Keynote Address

In his keynote address, Dr. William Chin, M.D., Executive Vice President, Scientific and Regulatory Affairs at PhRMA, advocated that collaborative partnerships are engines for innovation.

Pharmaceutical industry faces a myriad of challenges to provide new therapies for patients more effectively and efficiently. They include R&D costs rising much faster than product launches, significant patent expirations, incremental innovation defined more by payors than technologies, pricing pressure based on generic and other considerations, as well as increased regulatory expectations for higher safety and efficacy. A solution to these challenges is to create an environment that fosters higher level innovation. Such an environment is an ecosystem of academia, industry, government and NGOs to enable knowledge sharing and “shift the knowledge curve” to the left (Figure 1 and 2).

Dr. Chin described eight models of precompetitive collaboration based on whether participation and/or output are open or restricted, and gave specific examples of each model. A few collaboration examples, such as Alzheimer’s Disease Neuroimaging Initiative (ADNI), Accelerating Medicines Partnership (AMP), Project Data Sphere, and Transcerebro, were highlighted. Dr. Chin concluded his presentation by pointing out a few additional areas for potential collaborative partnerships, including efficacy and safety of biomarkers, target identification and validation, usage of innovative reagents and assays, as well as predictive animal and human disease models.
Enabling Technologies

Optimization of Enabling Technologies that support API process design and development will increase efficiency and effectiveness of key chemical development activities. This optimization can be achieved through collaborations among IQ member companies and between IQ members and industry vendors to focus on desired product enhancements and potentially holistic solutions.

The Enabling Technologies Working Group has identified five initial focus areas for technology optimization: Automation, Sampling and PAT, Continuous Processing, Particle Engineering, and Modeling. It has prioritized a list of specific project proposals, and identified eight proposals to carry forward. Currently, the Working Group is collaborating with the IQ Secretariat to define operating models that will appropriately share knowledge and best practices and to carry out a detailed assessment on academic or vendor collaborations. The Working Group has also put forth two topics for NIH Small Business Innovation Research grant proposals: Simple and Robust Reaction Progress Analyzer, and Online Real Time Metals Analysis at Low ppm Level.

Nonclinical to Clinical Translational Safety

The Preclinical Safety Leadership Group (DruSafe) is creating an industry-wide, precompetitive and collaborative database to determine the accuracy with which the interpretation of nonclinical safety assessments in animal models correctly predicts human risk in the early clinical development of biopharmaceuticals. This initiative aligns with the 2011 FDA Strategic Plan to enhance product safety by advancing regulatory science and modernizing toxicology.

Though similar in concept to the industry-wide concordance dataset created by HESI/ILSI, the DruSafe database will proactively track concordance; include exposure data, large and small molecules; and continue to expand with longer duration nonclinical and clinical study comparisons. The output from this work will help identify actual human and animal adverse event data that can help to define the reliability and potential limitations of nonclinical data and testing paradigms in predicting human safety in Phase 1 clinical trials.

This database will help achieve IQ’s mission of advancing science-based and scientifically-driven standards to support innovation in pharmaceutical development. In the process of building this database, DruSafe will address questions related to the value of rodent and non-rodent testing, current nonclinical safety study designs, the value of animal models in predicting human adverse events in the clinic, and the potential to optimize nonclinical animal testing in support of the 3Rs principle.

A major deliverable during drug development is the designation and justification of the active pharmaceutical ingredient starting material (API SM). Selection of the API SM, which defines the starting point for GMP processing during the synthesis of the drug substance (DS), continues to be a much debated topic. Industry practices for selection vary based on company experience and interpretation of regulatory guidances.

In 2011, the API and Analytical Leadership Groups established an API SM Working Group (WG) to assess how IQ member companies make important decisions around how to designate and justify API SMs and their associated regulatory practices. The API SM WG chose to define this area by posing three fundamental questions: (1) How has the regulatory perspective on API SM designation developed? (2) What are peer companies doing now and how many steps from the API SM to the DS have been typically required to control carry-over of impurities with special consideration for potential genotoxic impurities? (3) What should the industry do, if anything, to improve the current process?

