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MINI-REVIEW

Collaborations between Clinical Pharmacologists in Japan and in the United States - Report from the IQ CPLG and JPMA CPTF Meeting in Tokyo, Japan

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The International Consortium for Innovation and Quality in Pharmaceutical Development (IQ) Clinical Pharmacology Leadership Group (CPLG) held its first meeting of Japan-based representatives at Astellas Pharma headquarters in Tokyo on October 1, 2019. The meeting was also attended by Japan Pharmaceutical Manufactures Association (JPMA) Clinical Pharmacology Task Force (CPTF) members. Overall, nearly 30 clinical pharmacologists representing 14 companies attended the event. The meeting met its goal of enhancing mutual understanding of each organization's activities. In a number of break-out sessions, participants identified scientific topics for potential future collaboration between JPMA CPTF and IQ CPLG.

OVERVIEW OF INTERNATIONAL CONSORTIUM FOR INNOVATION AND QUALITY IN PHARMACEUTICAL DEVELOPMENT AND CLIICAL PHARMACOLOGY LEADERSHIP GROUP

The International Consortium for Innovation and Quality in Pharmaceutical Development (IQ Consortium) is a technically focused, cross functional organization with a mission of advancing science and technology to augment the capability of member companies to develop transformational solutions that benefit patients, regulators, and the broader research and development community. The IQ Consortium was formed in 2009 and is made up of more than 35 pharmaceutical and biotechnology companies (see full list in **Supplementary Materials**) engaged in innovative research and development. The IQ Consortium provides a platform for precompetitive information exchange, benchmarking, data sharing, and other joint initiatives.

The IQ Consortium consists of 10 discipline leadership groups (see full list in **Supplementary Materials**) including the Clinical Pharmacology Leadership Group (CPLG). The CPLG's mission is to address themes of experimental design, analysis, translational sciences, and the integration of nonclinical and clinical data to enable dosing and labeling recommendations. It also provides scientific counsel to the pharmaceutical industry, regulatory authorities, and academia striving to achieve two major goals: (1) to identify opportunities where existing development practices can be improved through evolution of study design, analysis, and regulatory guidance, and (2) to define new practices that facilitate learning and decision making for emerging technologies and new modalities. These goals serve the ultimate mission of providing optimal benefit to patients.

IQ operates through collaborations between its various leadership groups and more broadly with scientific and regulatory communities. The CPLG currently has 13 working groups focusing on various scientific topics (**Table 1**). Many of the CPLG working groups collaborate with other life sciences leadership groups within IQ. With the support of the secretariat, Faegre Drinker Biddle & Reath LLP (Washington, DC), IQ has established a precompetitive data sharing framework that allows for creation of individual custom databases. The dissemination of best practices and knowledge sharing is also achieved through benchmarking surveys, webinars, publications, public presentations, and discussion groups.

Externally, the IQ CPLG has collaborated with a number of organizations such as the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) working groups on E14 Question and Answer Revision 3 regarding thorough QT waiver[1,2] and Biopharmaceutics Classification System (BCS) classification for biowaivers.[3] Additionally, the IQ CPLG has collaborated with the European Federation of Pharmaceutical Industries and Associations (EFPIA) on providing comments on the European Medicines Agency's (EMA's) first-in-human trial guideline,[4] participated in annual scientific exchanges with the US Food and Drug Administration (FDA) Office of Clinical Pharmacology (OCP), and presented an industrial perspective on pharmacokinetic (PK) studies in organ impairment patients at an FDA Advisory Committee meeting.[5] The IQ CPLG had an introductory meeting with the Pharmaceuticals and Medical Devices Agency (PMDA) in September 2019.

Many companies are members of both the IQ CPLG and the Japan Pharmaceutical Manufacturers Association (JPMA) Clinical Pharmacology Task Force (CPTF).

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Table 1 Working Groups under the IQ Clinical Pharmacology Leadership Group (as of May 2020)

Working group	Deliverables	Collaborating
Guidance committee	Collect, compile, submit comments to national, international guidelines	
QSP (phase II)	Best practices for model qualification; education/information sharing with industry and the FDA	TALG
MIDD	Developing manuscript to support MIDD/FDA meetings; plan future MIDD workshop or webinar (collaborating with ISoP)	TALG
Pediatrics	Developed workshops, presentations, publications	
Blinding in exploratory clinical trials	Conducted industry survey and information collection	
New modalities exploratory group	Conducted industry survey to define scope; assessing results	
Innovative clinical trial design	Publishing manuscripts	
BCS Biowaivers (ICH M9)	Published manuscripts; coordinated with ICH; developing IQ webinar	DPLG, TALG
Transporters	Collecting data from industry into IQ database (non-clinical and clinical)	TALG
ADC	Collecting data from industry into IQ database	TALG
Organ impairment	Developing survey on industry practices and regulatory responses; developing presentation to the FDA	TALG
Patient-centric sampling	Best practices for implementing patient-centric sampling; understanding potential regulatory implications	TALG led
DDI M12 commenting group	Preparing for commenting to ICH M12	TALG led
Japan Subteam	Liaising with PMDA and JPMA	TALG
MABEL	Benchmarking survey; presentations; publishing manuscript (to sunset soon)	DruSafe, TALG
COVID-19	Sharing information on how companies are conducting clinical trials during COVID-19 with focus on pharmacokinetic and pharmacodynamic data gathering and missing data. Developing survey.	
Ophthalmics	Clarifying deliverable details and timelines	TALG, DruSafe

