



2022

YEAR IN REVIEW

 **DILI**

DRUG INDUCED LIVER INJURY



INTERNATIONAL CONSORTIUM for
INNOVATION & QUALITY
for PHARMACEUTICAL DEVELOPMENT

MESSAGE FROM THE IQ DILI CO-CHAIRS

Ajit Dash
Genentech



Alex Kiazand
AstraZeneca



Reflecting on 2022, we feel a sense of pride in the work and progress the IQ DILI Initiative has accomplished. Since its launch in 2016, the Initiative has built a strong and vibrant community of global experts across industry, academia, and regulatory agencies. Our community continues to grow as we develop high-impact deliverables addressing the challenges associated with monitoring and diagnosing drug-induced liver injury (DILI) in clinical trials and new drugs.

IQ DILI's success is only possible through its engaged members and external collaborators. After years of navigating a virtual environment in light of the pandemic, IQ DILI held its first in-person meeting in Washington, D.C. in November. We continue to make progress in developing new best practices, publications and data-sharing projects to improve clinical practice and research in DILI. In 2022, IQ DILI also conducted a detailed prioritization effort to identify and scope new projects and working groups.

We want to take this opportunity to share our gratitude for the support, engagement, and drive of our DILI participants. We look forward to another productive year. It has been a great pleasure serving as the IQ DILI Co-Chairs. We welcome the 2023 Co-Chairs, David and Meenal, as they lead IQ DILI to new heights.

2022 IQ DILI LEADERSHIP

PAST CO-CHAIRS

Dan Seekins
Bristol Myers Squibb

John Marcinak
AbbVie

CO-CHAIRS

Ajit Dash
Genentech

Alex Kiazand
AstraZeneca

CO-CHAIR ELECTS

David Brott
Takeda

Meenal Patwardhan
AbbVie

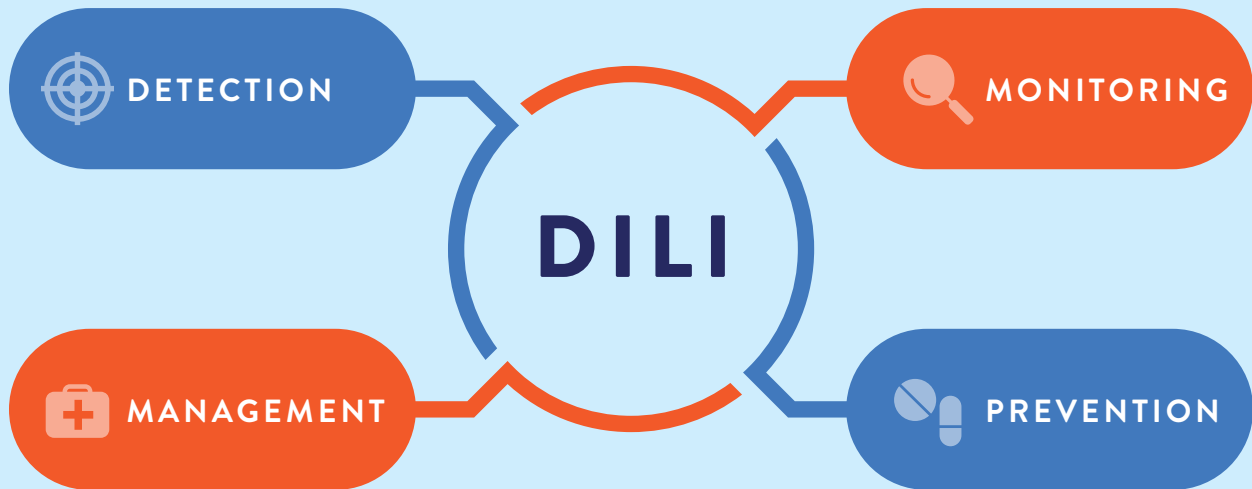
IQ DILI WELCOMES THE 2023 CO-CHAIR ELECTS

Judith Hey-Hadavi
Pfizer

Jesse Shick
Gilead

MISSION

The IQ-DILI Initiative is focused on defining best practices for the detection, monitoring, management and prevention of DILI in clinical trials and post-marketing pharmacovigilance programs.



IQ DILI MEMBER COMPANIES

AbbVie

Aligos

Amgen

AstraZeneca

Bayer

Bristol Myers Squibb

Daiichi Sankyo

Eli Lilly

Genentech

Gilead

GSK

Janssen

Merck

Mirum

Novartis

Otsuka

Pfizer

Sanofi

Takeda

IQ DILI INITIATIVE IMPACT



40+

Academic & regulatory experts engaged in IQ DILI activities



20+

Academic institutions & regulatory agencies represented



12

DILI publications under development



19

Member companies participating



10

Active working groups



5

Data-sharing projects



140+

In-person & virtual meetings held



6

Best practices & consensus guideline papers published

I Q D I L I

PUBLICATIONS

Cholestasis

Palmer, M, Regev, A, Lindor, K, Avigan, M, Dimick-Santos, L, Treem, W, Marcinak, JF, Lewis, JH, Anania, FA, Seekins, D, Shneider, BL, Chalasani, N. (2019). [Consensus guidelines: best practices for detection, assessment and management of suspected acute drug induced liver injury occurring during clinical trials in adults with chronic cholestatic liver disease](#). Aliment Pharmacol Ther.