To understand current practices on the designation and justification of API SM across the IQ Consortium the WG surveyed member companies on four key areas: (1) DS attributes, (2) API SM attributes, (3) control strategy, and (4) regulatory practices and strategy. Respondents submitted data on a total of 50 API SMs encompassing 24 DS case studies. Case studies in the later stages of development (92% beyond Phase 2) were well-represented. The size of this data set has allowed the Working Group to obtain a great deal of information about how companies approach and develop their API SM strategies. The data was summarized in two publications in Organic Process Research and Development (OPRD). A third is in preparation.
Drug-Drug Interaction Victim

Presentation by Dr. Tonika Bohnert, Biogen Idec

Metabolism-based drug-drug interactions (DDI), which result from modulation of metabolic clearance in the presence of another co-administered drug or a polymorphism of a certain drug metabolizing enzyme, remain a key hurdle in the drug development process. Throughout the course of drug development, it is standard practice to assess new chemical entities (NCEs) for their ability to be (1) a victim (affected substrate drug) of a DDI mediated by another co-administered drug or a polymorphic enzyme or (2) a perpetrator (interacting drug) of metabolism-based DDIs.

Regulatory agencies such as the FDA and EMA require that potential drug interaction risks are thoroughly investigated before a drug can be registered. IQ DDI Victim Working Group was formed to evaluate existing knowledge of in vitro methods, in vivo preclinical studies, and the use of modeling and simulation (M&S) to best estimate the potential of an NCE to be a victim of metabolic DDIs in the clinic.

One specific focus of this Working Group is to understand the route of clearance (fCL) and the fractional contribution of an enzyme (fm) to overall clearance of an NCE, as these are the two key parameters in determining the magnitude of a potential metabolic DDI risk of an NCE as a victim drug. This effort will review strategies that pharmaceutical companies currently use to predict route of clearance and fractional metabolism of drug metabolizing enzymes of an NCE in humans, including CYPs & common non-CYPs enzymes. Examples were given to illustrate the successful and unsuccessful prediction of clinical fractional clearance from preclinical studies, including possible explanations and proposed future remedies.

The application of mechanistic modeling (e.g. PBPK) and the impact they have on clinical DDI study design and de-risking victim drug liability was also discussed. Dr. Bohnert then proposed a strategy for model selection, including recommendations on a relevant model’s application at different stages encompassing drug discovery & development, from clinical candidate selection to late stage development.

ICH-Q10

Presentation by Dr. Steve Laurenz, AbbVie

In 2008, the International Conference on Harmonization published the ICH tripartite guideline titled, Pharmaceutical Quality System Q10. This guideline describes a model for an effective pharmaceutical quality system. As quoted in the document, “ICH Q10 describes one comprehensive model for an effective pharmaceutical quality system that is based on International Standards Organization (ISO) quality concepts, includes applicable Good Manufacturing Practice (GMP) regulations, and complements ICH Q8 “Pharmaceutical Development” and ICH Q9 “Quality Risk Management”. The GMP QA LG established a WG on how a business culture implements these principles effectively and efficiently. Members of the WG developed and conducted a survey to understand how IQ member companies implemented these concepts and identify existing challenges. The survey results shared areas of strength for implementing the ICH Q10 principles: knowledge management, management responsibilities, process performance and product quality, and the PQS. Many respondents had deeper concerns with areas within these quality elements where member companies would guidance. Quality risk management and change management revealed deeper concerns. Based on this information, the GMP QA LG has formed two WGs to address gaps. In addition, the IQ GMP LG is considering working with a PDA technical group to collaborate on a comprehensive guidance for ICH Q10.
Clinical Pharmacology for Pediatric Drug Development

Presentation by Dr. Konstantina Vanevski, Bayer

After its inauguration in August 2011, the CPLG Pediatric Working Group successfully organized the first industry mini-symposium at the Workshop “Facilitating Pediatric Research with Modelling and Simulation” at the University of Pennsylvania Children’s Hospital in 2012.

Since this mini-symposium, the CPLG Pediatric Working Group has joined forces with other IQ Leadership Groups (e.g. Preclinical Safety LG), the Pediatric Group from the FDA Office of Clinical Pharmacology, NIH/National Institute of Child Health and Human Development, and academia to organize a Pediatric Symposium on 4 June 2014 in Washington DC. During this event, an engaging and interaction discussion with approximately 75 experts in pediatric drug development covered the following topics:

- How do we translate juvenile toxicity data on a drug to pediatric clinical trial design?
- ICH E11 process (Clinical Investigation of Medicinal Products in the Pediatric Population): describe process, understand what it takes, plan how to move forward and organize dedicate meeting to address this process.
- FDA pediatric guidance documents: discuss how the recent updates on the M&S and pediatric guidance document affect pediatric drug development.
- Differences between EMA & FDA, using case examples from industry in
  - extrapolation from adults to children,
  - timelines for submission and content of Pediatric Investigation Plan (PIP) and Pediatric Written Request (PWR)
- pediatric labelling practices.

