Submicron particle characterization and benchmarking under Biologics leadership group of the IQ Consortium

Mario Hubert (Bristol Myers Squibb)

on behalf of "Subvisible particles" working group

Workshop: PROTEIN AGGREGATION MEASUREMENT IN BIOTHERAPEUTICS: ESTABLISHED AND EMERGING TECHNIQUES

University of Maryland School of Pharmacy, Dec-5-2016

Agenda

- Introduction
- IQ Consortium, Leadership groups
- Subvisible particles working group
- Benchmarking study for submicron particles
- Collaborations
- Conclusions

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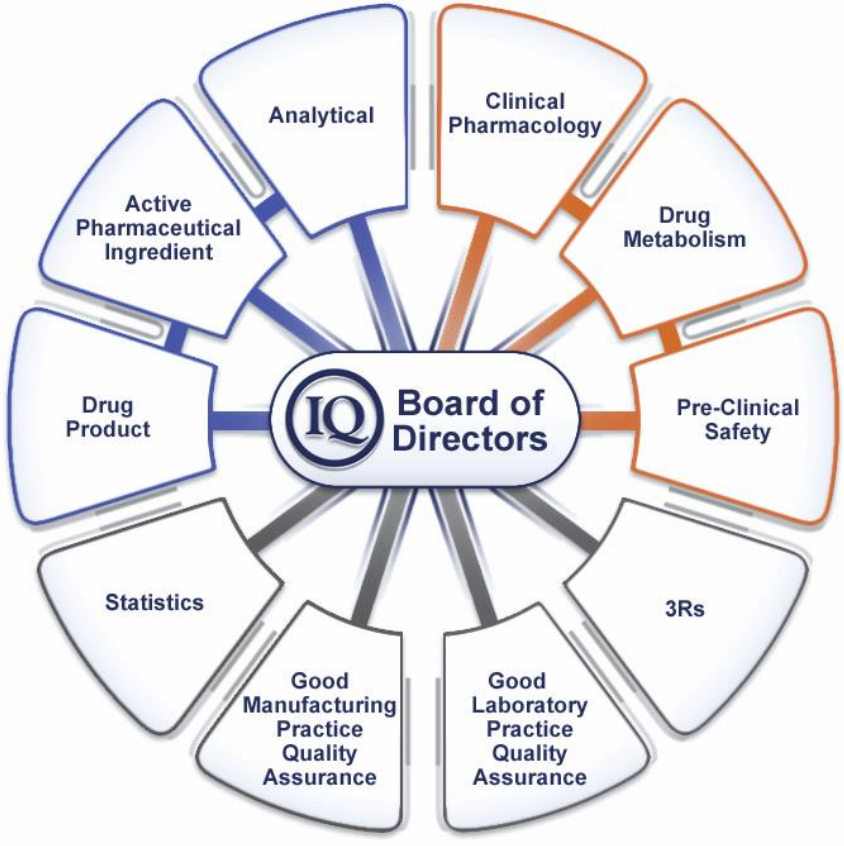
IQ Consortium

INTERNATIONAL CONSORTIUM for INNOVATION & QUALITY in PHARMACEUTICAL DEVELOPMENT

iqconsortium.org

- Formed in 2010.
- Mission:
- Advance science-based and scientifically-driven standards and regulations for pharmaceutical and biotechnology products worldwide

IQ Structure and Leadership groups



Analytical LG - Address issues related to analytical procedures and their validation, specifications, CMC documentation and compendial standards, and quality control testing

API LG - Advance phase- appropriate strategies that utilize efficient and sustainable processes to deliver high-quality drug substances

Drug Product LG - Influence the strategic direction of drug product development and manufacturing for the benefit of industry and patients

Biologics LG - encourage and support development of global science-based regulations for biologics

IQ membership

Member Companies

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

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Subvisible Particles – problem statement

- Subvisible Particles (SVP) is currently an ongoing FDA “hot topic”
- FDA expects characterization of particles in 0.1-100 um range as they are considered critical quality attributes and can potentially relate to drug product quality, safety/immunogenicity, efficacy, and potency.
- Currently no clear guidance on what to do and when to measure
- The question: What is the amount and range of submicron particles that patients have historically been exposed to? Should this be controlled, and if so to what level? is this being dealt with early in development? What sizes are looked at, when, where and how during product development?
- Are we doing the right thing? – looking at the right thing? – is there evidence for needing this? -how is this evidence (or lack thereof) being presented to the agency – what should be required and when?