Biomarkers

Roth, SE, Avigan, MI, Bourdet, D, Brott, D, Church, R, Dash, A, Keller, D, Sherratt, P, Watkins, PB, Westcott-Baker, L, Lentini, S, Merz, M, Ramaiah, L, Ramaiah, SK, Stanley, AM, Marcinak, J. (2019). [Next-Generation DILI Biomarkers: Prioritization of Biomarkers for Qualification and Best Practices for Biospecimen Collection in Drug Development](#). Clin. Pharmacol. Ther.

NASH

Regev, A, Palmer, M, Avigan, MI, Dimick-Santos, L, Treem, WR, Marcinak, JF, Seekins, D, Krishna, G, Anania, FA, Freston, JW, Lewis, JH, Sanyal, AJ, Chalasani, N. (2019). [Consensus guidelines: best practices for detection, assessment and management of suspected acute drug induced liver injury during clinical trials in patients with nonalcoholic steatohepatitis](#). Aliment Pharmacol Ther.

Immunotherapy

Regev, A, Avigan, MI, Kiazand, A, Vierling, JM, Lewis, JH, Omokaro, SO, Di Bisceglie, AM, Fontana RJ, Bonkovsky, HL, Freston, JW, Uetrecht, JP, Miller, ED, Pehlivanov, ND, Haquec, SA, Harrison, MJ, Kullak-Ublick, Li, H, GA, Patel, NN, Patwardhan, M, Price, KD, Watkins, PB, Chalasani, NP. (2020). [Best practices for detection, assessment and management of suspected immune-mediated liver injury caused by immune checkpoint inhibitors during drug development](#). Autoimmun.

Abnormal Baselines

Treem, WR, Palmer, M, Lonjon-Domanec, I, Seekins, D, Dimick-Santos, L, Avigan, MI, Marcinak, JF, Dash, A, Regev, A, Maller, E, Patwardhan, M, Lewis, JH, Rockey, DC, Di Bisceglie, AM, Freston, JW, Andrade, RJ, Chalasani, N. (2020). [Consensus Guidelines: Best Practices for Detection, Assessment and Management of Suspected Acute Drug-Induced Liver Injury During Clinical Trials in Adults with Chronic Viral Hepatitis and Adults with Cirrhosis Secondary to Hepatitis B, C and Nonalcoholic Steatohepatitis](#). Drug Saf.

Causality Assessment

Hey-Hadavi, J., Seekins, D., Palmer, M. Coffey, D., Caminis, J., Abdullaev, S., Patwardhan, M., Tyler, H., Raheja, R., Stanley, A., Pineda-Salgado, L, Bourdet, D.L., Andrade, R.A., Hayashi, P.H., Dimick-Santos, L, Rockey, D.C., Estilo, A. (2021). [Overview of Causality Assessment for Drug-Induced Liver Injury \(DILI\) in Clinical Trials](#). Drug Saf.



MORE PUBLICATIONS TO COME IN 2023

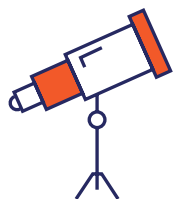
2022

ACCOMPLISHMENTS



Expanding Membership

- IQ DILI Trial Membership Program was extended until 2023
- Amgen was welcomed as a new member of the IQ DILI Initiative



Increasing Visibility and Outreach

- IQ DILI participated in the World Drug Safety Conference “U.S. Hepatic Safety and DILI” panel discussion on October 5, 2022
- CIOMS featured the Initiative in their July 2022 newsletter
- In November, the DILI Initiative held its first face-to-face meeting since the start of the pandemic; distinguished academic and regulatory guests expressed strong interest in the Consortium’s work



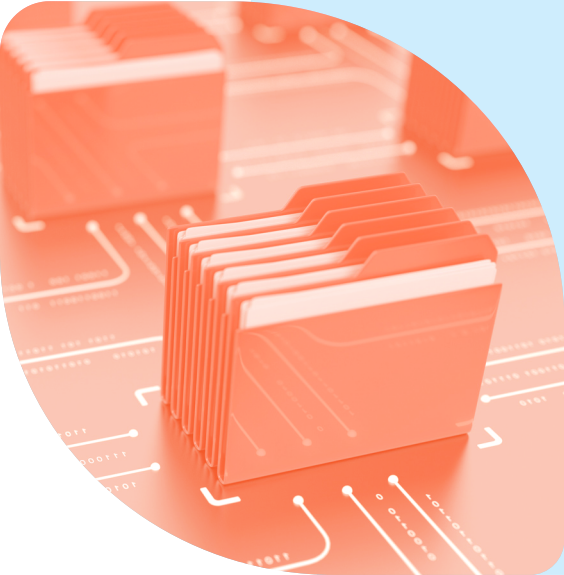
Launching New Activities

- IQ DILI successfully launched three scoping teams for next phase topics
- The DILI in New Gene Therapy scoping team was approved to be formally established as an IQ DILI working group
- The Nonclinical Working Group initiated new projects
- The Immunotherapy Working Group launched a new CAR-T cell sub-team



Facilitating Data Sharing

- The Causality Working Group completed their survey to define gaps and understand current practices regarding rechallenge
- In collaboration with NIDDK, the Pediatrics Working Group commenced analysis of long-term registry data on hundreds of patients with biliary atresia
- The Nonclinical Working Group launched a survey to assess changing practices in non-clinical DILI risk assessments



THE VALUE OF DATA SHARING

The IQ DILI Data Sharing Committee supports and provides guidance to Working Groups that embark on data-sharing activities. The committee develops roadmap and infrastructure to address priority research questions.

