization in model development, vetting, and documentation, and propose a framework for transparent reporting of results from QSP modeling exercises.

In total, the QSP community has taken a deliberative approach to address key questions facing the discipline. Namely, the specific applications of QSP to drug development have been illuminated through case studies and landscaping; enabling technological capabilities have been articulated by end users; and best practices in communicating model context of use, development, validation/verification, and impact have been proposed. Expectations seem to be appropriately set against which to benchmark gains afforded by QSP in drug development.

OUTSTANDING QUESTIONS

The biggest return on investment for QSP is likely in drug discovery and development. As a result, we might hypothesize that the success of QSP in therapeutic product development will be largely (though not entirely) driven by pharmaceutical company capability and acceptance, as opposed to regulatory acceptance. This point is debatable, and the important question around the role of regulatory scientists in evaluating QSP models and output in regulatory decision making should be publicly discussed. Parenthetically, the role of academic researchers should not be underestimated given that the strength of the mechanistic knowledge base that drives QSP is dependent on basic, translational, and clinical research performed in academic research environments.

The US Food and Drug Administration (FDA) has had increasing experience in evaluating QSP approaches in

regulatory submissions (**Figure 2**). Excluding PBPK, most of our experience has been in the design space (i.e., investigational new drug submissions), with limited experience in the evaluation of QSP in new drug applications or biologics license applications. Additionally, when used in regulatory submissions, QSP has largely been one supportive piece of a larger evidentiary package (e.g., in support of dosing regimen justification). Therefore, a key question is what the evidentiary framework and regulatory expectations are for model credibility assessment based on various use contexts. This, of course, is not unique to QSP and has been a recurring theme in MIDD.

When is the optimal time to engage with regulatory authorities on discussions about QSP in specific product development programs? We have previously identified “insufficient opportunity for real-time engagement between sponsors and regulators on the merits and constraints of a particular MIDD strategy in a specific drug development context” as a rate-limiting factor to uptake of MIDD.⁹ Given that a majority of QSP models are initiated in early discovery and development, model development is complex and time variable, and many applications are for internal company planning purposes, thoughtful consideration must be given to the appropriate stage in development and mechanism by which to engage with regulators, as well as the purpose of such engagement.

As with other quantitative sciences, we have found it helpful to think about what the intended purpose and context for use would be for a given quantitative approach. For example, is the modeling (with or without accompanying simulation) intended to be mechanistically explanatory of an observed phenomenon? Is the exercise intended to be used for clinical trial planning? Is the output intended to stand in for a clinical trial? These are very different situations that would necessitate different conversations between a drug developer and regulatory agency. Some may not necessitate a conversation at all, whereas others would clearly entail explicit and nuanced dialogue around model credibility, decision risk, and resulting evidentiary requirements.

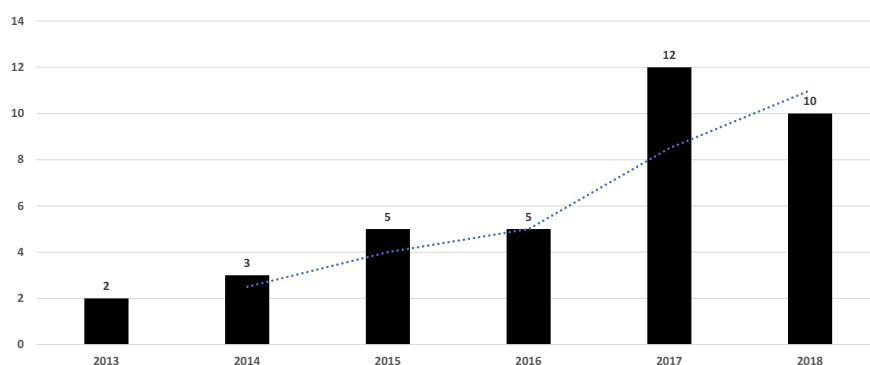


Figure 2 Quantitative systems pharmacology (QSP) submissions to the US Food and Drug Administration (FDA) over time. Number of regulatory submissions to the FDA containing QSP information over time. Regulatory submissions include investigational new drug (IND) applications, new drug applications (NDAs), and biologics license applications (BLAs). Submissions were identified through direct query of review staff in the FDA Office of Clinical Pharmacology; the graph should be considered an estimate. The hashed line represents the moving average number of submissions.

Many stakeholders are working to clearly define the QSP space. We anticipate that, as the science develops and more examples of QSP application reach the regulatory doorstep, further engagement among scientists involved in MIDD will be important and welcome.

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