Subvisible particles work. group

Team member

Mario Hubert (BMS)
Satish Singh (Pfizer)
Stephanie Fischmann (Abbvie)
Ankit Patel (Genentech)
Scott Aldrich (Ultramikro)
Linda Narhi (Amgen)
Dennis Yang (Eli Lilly)
Klaus Wuchner (Jansen, J&J)
Afonina Nataliya (-)
Tetsuo Torisu (Takeda)
Valentyn Antochshuk (Merck)
Anacelia Rios (Roche)
Tapan Das (BMS)
Haihong Fan (GSK)
George Bou-Assaf (Biogen)
Stan Kwok (Seattle Genetics)

Past team member

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Andrew Weiskopf (Biogen)
Atanas Koulov (Roche)
Mark Brader (Biogen Idec)
Jun Liu (Genentech)
John F. Ryan (Baxter)
Jamie Moore (Genentech)

Subvisible Particles – prior work

- Overlooking subvisible particles in therapeutic protein products. Gaps that may compromise product quality
  - Carpenter JF, Randolph TW, Jiskoot W, Crommelin DJ, Middaugh CR, Winter G, Fan YX, Kirshner S, Verthelyi D, Kozlowski S, Clouse KA, Swann PG, Rosenberg A, Cherney B. 2009. J Pharm Sci 98:1201–1205.
- An industry perspective on the monitoring of subvisible particles as a quality attribute for protein therapeutics,
  - Singh S (Pfizer), Afonina N (BMS), Awwad M (Pfizer), Bechtold-Peters K (Boehringer), Blue JT (Merck), Chou D (Genzyme), Cromwell M (Genentech), Krause HJ (Abbott / AbbVie), Mahler HC (Hoffman-LaRoche), Meyer BK (Merck), Narhi L (Amgen), Nesta DP (GSK), Spitznagel T (Human Genome Sciences)., J Pharm Sci. 2010 Aug;99(8):3302-21
- Subvisible (2–100 um) Particle Analysis During Biotherapeutic Drug Product Development: Part 1 Considerations and Strategy.
  - L. Narhi, V. Corvari, D.C. Ripple, N. Afonina, I. Cechini, M. R. Defelippis, P. Garidel, A. Herre, A. V. Koulov, T. LubinieckiI, H. C. Mahler, P. Mangiagalli, D. Nesta, B. Perez-Ramirez, A. Polozova, M. Rossi, R. Schmidt, R. Simler, S. Singh, T. M. Spitznagel, A. Weiskopf, K. Wuchner. Journal of Pharmaceutical Sciences, Vol. 104, 1899–1908 (2015)

Our working group ideas

- Focus on various particle size ranges
- Correlation of particles across size ranges (from nm to um)
- Technical evaluation of various techniques (NTA, RMM, flow cytometry, DLS, AUC, microscopy, Coulter, SLS, FFF …). Limitations, challenges, variability, robustness, Experience.
- Round Robin for NTA, RMM etc. for standards

Subvisible particles WG – Mission statement

The measurement and characterization of particles in the submicron size range (0.1 ~ 2 um) in biotherapeutic products has recently become viable with technical developments in instrumentation.

However, the robustness of the technologies and their proper use is still being explored.

