INTERNATIONAL CONSORTIUM *for*
INNOVATION & QUALITY
in PHARMACEUTICAL DEVELOPMENT

Physicochemical In-use Studies: Industry Experts Insights

Isabella de Jong, Genentech
Jing Liu, Seagen

on behalf of IQ working group 'Physiochemical In-Use Stability Testing'

CASSS CMC Strategy Forum, 24th. Jan. 2022

Outline

Problem statement

Physiochemical In-Use Stability Testing Working Group

- Harmonized approach to conduct in-use study

Regulatory guidance

- Different interpretations & implementation from different companies.

Complications in practice

- Selection of testing materials
- Study design strategy – a possible solution
- Analytical methods & acceptance criteria

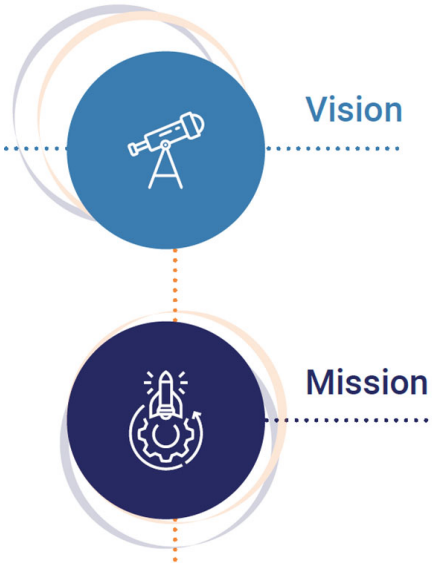
Conclusions

Problem Statement

- In-use stability and compatibility studies are critical to demonstrate product quality during administration
- Minimal guidance on Biologics in-use stability testing. Each country or region has different or unwritten expectations, causing challenges for global submissions.
- Administration components in fluid path highly diversified across clinical sites.
- Assay performance strongly affected by in-use matrix; challenging to set appropriate acceptance criteria
- Diversified approaches utilized by pharmaceutical companies to conduct in-use stability studies.

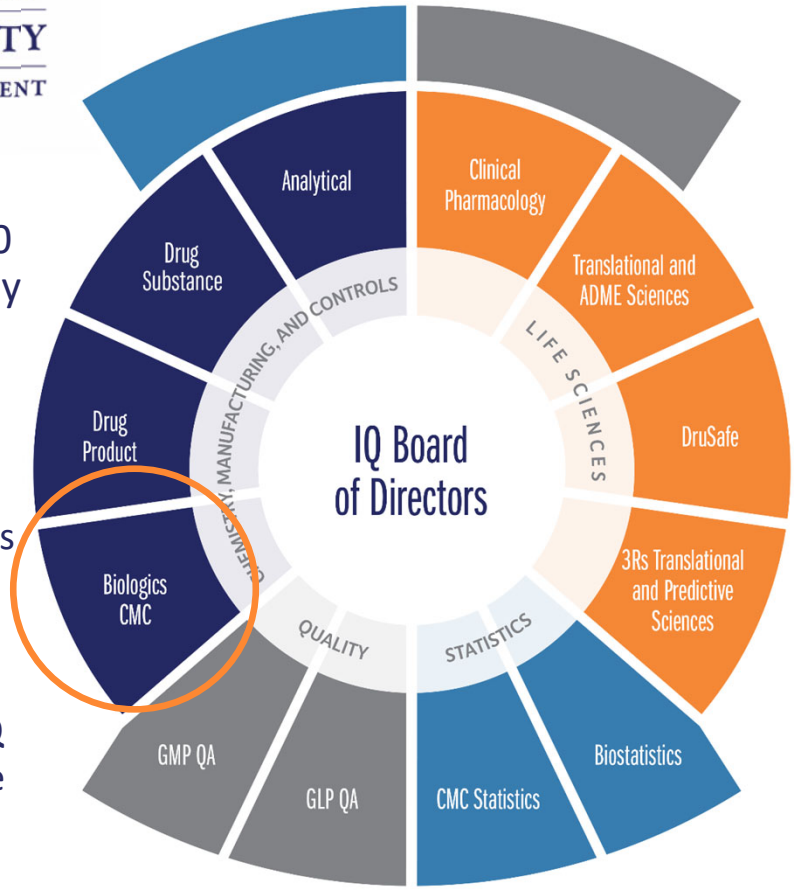
INTERNATIONAL CONSORTIUM for INNOVATION & QUALITY in PHARMACEUTICAL DEVELOPMENT

The International Consortium for Innovation and Quality in Pharmaceutical Development (IQ Consortium) was established in 2010 as a technically-focused, not-for-profit organization comprised of nearly 40 pharmaceutical and biotechnology companies.



