IVIVE of Transporter-Mediated Clinical Drug-Drug Interactions in Industry –

An Update from the IQ Transporter Working Group

Kari Morrissey, Genentech

on behalf of the IQ DMLG/CPLG Transporter Working Group

ITCW3

March 14, 2017

Current IQ DMLG/CPLG Transporter Working Group Members

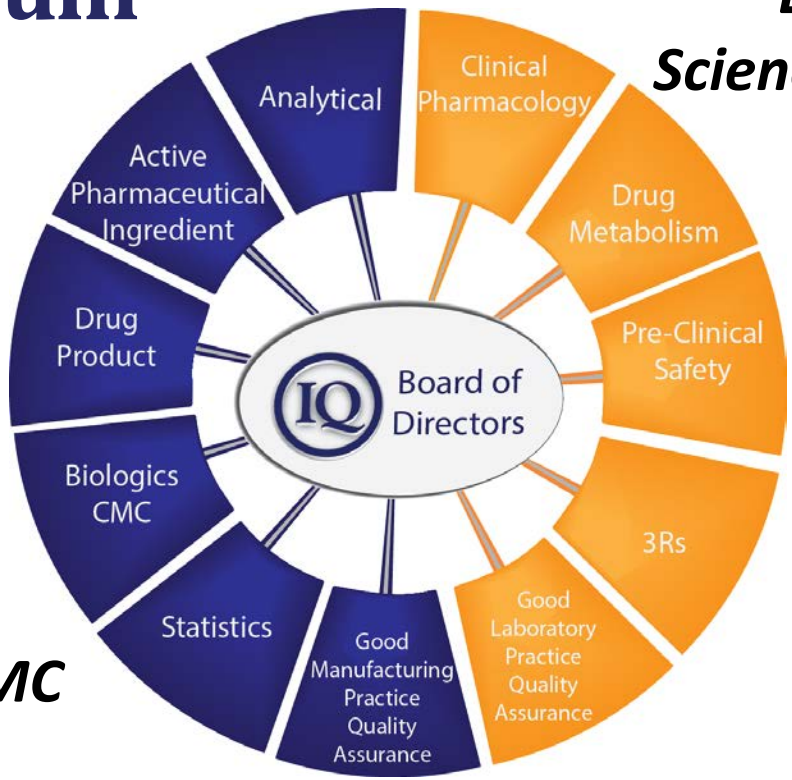
Proposal Architect: Marcel Hop (Genentech)

Kate Hillgren (Lilly) – *Group Leader*
Kari Morrissey (Genentech) – *Group Leader*
Xiaoyan Chu (Merck) – *In Vitro Group Lead*
Bo Feng (Pfizer)
Daniel Bow (AbbVie)
Guangqing Xiao (Biogen Idec)
Hugues Chanteux (UCB)
Imad Hanna (Novartis)
Joe Polli (GSK)
Katherine Fenner (AZ)
Laurent Salphati (Genentech)
Liping Pan (Takeda)
Nathan Pfeifer (Theravance)

Jim Keirns (Astellas) – *Sponsor*
Steve Hall (Lilly) – *Sponsor*
Satish Dayal (Eisai) – *In Vivo Group Lead*
Diane Phillips (Lilly)
Hui Tian (EMD Serono)
Kelly Mahar (GSK)
Liyue Huang (Amgen)
Mitch Taub (Boehringer Ingelheim)
Nathalie Chauret (Vertex)
Praveen Bahadduri (Sanofi)
Shannon Dallas (J&J)
Yan Zhang (Incyte)

Overview of IQ Consortium

The International Consortium for Innovation and Quality in Pharmaceutical Development (IQ) is a **technically-focused organization** of pharmaceutical and biotechnology companies 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 R&D community.



Life Sciences

CMC

IQ Member Companies:

AbbVie
Agios
Alexion
Alkermes
Allergan
Amgen, Inc.
Astellas
AstraZeneca
Baxter Healthcare
Bayer HealthCare
Biogen
Blueprint Medicines
Boehringer Ingelheim
Bristol-Myers Squibb
Celgene
Daiichi Sankyo
Eisai, Inc.
Eli Lilly and Company
EMD Serono
Endo Pharmaceuticals
Genentech
Gilead Sciences
GlaxoSmithKline
Incyte Corporation
Infinity
Ironwood Pharmaceuticals
Johnson & Johnson
Merck & Co.
Novartis
Otsuka
Pfizer
Pierre Fabre
Roche
Sanofi
Seattle Genetics
Shire
Sunovion
Takeda
Teva
Theravance Biopharma
UCB Pharma
Vertex, Inc.

Project Overview

Problem Statement:

Data from transporter DDI studies can be challenging to interpret due to poor in vitro to in vivo correlation as victims are frequently substrates of multiple transporters and inhibitors may inhibit multiple transporters/enzymes. Consequently, the need for and timing of clinical transporter DDI studies could benefit from additional scholarship.

IQ DMLG/CPLG Transporter Project Overview:

Collect in vitro and clinical transporter data on member company drugs and NMEs to:

(1) probe the in vitro to in vivo correlation of transporter drug interactions

(2) identify the overall magnitude of the interactions, their clinical implications, and evaluate the regulatory decision trees.

Data Collection

- **In vitro transporter studies**
  - Basic study design
  - Individual transporter assay results
- **Clinical transporter studies**
  - Reason for study initiation
  - Basic study design
  - Mean pharmacokinetic results
  - Clinical implications
- **Basic compound information** necessary for the interpretation of in vitro and clinical studies

Expected Results

The overall goal is to improve our understanding and risk management of clinical transporter-mediated DDIs, through:

- The evaluation of transporter decision trees and, if appropriate, suggest refinement(s).
- An improved understanding of predictability of clinically relevant transporter-mediated DDIs from in vitro data.
- The determination of the magnitude of transporter-mediated DDIs using clinical data for compounds from various companies, therapeutic areas/targets, and probe substrates/inhibitors.
- Understanding the clinical implications of transporter based drug-drug interactions.

Summary of results will be communicated in a white paper (expected: mid 2018)


Thank you!

Transporters of Interest

In alphabetical order

- BCRP
- BSEP
- MATE1
- MATE2K
- MRP2
- MRP3
- MRP4
- NTCP
- OAT1
- OAT2
- OAT3
- OAT4
- OATP1A2
- OATP1B1
- OATP1B3
- OATP2B1
- OATP4C1
- OCT1
- OCT2
- OCT3
- OST alpha/beta
- PEPT1
- P-gp