Pediatric Drug Formulations

Presentation by Dr. Tzuchi (Rob) Ju, AbbVie

The DPLG Pediatric Working Group was formed in November 2012 with the mission of bringing together key stakeholders to advance pediatric formulation development and regulatory harmonization globally.

A major accomplishment of the WG was the completion of a global survey on current status of pediatric drug development and gaps. The survey results were presented during the EuPFI annual meeting in September 2014 and during a webinar hosted by Global Research in Paediatrics (GRIP), a UK-based a network of scientists aiming to stimulate and facilitate the development and safe use of medicines in children). Both presentations were well-received.

Another major accomplishment of the WG was the establishment of a formal partnership with EuPFI (European Pediatric Formulation Initiative, an influential consortium in pediatric development) to jointly address critical areas that were identified from the survey. Some of the critical areas include:

- Age-appropriate dosage forms acceptable in different regions of the world;
- Lack of clarity and misalignment between FDA and EMA on type and amounts of excipients that can be used in pediatric formulations;
- Need for improved and standardized methods to assess palatability and taste; and
- Need for increased understanding of biopharmaceutics in pediatric subjects.

The Working Group’s foci for the coming two years include promotion of global regulatory alignment, working with FDA to develop a global case study “database”, and developing reflection papers or position papers in excipient use, age-appropriate formulations, palatability, and biopharmaceutics.

Dr. Tzuchi (Rob) Ju presents on IQ Drug Product Pediatric WG Formulations.
The IQ 3Rs Leadership Group (LG) is a first-of-its-kind collaboration specifically focused on coordinating and championing efforts to reduce animal use in the development of novel therapeutics. Scientists in vastly different fields within Pharma are concerned with this topic.

For example, interests in application of blood micro-sampling by colleagues in the drug metabolism community could limit the need for animals added to a study design to accommodate the volume requirements of traditional pharmacokinetic analyses. Preclinical safety colleagues are interested in broadening the use of in vitro and in silico modeling approaches that might identify compounds likely to fail in subsequent in vivo studies preventing those studies from being done. Refinements in the application of 2-year carcinogenicity bioassays (studies with large numbers of animals) might also reduce overall animal use for preclinical safety. The 3Rs LG is looking to create partnerships between Pharma groups that traditionally use animals.

The Regulatory Outreach Working Group of the 3Rs LG is interested in engaging a stakeholder with considerable influence on animal use in drug development. The pharmaceutical industry is a highly regulated industry where significant expectations for testing (including animal testing) exist throughout the world. Those expectations are well-defined in some areas (preclinical safety) and less so in others (efficacy testing). This working group is attempting to engage regulators to understand the distinction between real and perceived expectations that might influence animal use to support regulatory submissions, identify their perspectives on areas for animal use refinement, and also partner with related agencies that have a role in validating non-animal approaches.

The WG’s ultimate goal is to foster optimized use of animals to support the development of safe and effective medicines by applying the most impactful scientific practices, animal-based or otherwise.

Collaboration between Sponsors and CROs:
Understanding the Impact of Timeline Pressure on the 3Rs

This WG is a collaboration between Sponsors and CROs to understand the impact of timeline pressure on the 3Rs.

Sponsors and CROs work under timeline pressure to produce data supporting pharmaceutical development, yet individuals involved in outsourcing from both parties may not be fully aware of timeline impacts on study integrity, animal welfare, and regulatory compliance.

A team of 3Rs members and select CRO leaders collaborated to develop a quick training tool that would raise awareness of potential repercussions of timing decisions, provide common language for discussion, and increase mutual understanding of the outsourcing process/study planning.

Currently, the training is being piloted with individuals in both sponsor and CRO organizations. Feedback is being collected to evaluate the efficacy of the program, and inform future steps including revision and possible promulgation to the industry.
2014 IQ Recognition Award Recipients

John Orr
The Analytical Leadership Group would like to recognize John for his outstanding leadership and dedication to the Analytical Leadership where he has served as Vice Chair and Chair in the past two years. His contributions to IQ also include co-authoring the recent PAT publication, an ACS Editors' Choice article, co-authoring a publication on API Starting Materials, and recently co-chairing the 2014 CMC Leadership group Summit in Philadelphia. We thank him for his diligence and hard work, and we are proud to present him with this recognition.

Qinggang Wang
The Analytical Leadership Group would like to recognize Qinggang for his exemplary leadership of the Analytical Methods Comparability (AMG) working group. Under his leadership, the WG is set to publish a white paper highlighting a risk-based approach to method comparability which the FDA has agreed to review. Due to this interest, the group is looking to develop additional partnerships on key topics of interest to the FDA and industry in the near future.

