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PERSPECTIVE

GPS for QSP: A Summary of the ACoP6 Symposium on Quantitative Systems Pharmacology and a Stage for Near-Term Efforts in the Field

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Quantitative Systems Pharmacology (QSP) is experiencing increased application in the drug discovery and development process. Like its older sibling, systems biology, the QSP field is comprised of a mix of established disciplines and methods, from molecular biology to engineering to pharmacometrics.[1] As a result, there exist critical segments of the discipline that differ dramatically in approach and a need to bring these groups together toward a common goal.
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This article provides a summary, conclusions, and actions resulting from the symposium entitled "GPS for QSP: Where We've Been, Where We Are and Where We're Going," which took place during the Sixth Annual American Conference on Pharmacometrics (ACoP6) in Washington, DC on October 6, 2015. The symposium sought 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. Like most fields, this area has evolved from independent, innovative efforts rather than from an overarching, strategic plan. While this diversity is largely responsible for the success of QSP today, it essentially represents the beginning of an emerging discipline. The goal of the session was to explore how history has shaped QSP and to use that understanding to set a course for its advancement as a scientific and practical discipline. The symposium included presentations by industrial, academic, and regulatory scientists followed by a panel discussion that produced three main themes as critical for the future success of QSP as a discipline. These themes resulted in new goals within the International Society of Pharmacometrics' (ISoP) Special Interest Group (SIG) on QSP to engage the community to address them.

THEME 1: BUILDING EFFECTIVE TEAMS

The first theme that developed from the symposium was the need for effective integration of researchers working in all aspects of QSP, within and across academic, industry, and regulatory sectors. In order to truly optimize this newly emerging discipline, establishing multidisciplinary teams to bring together scientists with a variety of educational backgrounds, including mathematics and engineering as well as physical, biological, and pharmaceutical sciences, has been shown to maximize results and impact. Without effective team-building efforts, there is a risk that QSP practitioners may be working in siloes with colleagues of similar backgrounds and this may limit the opportunity for creative and innovative problem solving.

Improved collaboration between QSP researchers can be achieved through training, communication, and focused efforts. Several ideas for the seamless integration of the fields of "quantitative" and "systems" pharmacology were discussed, including:

- Development of integrated (university-level) QSP training programs that include components of experimentation, systems biology and pharmacology, and pharmacometrics to prepare our next generation of QSP practitioners. Such individuals may be well suited to lead a path in seamlessly merging the concepts of "top-down" and "bottom-up" approaches by effectively hybridizing parts of pharmacometrics, systems biology, and QSP.
- Formation of small, cross-disciplinary QSP teams focused on addressing key questions, gaining alignment with key stakeholders, and informing drug discovery and development decisions, as opposed to focusing on the model *per se*.
- Adoption of "middle-out" approaches as effective strategies to bridge potential knowledge gaps between traditional systems biology and pharmacometrics approaches.
- A cultural shift that rewards teamwork, encourages intellectual synergy, and promotes alternative approaches that offer unique and previously unavailable solutions to problems.
- Enabling teams with real-time simulation and visualization tools to facilitate effective discussions and model development as well as enhancing their ability to share and drive decisions within broader teams.

Considering these points, the QSP SIG has formed multidiscipline and multisector member-led working groups. Drawing on expertise from academic, industry, and regulatory scientists from various fields including engineering, pharmacometrics, systems biology, and bioinformatics, these groups will focus on the identification, collection, and sharing of experiences and information to enable teams to successfully apply and

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integrate pharmacometrics and systems pharmacology analyses. Through these cross-disciplinary interactions, we envision that commonalities and complementary approaches will be identified and educational materials developed to highlight best practices for effective QSP team building.