ADC, antibody-drug conjugate; BCS, Biopharmaceutics Classification System; COVID-19, coronavirus disease 2019; DDI, drug-drug interaction; DPLG, Drug Product Leadership Group; DruSafe, Drug Safety Leadership Group; FDA, US Food and Drug Administration; ICH, International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use; IQ, International Consortium for Innovation and Quality in Pharmaceutical Development; ISoP, International Society of Pharmacometrics; JPMA, Japan Pharmaceutical Manufacturers Association; MABEL, minimum anticipated biological effect Level; MIDD, Model Informed Drug Development; PMDA, Pharmaceuticals and Medical Devices Agency, Japan; QSP, Quantitative System Pharmacology; TALG, Translational and Absorption, Distribution, Metabolism, and Excretion (ADME) Sciences Leadership Group.

OVERVIEW OF JPMA CLINICAL PHARMACOLOGY TASK FORCE

The JPMA is a voluntary association of research-oriented pharmaceutical companies in Japan. It was established in 1968 and consists of 72 member companies as of April 2019. The CPTF belongs to the Clinical Evaluation Panel, Drug Evaluation Committee of the JPMA, and is made up of 19 member companies as of October 2019 (see full list in **Supplementary Materials**).

The purpose of the JPMA CPTF is to (1) investigate issues associated with the application and implementation of clinical pharmacology and PKs in clinical development, (2) communicate with regulatory agencies, PMDA/Ministry of Health, Labour, and Welfare (MHLW), and to provide insights on the drug application, review, and approval process in Japan. The JPMA CPTF has three current areas of focus: the design of clinical pharmacology studies, the use of clinical biomarkers, and pharmacometrics, and has established working groups for each of these. The JPMA CPTF holds roundtables with the Japan PMDA. The most recent on the topic of model-informed drug development (MIDD) was held in February 2020. The JPMA and academics also provide input as co-authors on relevant PMDA's guidelines development. Examples include a Guideline on Population Pharmacokinetic and Pharmacodynamic Analysis published in May 2019,[6] and guidances on exposure-response analysis, and physiologically-based pharmacokinetic (PBPK) model analysis, which were recently issued for public consultation.

OUTPUTS FROM BREAK-OUT DISCUSSION SESSIONS

Both IQ CPLG and JPMA CPTF have ongoing efforts to seek collaborations with the PMDA. Nearly 30 clinical pharmacologists representing 14 companies (**Figure 1**) participated in the October 1st meeting. They formed two break-out sessions, and identified (1) topics on which JPMA CPTF and IQ CPLG could collaborate, and (2) clinical pharmacology-related topics that could be discussed with the PMDA.

IQ CPLG and JPMA portfolios: Identifying areas for collaboration on scientific topics

Some areas of common interest to both organizations include:

1. Application of PBPK, including evaluating mechanisms of absorption and dissolution for oral products. Under the Japanese regulatory guideline of clinical pharmacology for clinical development, it is necessary for a sponsor to investigate food effects on a drug using a final formulation, which should be bioequivalent to a commercial formulation. In

Figure 1 Participants of the International Consortium for Innovation and Quality in Pharmaceutical Development Clinical Pharmacology Leadership Group and Japan Pharmaceutical Manufactures Association Clinical Pharmacology Task Force Meeting at Astellas Pharma Headquarters in Tokyo, Japan

the United States and the European Union, however, food effect studies tend to be conducted at an earlier stage in the development process. The CPLG is participating in a working group with the TALG to gather clinical food effect data in order to help refine the strategy to study food effect during development. The outcome of this work may aid the development of guidelines on when it is acceptable to waive food effect studies using the final formulation. In addition, investigation of theoretical ethnic differences in the absorption phase is a topic of mutual interest to drug developers and regulators.