To be the leading science-based organization advancing innovative solutions to biomedical problems and enabling pharmaceutical companies to bring quality medicines to patients.

As a technically-focused organization of pharmaceutical and biotechnology companies**, IQ advances science and technology** to augment the capability of member companies to bring transformational solutions that benefit patients, regulators and the broader R&D community.



https://iqconsortium.org

IQ WG Mission & Deliverables

Harvest existing knowledge and publish best practices recommendations for specified type of molecules

- Focus on conventional biologics in phase I: antibody-based therapeutics, peptides, proteins, (non-mRNA) vaccines.
- Harmonized approach to conduct in-use stability & compatiblity study
  - Selection of administration material (material of contact) & DP (process, batch, age)
  - Selection of analytical methods for in-use study & acceptance criteria
  - Appropriate quality standard to conduct in-use study
- Harmonized approach to communicate in-use stability to clinics and regulatory agencies

IQ Physicochemical In-Use Stability Working Group

Working group formed by members across industry

Jennifer Litowski, Amgen
Camilla Santos, Amgen
Leanne Amery, AstraZeneca
Mina Emamzadeh, AstraZeneca
Andrew Massetti, Biogen
Shekhawat Dushyant, Eli Lilly
Jonas Fast, Roche
Isabella De Jong, Genentech/Roche
Kavita Mistry, Genentech/Roche

Melissa Shuman, GlaxoSmithKline
Florian Gasser, Novartis
Markus Bluemel (co-chair), Novartis
Amy St. Charles, Pfizer
Sarah Weiser, Pfizer
Jing Liu (co-chair), Seagen
Camille Dagallier, Sanofi
Christian Urban, Sanofi
Shyam Mehta, Teva Pharmaceuticals
Subramanian Srishty, Teva Pharmaceuticals

Regulatory Guidance Leaves Big Room for Interpretation

ICH Q1A R2 Section 2.2.7 & ICH Q8 R2 Section II. F Compatibility

High-level expectations regarding in-use stability and compatibility to support labeling.

USP <1049> Stability after Reconstitution of Freeze-Dried Product (6.6),

General expectation regarding stability of reconstituted freeze-dried product.

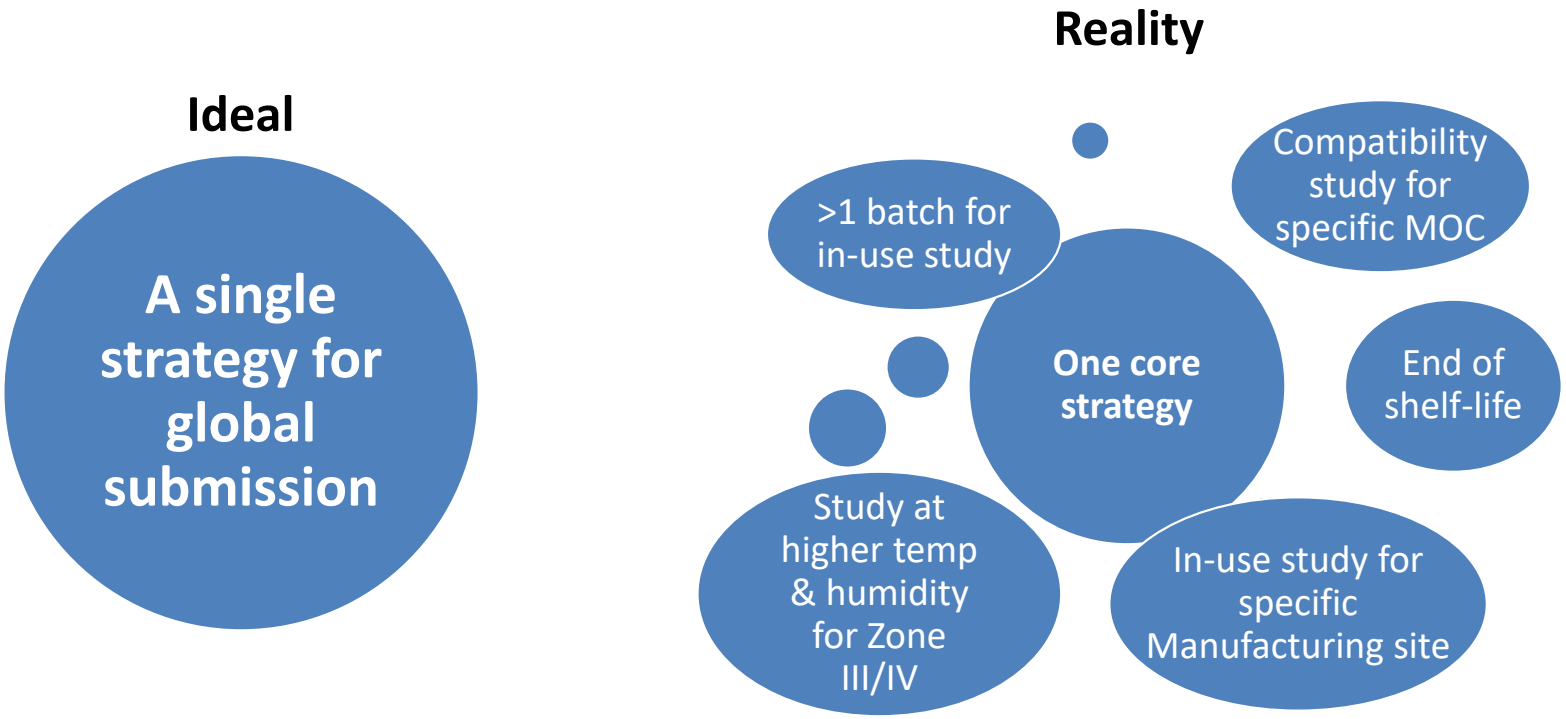
EMA CHMP/SWP/28367/07 (Section 5.3)