OBJECTIVE

- Facilitate selection of initial research proposals along with data access (new or existing) to allow analysis and publication
- Create a capability to allow evaluation, prioritization and execution of research concepts of interest to IQ DILI, creation and maintenance of database and analytic support

APPROACH

- Conduct a needs evaluation based on IQ DILI priority questions
- Conduct a landscape assessment to evaluate available data-sharing mechanisms and identify possible synergies with external clinical database efforts (e.g., Transcelerate)

EXPECTED OUTCOMES

- Identify both near-term opportunities and gaps that IQ DILI may need to fill as part of future efforts
- Create tools to support the development of working group research questions into data-sharing projects (e.g., prioritization scoring system, concept sheets, analytic plans and publication plans)
- Identify bioinformatics needs and resources

DATA SHARING & SURVEY PROJECTS

**Causality Assessment:
Liver Biopsy in Rechallenge Survey**

**Abnormal Baselines:
Normal Fluctuation vs DILI**

**Best Practices in Nonclinical
DILI Risk Assessment Survey**

**Biliary Atresia Natural
History, Baselines & Thresholds**



WORKING GROUPS

Allows experts in clinical DILI to discuss and publish on key topics that present challenges to preventing, diagnosing, monitoring and managing DILI in patients.

NEXT PHASE TOPICS

In 2022, IQ DILI companies prioritized topics of interest to launch new IQ DILI working groups and activities. Four topics were selected to move forward with scoping:

DILI in New Gene Therapy Drugs

DILI with Large Molecule Biologics

DILI in Clinical Management

CAR-T Cell Induced Hepatotoxicity
(Sub-team of Immunotherapy Working Group)

WORKING GROUP SPOTLIGHT

PEDIATRIC WORKING GROUP

Both subgroups of the Pediatric Working Group have continued to develop their papers on 1) normal ranges of liver enzymes and bilirubin in infants and children that should be used in interventional trials; and 2) fluctuations in liver tests in patients with biliary atresia and recommendations for criteria for increased monitoring, holding and stopping drug in interventional drug trials in biliary atresia. The second paper is a unique data sharing project between IQ DILI and the NIH sponsored ChiLDRen registry that makes use of the long-term registry data on hundreds of patients with biliary atresia that has been maintained and curated for more than 15 years. Drafts of these papers for review by our joint industry, academic and regulatory colleagues are expected by Q2-Q3, 2023.

THE POWER OF COLLABORATION

Reflections from IQ DILI Members



John Marcinak
AbbVie

Learning about DILI, so we could influence our own programs and make well-informed decisions. Also important was the academic and regulatory participation.



Anna Fettiplace
AstraZeneca

I most enjoyed meeting industry colleagues and secretariat face-to-face for the first time. Really important to working relationships to have met at least once face-to-face. I feel more embedded in the IQ DILI consortium, too.



Anju Garg
Sanofi

IQ DILI allows for industry-academia-regulatory agency collaboration. Topics that are particularly interesting to the company are ICI, Immunosuppression and post-marketing topics.



Lila Ramaiah
Pfizer

DILI is prioritized for external science and technology investments by our company since it remains an important cause of safety-related drug attrition. Preclinically, there is need for improved screening tools, while clinically there is need for novel biomarkers and drug development tools enabling safety risk detection, monitoring and management. For these reasons, senior leadership from preclinical and clinical organizations supported the decision to engage in the IQ DILI Initiative.

SECRETARIAT SUPPORT

IQ DILI Initiative is an affiliate of the [International Consortium for Innovation and Quality in Pharmaceutical Development \(IQ\)](#).

Consisting of attorneys, scientists and project managers, Faegre Drinker's consortium management team serves as the IQ DILI Secretariat and executes central legal and administrative tasks. Team support includes developing consensus positions on strategic initiatives and projects by facilitating member company decision-making processes within the IQ DILI:

- Ensuring antitrust compliance by providing training, oversight and ad hoc legal counsel
- Providing broad scientific, project management, legal and administrative support
- Providing the Steering Committee with robust strategic, operational and planning support, including agendas, minutes, and presentations for meetings and teleconferences
- Supporting the exploration and scoping of data-sharing initiatives
- Reviewing manuscripts under development to ensure antitrust compliance
- Facilitating IQ DILI's external collaborations
- Managing internal and external communications
- Managing IQ DILI's website
- Providing venue and logistical support for in-person meetings



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