2. Methods of assessing ethnic difference in pharmacokinetics. Ethnic PK/pharmacodynamic comparison in phase I studies supported by pharmacogenetic analysis and pharmacometrics analysis, including PBPK modeling, are commonly used methods to assess ethnic differences in PKs. From the global phase I study design perspective, ICH[7] recommends conducting global phase I trials and to enroll Japanese subjects as an additional cohort. Further understanding any flexibility in global phase I study design regarding the PMDA requirements would be useful to sponsors. There are different design options. Two options are including a separate Japanese cohort or randomizing Japanese subjects to each dose cohort with non-Japanese subjects. It is also important to consider the PMDA's requirements on data when designing a global phase I study. For example, the PMDA usually requires a sponsor to provide a summary of PK parameters, such as mean ± SD meaning at least three Japanese subjects would be needed in each cohort.
3. Phase I data package required before joining multiregional clinical trials and the required clinical pharmacology data package for a Japanese new drug application. Investigation of these data packages are related to the topic b) above. In addition, mutual use of PK data, if available, from other East Asian populations is a topic of interest.
4. Precompetitive sharing of quantitative systems pharmacology (QSP) models. QSP model building is a major endeavor because of the complexity. Each member company has individual models and approaches. Regulatory agencies may not have the resources or expertise to evaluate the validity of QSP models submitted by a sponsor especially in the context of a time constrained review cycle. Sharing general aspects of model development and features across companies for communication to regulators could enhance understanding and utility of QSP modeling. Further topics for potential discussion include, but are not limited to, determination of the optimal clinical development stage to apply QSP. The IQ CPLG currently has a QSP working group and JPMA is discussing QSP in its clinical biomarkers working group. There is an opportunity for information/knowledge sharing between these groups.
5. Improving understanding of the role of clinical pharmacology with respect to development of new therapeutic modalities. The CPLG has a new working group established on new modalities focusing specifically on cell and gene therapies.

Potential areas for regulatory/scientific interaction with the PMDA

"Proactively building consensus with global regulators on issues and opportunities to advance innovation and quality in pharmaceutical development" is one of IQ's strategic objectives. Two break-out groups discussed potential topics that could form the basis of interactions with the PMDA to achieve this IQ objective.

There are many IQ topics that could potentially be discussed with the PMDA and would likely be of interest to the Agency. Such topics include: QSP, Minimal Anticipated Biological Effect Level, transporter-based drug-drug interactions, innovative clinical trials (including digital, wearable technologies), PBPK modeling in pediatrics, organ impairment, food effect, formulation development, absorption, pediatric extrapolation, blinding in exploratory clinical trials, antibody-drug conjugate, MIDD, and new modalities. Participants agreed that an IQ Japan Subgroup should be formed, which would allow efficient interaction with the PMDA and to continue regular information sharing between IQ CPLG and JPMA. Ideas for collaborations with the PMDA on scientific topics include the following:

1. The clarification of the regulatory path in Japan for MIDD consultation and communication with the

PMDA could be an immediate/short-term topic. There are proposals for IQ CPLG member companies to publish or present experiences with respect to the FDA MIDD pilot program. Sharing MIDD case studies and the impact on labeling and/or development decision making would be of value to highlight the value of MIDD in decision making within the PMDA.
2. A longer-term interest is to form collaborations between JPMA and IQ for interactions with the PMDA. The two organizations could identify topics of mutual interest, initiate a working group to develop content, and consider appropriate types of information gathering (e.g., survey, data collection, and other). Topics could be focused on Asia-specific issues. Two examples are the necessity for the inclusion of Asian populations in clinical trials and ethno-PK studies in Asia.
3. IQ CPLG has a guidance committee (see **Table 1**) that has been actively reviewing and commenting on draft guidances issued by the FDA and the EMA. Activities for this committee could be expanded to include PMDA draft guidances as well. This would help promote consistency in regulatory requirements across regions.
4. Waivers for *in vitro* bioequivalence studies based on BCS is another potential area for collaboration with the PMDA. The IQ CPLG BCS Biowaivers (ICH M9) working group (see **Table 1**) has published a scientific white paper, which may further share case studies to facilitate the implementation of ICH M13 in Japan.

CONCLUSION AND FUTURE ACTIONS

The IQ CPLG successfully held a meeting with its Japan-based representatives at Astellas Pharma headquarters in Tokyo on October 1, 2019. This was the first IQ meeting to be held in Japan and was also attended by members of JPMA CPTF. The meeting provided a venue to foster and enhance the mutual understanding of the capabilities, portfolios, strategic focus, and current projects of the two organizations. Meeting participants expressed enthusiasm for future collaborations between the two organizations with the aim of advancing the discipline of clinical pharmacology through enhancement of state-of-the-art approaches in drug development in Japan.

The IQ CPLG leadership has reported on this meeting to CPLG members and to other leadership groups in the IQ Consortium. An IQ CPLG Japan Subgroup is being convened as a working team to advance some of the meeting outputs.

Supporting Information. Supplementary information accompanies this paper on the *Clinical and Translational Science* website (www.cts-journal.com).

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