General expectation that the low-dose products should have suitable formulation for stability and demonstrate compatibility with in-use containers and primary packaging materials

CPMP/QWP/2934/99, note for guidance on in-use stability testing of human medicinal products

More detailed instructions on batch number, selection criteria of testing materials, and testing design.

Unwritten Expectations Causing Challenges for Global Submission



Fluid Path Material of Construction (MOC)

Polymers such as PVC, PO, PE, EVA, PU, PBD, PES, PS, silicone, and other materials such as stainless steel, etc…

MOCs and Study Design

There are various strategies for study designs, and deciding which administration MOCs to test:

Material contact duration: extended (eg. IV Bag) or transient (eg. Luer connector)

Clinical phase: (PhI/II, PhIII, BLA/IMA)

Bracketing of protein concentration to support dose ranges

Route of administration: IV, SC, IVT, etc

Types of polymer: (e.g., PVC vs polyolefins as a general class)

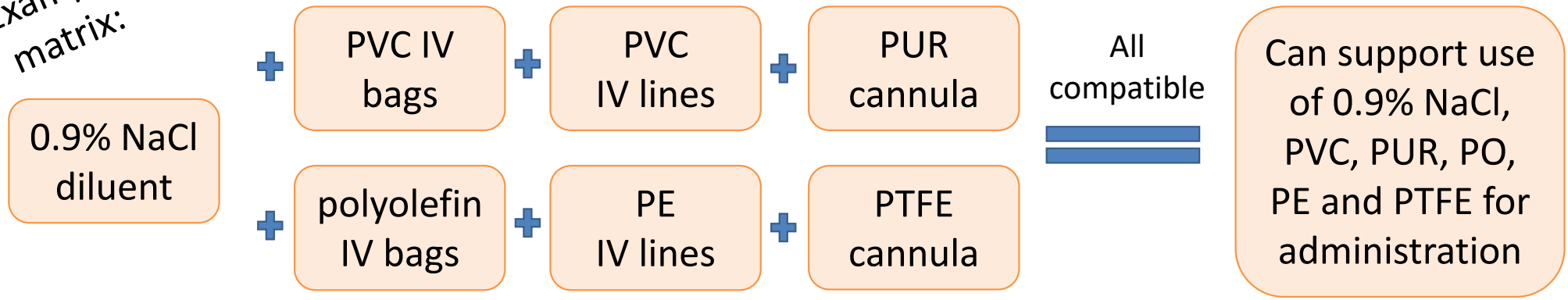
Clinical site choice of materials or market/biosimilar competition

Matrixing Approach to In-use Study Design

There are various strategies for study designs, and deciding which administration MOCs to test:

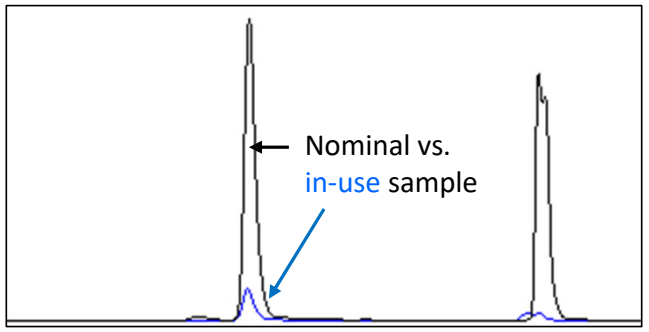
Matrixing of commercially available administration components preferred option versus testing every combination of line, IV bag and diluent

Example matrix:



Select the Right Methods
to demonstrate quality at end of in-use period

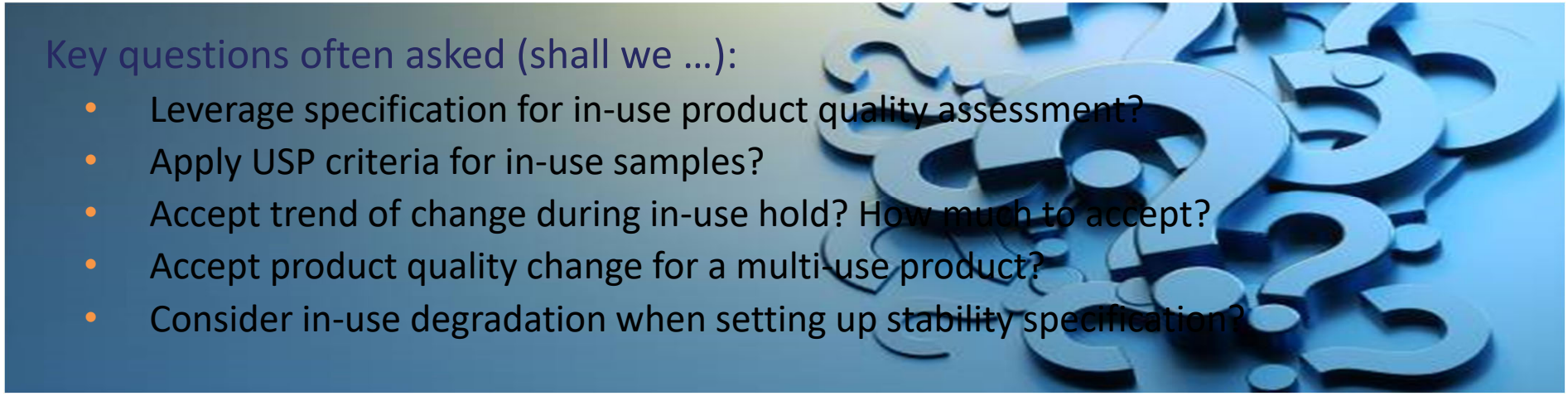
- Qualified analytical methodology not directly usable
  - Outside assay qualification range
  - Strong in-use matrix impact



- Test quality attributes with suitable assays in phase dependent manner

Common Tests	As Applicable: Test & Assess	If Feasible:
Protein content	Product related variants or impurities	Potency All modes of action Test must have adequate precision
Color, clarity, visible particles	Soluble aggregates Sub-visible particles	

Now that we tested, how do we assess the data …?



Key questions often asked (shall we …):

- Leverage specification for in-use product quality assessment?
- Apply USP criteria for in-use samples?
- Accept trend of change during in-use hold? How much to accept?
- Accept product quality change for a multi-use product?
- Consider in-use degradation when setting up stability specification?

There are several options to select acceptance criteria:

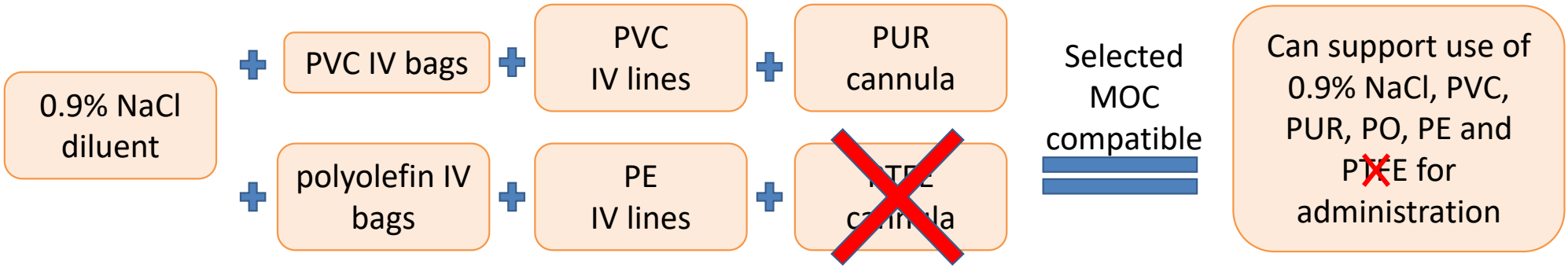
Absence of foreign visible particles

Acceptable change within specification

No meaningful changes compared to initial values

Case Study:
Assessment of Compatibility Using Matrixing Approach

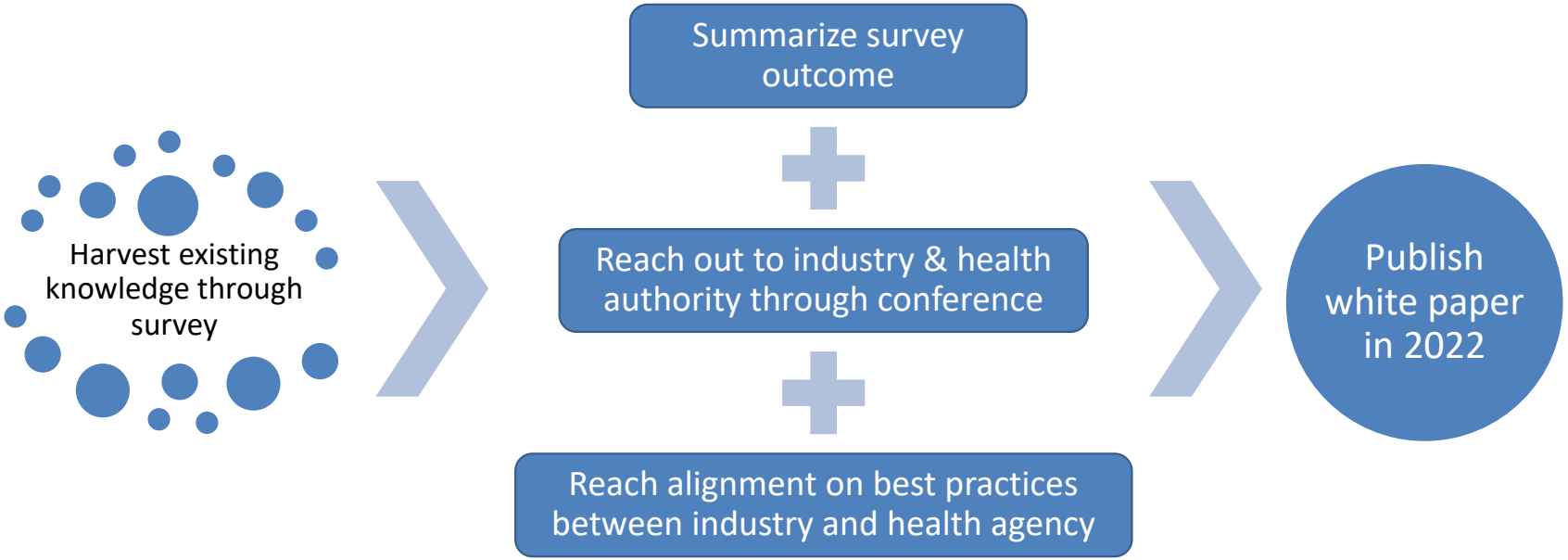
Bracketing approach for protein concentration to cover lowest and highest clinical dose ranges



Poor recovery of protein observed: Troubleshooting of 2nd IV set-up indicates unacceptable level of protein adsorption to PTFE cannula at lowest dose cohorts.

Mitigation: only enable use of PUR cannula for PhI clinical studies for initial dose cohorts.

IQ Working Group Status



Conclusions

In-use stability requires close collaborations across industry

- Suppliers for administration devices
- Pharmaceutical companies
- Regulatory agencies
- Clinical sites

Harmonized approach is strongly desired and benefit all parties

Acknowledgement

This presentation was developed with the support of the International Consortium for Innovation and Quality in Pharmaceutical Development (IQ, www.iqconsortium.org). IQ is a not-for-profit 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 research and development community.

IQ Physiochemical In-Use Stability Testing WG members

Markus Bluemel

Shyam Mehta

Dushyant Shekhawat

Melissa Shuman

IQ Secretariat

Jillian Brady

Catherine E. Graveline

Maja Leah Marshall