INTERNATIONAL CONSORTIUM for INNOVATION & QUALITY in PHARMACEUTICAL DEVELOPMENT

Best Practices for Design and Performance of In-Use Stability and Compatibility Studies

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on behalf of IQ working group 'Physiochemical In-Use Stability Testing'
CMC Strategic Forum, CASSS, Stockholm Oct. 16-18, 2023

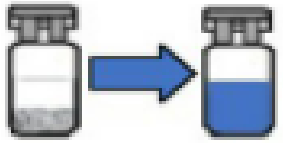
What is In-Use Compatibility?

- Cover manipulations of Drug Product (DP) by the patient or health care provider
- From breaking the seal of the container-closure system for dose preparation through patient delivery
- Distinct from stability in the primary container

IV Infusion

Subcutaneous injection

Reconstituted vial



Goals:

- Demonstrates accurate dosing (drug recovery) and product quality after contact with materials and manipulation expected of administration to patients
- Set *clinical hold times*, *contact materials*, *diluents* and *expected dosing concentrations* (after dilution)

Regulatory Guidance Leaves Considerable Room for Interpretation

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

General expectation on stability of reconstituted freeze-dried product

CPMP/QWP/2934/99, in-use stability testing of human medicinal products

More detailed instructions on batch number, testing materials and design

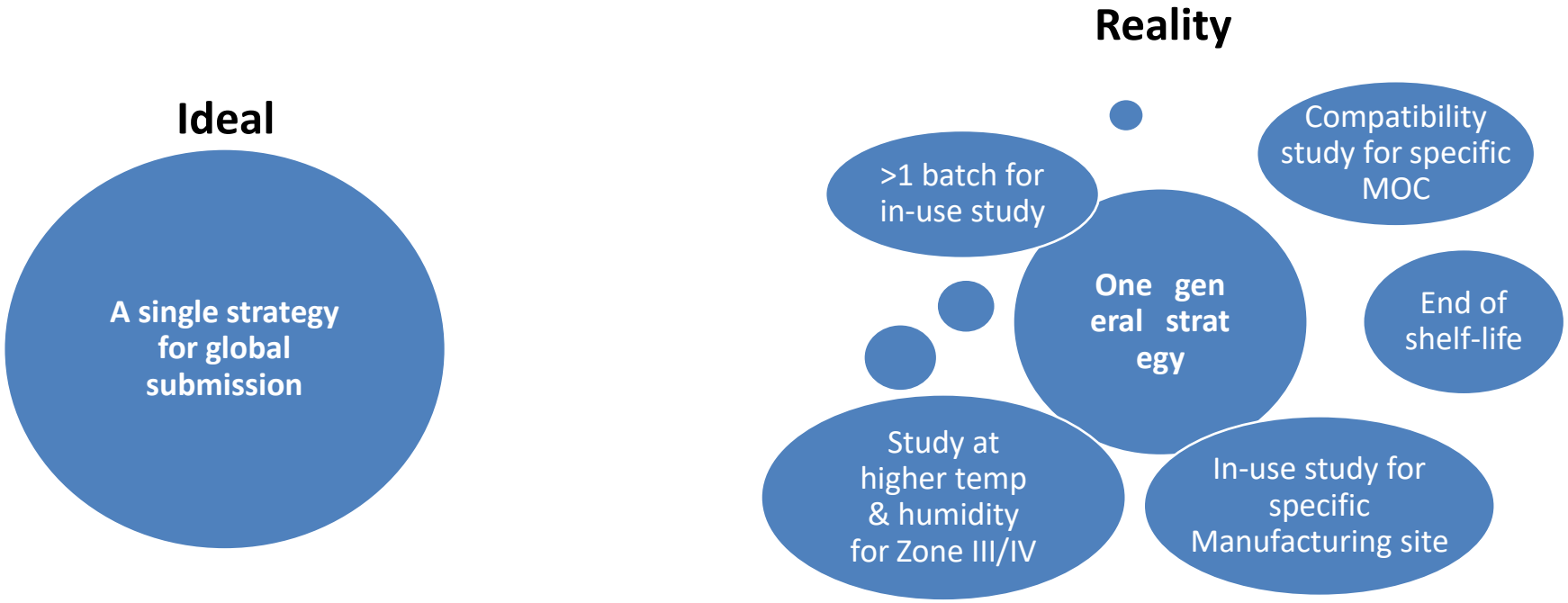
ICH Q1A R2 & ICH Q8 R2

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

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

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

Lack of Written and Harmonized Guidance/Expectations Causes Challenges for Global Submission