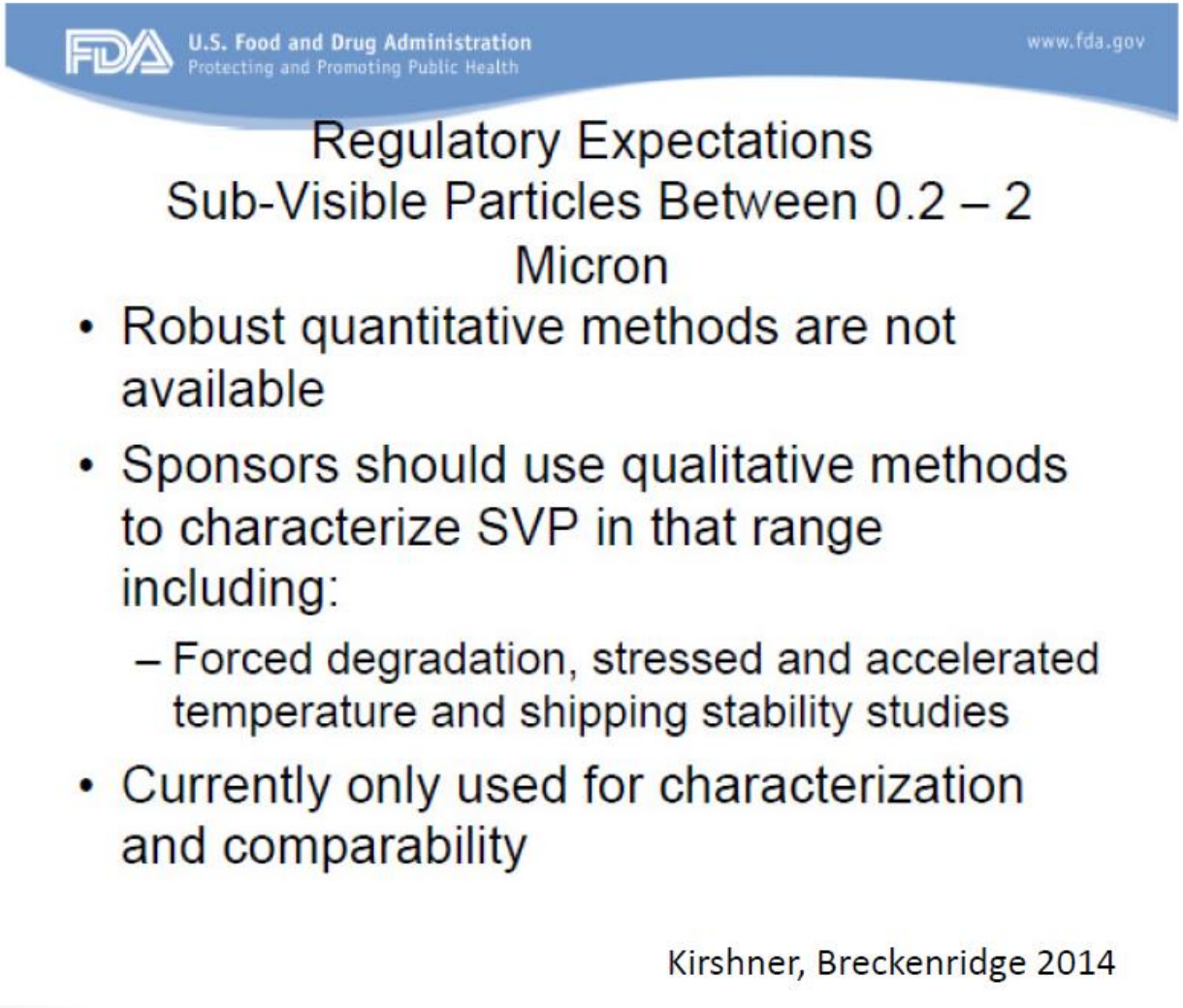
Furthermore, there is no benchmark or historical data to which the results obtained from such measurements can be compared, to help guide the development scientist.

What is a reasonable number of sub micron particles to expect in protein therapeutics? How many particles of this size are present, and what is the range in amounts of particles in products on the market or in the clinic?

The objective of this working group under the IQ Consortium is to

- Publish (anonymized) data from various laboratories on clinical or marketed products to enable development scientists to benchmark their own programs.
- Share analytical experience with the technologies to stimulate further technical and methodological developments in this area
- Discuss the regulatory requirements in this area to aid development scientists in interpreting their data and inform risk assessment and regulatory strategy

Subvisible particles work. group



Subvisible particles work. group

- Plan
  - Collect 0.1-2 um data for drug product presentations
  - Each sample measured in triplicates and ideally multiple lots measured for each product
  - Capture sample info and preparation.
  - Regularly measure calibration (NIST if available) standards to verify instrument performance
- Outcome/Deliverables – White paper
  - What is population/variability of 0.1-2 um particles in the products
  - What is value in measuring or monitoring 0.1-2 um particles
  - Is there value in characterization of these particles or just counting
  - Is there a need for specification: this could be informed by variability in results, tie to larger particles, etc.
  - What are risks actually associated with these kinds of particles
  - When to use and when not to use various techniques
  - Which lots (Dev/Preclin/Clin/PV) should be measured

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Methods

- NTA method is based on article
  - Filipe V, Hawe A, Jiskoot W. Critical Evaluation of Nanoparticle Tracking Analysis (NTA) by NanoSight for the Measurement of Nanoparticles and Protein Aggregates. 2010. Pharm Res, 27, (5)
  - Analyst is free to modify the method if it is required by their product
  - Samples are measured in triplicates
  - 200 nm polystyrene microsphere standard is measured in triplicates on regular basis (Nanosphere Size Standards from ThermoScientific 3000 Series)