THEME 2: BUILDING MUTUALLY BENEFICIAL CROSS-SECTOR COLLABORATIONS

Like other scientific fields, QSP will benefit from a diversity of perspectives and approaches. The speakers' presentations highlighted multiple opportunities related to establishing and maintaining effective QSP collaborations among academic, industrial, and regulatory groups. The panel discussion explored how to improve these interactions, leading to several key points:

- The issues facing industry are not widely known within the academic sector, and nonindustry researchers may have limited exposure to the complexities of the drug discovery and development process. Effective education and communication are necessary to promote successful collaborations.
- When statements-of-work are created, the respective goals of academic and industry researchers and key questions to be assessed must be considered and clearly defined. Pursuing new knowledge in tandem with pursuing a new therapy is necessary for collaboration to be successful, but the task of effectively managing the integration of such goals should not be underestimated.
- Industry has shown success in vertical integration (i.e., scaling subcellular pathway models up to organism) but has lacked significant success in horizontal model integration (broadening a network to encompass a more comprehensive biological representation). Academic laboratories have shown promise in this area, thus yielding a potential area for future collaborations.
- Because of the breadth of the science and wide range of expertise in QSP, aspects of this work are developed across departments, such as preclinical discovery, bioinformatics, and quantitative pharmacology (PKPD) among others, and this is not consistent between companies. QSP methods, approaches, and concepts can be enhanced by integrating this spectrum of computational endeavors within each company. Improved integration will also enhance external collaborations with academic researchers and regulatory scientists.
- When a collaborative project is initially formalized, tangibles such as publication rights and patent ownership should be addressed explicitly. Although these issues should ultimately be handled within an individual collaboration agreement, the community should develop best practices that can be widely accepted and promoted to ensure key decisions are addressed during the formation of collaborations.

Considering these points, the QSP SIG has recognized the need for efforts in education, communications, and focused discussions dedicated to facilitating a better atmosphere of collaboration between academia, industry, and regulatory agencies. Much of this could be accomplished via cross-sector programming and attendance at meetings and conferences. Longer-term goals are sighted on targeting specific scientific needs in QSP that could be met via avenues of collaboration like precompetitive consortia that may also include regulatory agency participation.

THEME 3: BUILDING A COMMUNITY

The final theme that developed from the session was the need to advance QSP as a scientific discipline, through community efforts. The formation of the ISoP QSP SIG and our member-led working groups are one step toward this goal. However, there is simply too much to be done; a broad range of experience, ideas, and insight are necessary for the success and continued advancement of the field. To this end, the SIG is working closely with QSP focus groups in other professional organizations, including the American Association of Pharmaceutical Scientists (AAPS), American Society of Clinical Pharmacology & Therapeutics (ASCPT), International Pharmaceutical Federation (FIP), and the UK QSP Network, to publish articles and organize programming at key meetings to continue engagement within and outside the QSP community.

There are a number of questions we hope to address through community-based efforts and consensus, including:

- What is the best way for industry to engage academia to begin a productive dialog towards improved understanding of key needs in pharmaceutical R&D?
- What is the most productive way for academia to engage with industry?
- How should scientists who approach problems using the methods of QSP be trained for a career in industry?
- Will a cross-disciplinary curriculum emerge as a foundation for QSP modeling, or are there advantages to developing collaborative teams consisting of specialists in core competencies?
- What new software and tools, such as real-time simulation and visualization, are needed to enable optimal impact of QSP?
- How can QSP data and models be made more accessible?
- What can be done to help pharmaceutical organizations optimally employ QSP experts and gain the most return on investment in the practice?
- How can industry promote and support seamlessly integrated, cross-disciplinary QSP teams?
- How can we facilitate the adoption of QSP as a universally accepted research paradigm that is applied across the pipeline?

CONCLUSION

The GPS for QSP symposium resulted in a forum for practitioners and those interested in the discipline to describe and debate open issues deemed most important to its advancement. Although many of the outstanding issues associated with QSP were highlighted, the authors acknowledge there are important issues that were not specifically focused on, such as use and acceptance of QSP models in regulatory submissions and learning from the establishment of guidance and qualification standards from more settled disciplines, like physiologically based pharmacokinetic modeling. We encourage interested readers to become involved in the discussion and future of QSP. These efforts require the active participation of QSP and pharmacometrics communities to engage in and lead them to fruition. If interested, we encourage you to take action, including but not limited to 1) contacting the authors of this article for more information on getting involved with these efforts, 2) joining and becoming involved in professional organizations focused on QSP as well as ones specializing in disease areas, and 3) publishing articles and presenting successes and highlighting areas for

improvement. The next major public update on the progress and continuing goals of this group is planned for ACoP8 in 2017.

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Disclaimer. The comments expressed here are those of the authors and not necessarily those of the companies or institutions who employ them.

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