Raja Mangipuddi
The Preclinical Safety Leadership Group would like to recognize Raja for his excellent coordination and authorship of the first manuscript/letter from the PSLG DruSafe entitled “Use of Animals for Toxicology Testing is Necessary to Ensure Patient Safety in Pharmaceutical Development”. There is an active debate in toxicology literature about the utility of animal testing as it relates to alternative in-vitro paradigms. To provide a balanced perspective and to add to this discourse Raja reviewed current paradigms, explored alternatives, and created a vision for the future. This Editor in Chief of the journal Regulatory Toxicology and Pharmacology, recognizing the importance and timeliness of this letter, recommended that the authors expand the letter to either a commentary or a full article. The resulting piece underwent an expedited review and was accepted within two weeks of its submission.

Roy Kerlin
The Preclinical Safety Leadership Group would like to recognize Roy for his role in presenting and leading the discussion between IQ PSLG DruSafe and FDA Pharm/Tox Supervisors on July 30th, we would like to present Roy with the IQ Recognition award. Roy’s detailed approach to recognizing Adverse versus non-Adverse findings in non-clinical toxicity studies elicited a robust discussion from FDA Supervisors, which garnered support for the overall proposals. The presentation also prompted DruSafe member companies to reconsider their own practices in hopes of achieving higher success rates with submissions. Roy and his co-authors plan to publish these Best Practices in a manuscript next year. This strong performance will potentially strengthen the IQ-FDA relationship, facilitating future interactions.

Dennis O’Connor
The Good Manufacturing Practices Quality Assurance Leadership Group would like to recognize Dennis for his energizing leadership and dedication to the GMP QA LG. With membership floundering, Dennis generated a survey to determine the LG’s mission and worked tirelessly to engage members on a clearly articulated goal. He spearheaded collaboration between the GLP and GMP groups in hopes of engaging industries outside of Pharma in the implementation of innovative quality solutions. He has been an active member of the ICH Q10 WG and leads the newly established Change Management Working Group.

Hannah Jones
The Drug Metabolism Leadership Group would like to recognize Hannah and Stephen as leaders of the PBPK Working Group, a collaborative working group between DMLG and CPLG. Hannah led the rapid creation of a consolidated position on best practices and parameter definitions in providing modeling data to answer important questions regarding drug disposition, metabolism and drug interactions. This resulted in publication of a seminal white paper on behalf of IQ entitled “Physiologically Based Pharmacokinetic Modeling in Drug Discovery and Development.” She has also used the WG output to lead an FDA sponsored workshop on the topic, which may provide the basis of a new draft PBPK FDA guidance.

Steve led the PBPK Working Group to its rapid publication of a white paper on PBPK modeling for drug development. The paper, which focuses on many key issues related to regulatory submissions, served as the basis for a joint IQ-FDA workshop and is expected to be the framework for an upcoming FDA PBPK draft guidance.

Greg Slatter
The Drug Metabolism Leadership Group would like to recognize Greg for his fantastic leadership of a DMLG working group on the development of best practices for assessment of in vivo human metabolism and disposition. Greg led the group in creating a survey to understand how companies use traditional human ADME tracer studies versus newer MS-based profiling techniques in providing earlier characterization of circulating human metabolites per recent MIST FDA guidelines. The group’s work resulted in a white paper publication, numerous conference posters and talks and a IQ member webinar.

Letty Medina
The 3Rs Leadership Group would like to recognize Letty for her leadership in the 3Rs LG. She led the group in creating a cross-company survey and in publishing numerous papers for the 3Rs, including a review on the harmonization of animal needs and the work of CROs. She is one of two editors-in-chief of a special issue for the Journal of Laboratory Animal Science on science and the 3Rs. Letty is professional, passionate and dedicated to ensuring the science needed for drug discovery and development is balanced with the science of animal well-being and welfare.
Symposium Panelists

Following the IQ Working Group presentations, there was panel discussion on the strategies for overcoming obstacles in pre-competitive collaboration and innovation. The panel was comprised of:

- Moderator: Ingrid Mergelsberg, Merck
- Steve King, AbbVie
- Margaret Faul, Amgen
- Tom Monticello, Amgen
- Donna Clemons, AbbVie
- Akitunde Bello, Pfizer

Panel Discussion: Drs. Steve King, Margaret Faul, Donna Clemons, Akitunde Bello, Tom Monticello, and Ingrid Mergelsberg (left to right) fielded questions from the audience.

Save the date for next year’s Symposium on October 8, 2015!