- RMM method
  - Defined by our team
  - Analyst is free to modify the method if it is required by their product
  - Samples are measured in triplicates
  - 1 um polystyrene microsphere standard is measured in triplicates on regular bases (NIST-traceble size standard, Thermo Scientific, Cat# 4010A)

Data sharing challenge

- Several ideas on data sharing
  - One person from the working group would collect the blinded data from teammates
  - Third party (NIST, IQ secretariat …) would collect the blinded data and blind the data source

- Solution
  - IQ secretariat: Drinker Biddle & Reath LLP built a database for our working group that enables double blinding of the data
  - Each company had to sign two legal documents (general database framework agreement and particular working group database agreement) before being able to contribute and view data in the database.

Database

Sample Meta data information

	A	B	C	D	E	F	G	H	I	J
1	GENERAL SAMPLE INFORMATION									
2										
3										
4	Sample or Standard used	Sample Designation (Use same value for same chemical)	Sample Lot Number	Standard Lot Number	Run Number (Repeat)	Sample type: Lyo / Liquid / Other	Sample type: Other	Package: Vial / Pre-filled syringe / Other	Package: Other	protein conc.: <5 5-50 50-100 >100 mg/mL
5										
6	END									
7										

Liquid
Lyo
Other

Database

Nanosight (NTA) data

K	L	M	N	O	P	Q	R	S	T	U	V	W	X	Y
NANOSIGHT RESULTS FOR THE MEASURED SAMPLE														
Dilution factor	Total Valid Counts (particles/run)	Concentration** (Particles/mL)	Mean, [nm]	SD (instrument) nm	D90, nm	Particle Size 0-50 nm	Particle Size 50-70 nm	Particle Size 70-90 nm	Particle Size 90-110 nm	Particle Size 110-130 nm	Particle Size 130-150 nm	Particle Size 150-170 nm	Particle Size 170-190 nm	Particle Size 190-210 nm

Archimedes (RMM) data

BP	BQ	BR	BS	BT	BU	BV	BW	BX	BY	BZ	CA	CB	CC	CD	CE
ARCHIMEDES RESULTS FOR THE MEASURED SAMPLE															
										positive bouyancy					
Particle Density [g/cc]	Solution Density [g/cc]	# of Particles Measured [-]	Sensor Type	Dilution factor	Elapsed time (hh:mm:ss)	Sample Temperature [C]	Particle Range (um)	LOD [mHz]	LOD [um]	counts in 0.2-0.3 um [#/mL]	counts in 0.3-0.4 um [#/mL]	counts in 0.4-0.5 um [#/mL]	counts in 0.5-0.6 um [#/mL]	counts in 0.6-0.7 um [#/mL]	counts in 0.7-0.8 um [#/mL]
			Micro												
			Micro												
			Nano												

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Collaborations

- **NIST (Kurt Benkstein, Dean Ripple)**
  - Idea of adding “Round Robin” arm to our benchmarking study
  - Possible materials
    - NIST mAb – concerns about pre-stressing, storage and shipping
    - ETFE – potential clogging of RMM, larger density than proteinaceous particles
    - Mixture of Polystyrene latex (PSL) and PMMA beads. The mixture in glycerol/water could have a particle suspension of both positive and negative buoyant mass, and with two levels of refractive index difference between particle and fluid.
  - Samples: Mixture of PMMA (mixture of 5 “monomodal” standards from ~100 to 1100 nm) spiked with ~200 or ~500 nm PSL standards. Three PMMA mixture concentration samples were prepared (10^6, 10^7, 10^8 particles/mL)
  - Initial testing done by BMS (Mario Hubert, Wenhua Wang) and Elli Lilly (Dennis Yang, Dawn Norris)
  - Measured concentration different from anticipated. RMM did not see anything smaller than ~400 nm.

Collaborations

- **Genentech/Roche (Ankit Patel)**
  - Idea of adding “Round Robin” arm to our benchmarking study
  - Will share their protein standard with our working group so that we can gauge performance of our NTA and RMM instruments on real protein sample rather than just calibration standards
  - MTA between Roche and other companies
  - protein particles generated from thermal stress of Bovine serum albumin (BSA)

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Conclusions

- I wanted to
  - Introduce you to IQ Consortium
  - Share with you objectives and plans of our Subvisible particles working group
  - Hear your comments and/or suggestions regarding our goals/work.

Acknowledgment

- IQ Secretariat
- IQ Analytical Leadership group
- IQ Biologics Leadership group

- Current and past members of “Subvisible particles” working group

Subvisible particles work. group

Team member

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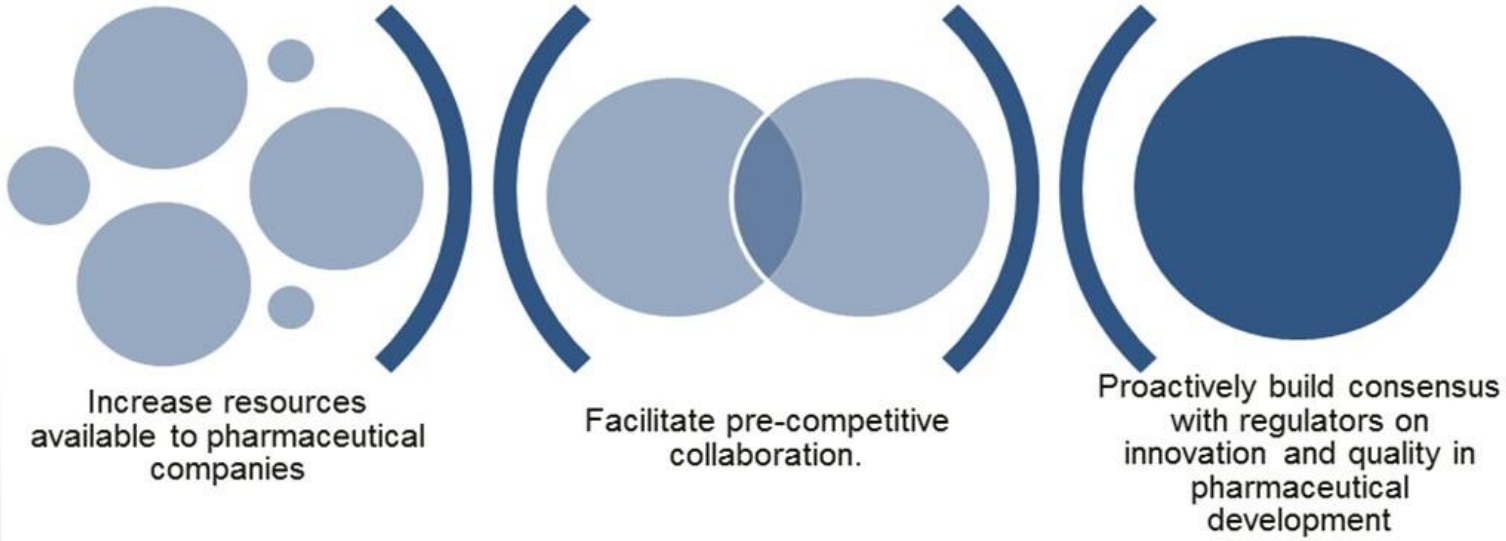
Thank You for Your Attention!

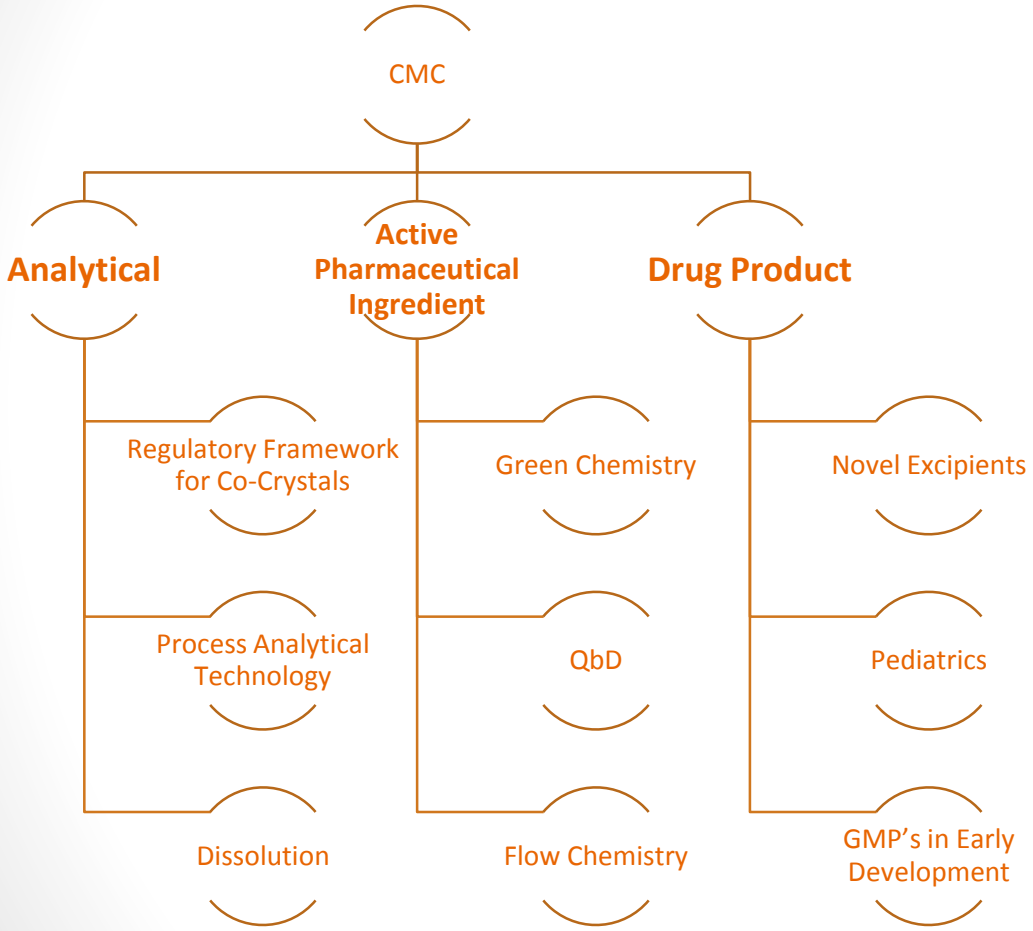
IQ Consortium

- IQ provides a sustained platform for information exchange, benchmarking, research, and other joint initiatives.
- The Consortium facilitates constructive exchange through publications, scientific conferences, workshops and roundtables, and regulatory interactions.



CMC

LGs &



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IQ Events

- "Implementation of SEND" SOT session – March 2015
- 2014 Lifecycles Approach to Validation of Analytical Procedures Workshop – December 2014
- Allotrope Foundation 2014 US Cross-Industry Workshop – October 2014
- 2014 IQ Consortium Symposium – "Innovation through Pre-competitive Collaboration" – October 2014
- Pediatrics WG Survey Results Presentation at EuPFI Conference – September 2014
- CPLG Pediatrics Workshop – June 2014
- PSLG organized "Translational Safety" SOT session (most attended session of the conference) – March 2014
- 3Rs Sharing Conference: Paving the Path to Regulatory Acceptance and Alternative Methods – February 2014
- GMPs in Early Development workshop – February 2014
- PAT WG Sponsored Session at IFPAC 2014, 2013, and 2012 "Multivariate Model Validation in a Quality Environment"
- IQ Symposium "Pharma Landscape in 2020" – November 2013
- "Data Driven Drug Development" Conference (co-sponsored with IIR) – January 2013
- IQ Symposium "Innovative Approaches to Quality" – December 2012
- IQ Symposium "Innovation" – November 2011

Events with FDA

Proactively building consensus with regulators

- **AACR/FDA/IQ Oncology Dose Finding Workshop** – May 2015
- **Physiologically-based Pharmacokinetic Workshop** at the FDA – March 2014
- Symposium on *"**Developing Microphysiological Systems for Use as Regulatory Tools – Challenges and Opportunities**"* – co-sponsored by FDA, NIH, EPA, IQ and other federal agencies (May 2013)
- IQ CPLG/DMLG Roundtable with FDA Office of Clinical Pharmacology on "***Model-Based Drug Development***" (Jun 2013)
- IQ 3Rs/PSLG Roundtable with FDA and CAAT on "***Enhancing 3Rs in Toxicology Studies***" (Jul 2013)
- **"Therapeutic Protein – Drug Interaction**" Workshop (co-sponsored with FDA) – June 2012

Webinars

- Neonatal Pharmaceutical Development Webinar – Q1 2015
- IQ Drug Metabolism PK/PD Working Group Webinar – Q3 2014
- IQ Drug Metabolism PBPK Working Group Webinar – Q2 2014
- 3Rs Role in Drug Discovery and Development – Q2 2014
- IQ DMLG Metabolites Webinar – June 2014
- Allotrope Framework – May 2014
- IQ Green Chemistry Webinar – April 2014
- Current Industry Practices in the in vivo Assessment of Human Drug Metabolism – October 2013
- Allotrope Foundation – May 2013
- Physiologically-based Pharmacokinetic Modeling – April 2013
- Preclinical Approaches to Suicidal Behavior – January 2013