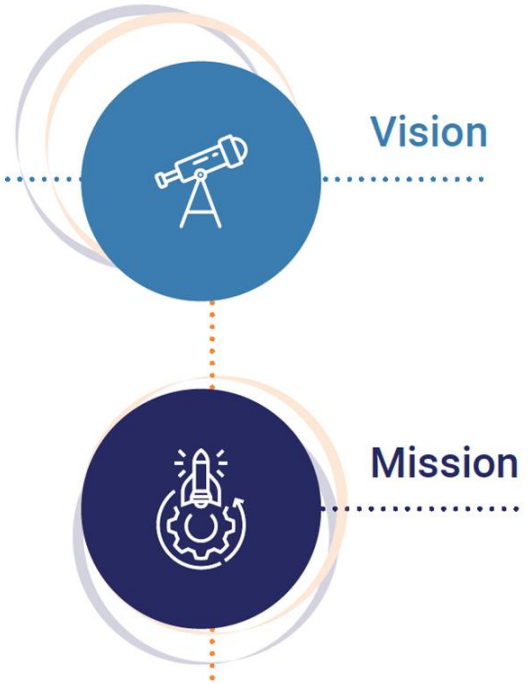


Result

- **Repetition** of studies if initial data package considered insufficient
- **Country specific** labels or guidance for clinical use (Lifecycle management challenge)
- **Limited possibilities** to leverage prior knowledge

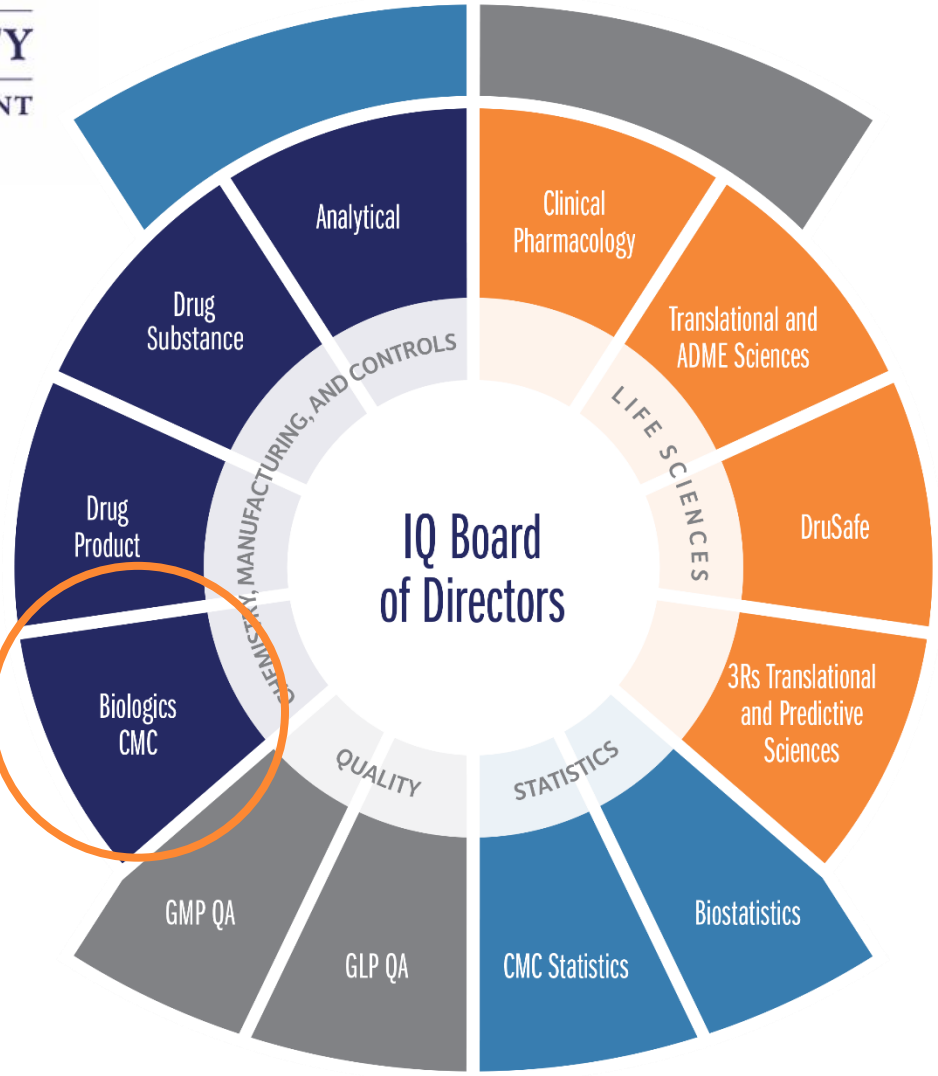
INTERNATIONAL CONSORTIUM for INNOVATION & QUALITY in PHARMACEUTICAL DEVELOPMENT

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 Working Group – describing industry best practices and study design recommendations

- 12 different companies & Regulatory representative participation
- Harvested prior knowledge
- Published best practices recommendations
- Focused on conventional biologics: antibody-based therapeutics, peptides, proteins, (non-mRNA) vaccines
- Harmonized approach to conduct in-use stability & compatibility studies
- Selection of Drug Product (process, batch, age) & administration materials (material of contact)
- Selection of analytical methods, acceptance criteria, appropriate quality standard to conduct
- Harmonized approach to communicate in-use stability to clinics and regulatory agencies

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Review

Current Industry Best Practice on in-use Stability and Compatibility Studies for Biological Products

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When is compatibility tested? Before patients are dosed!

Clinical Phase

- Very **wide dose range** to support dose ranging studies
- Test **limited materials & hold conditions**
- Data in **IND/CTA** filings
- Supports **instructions to clinical trial sites**

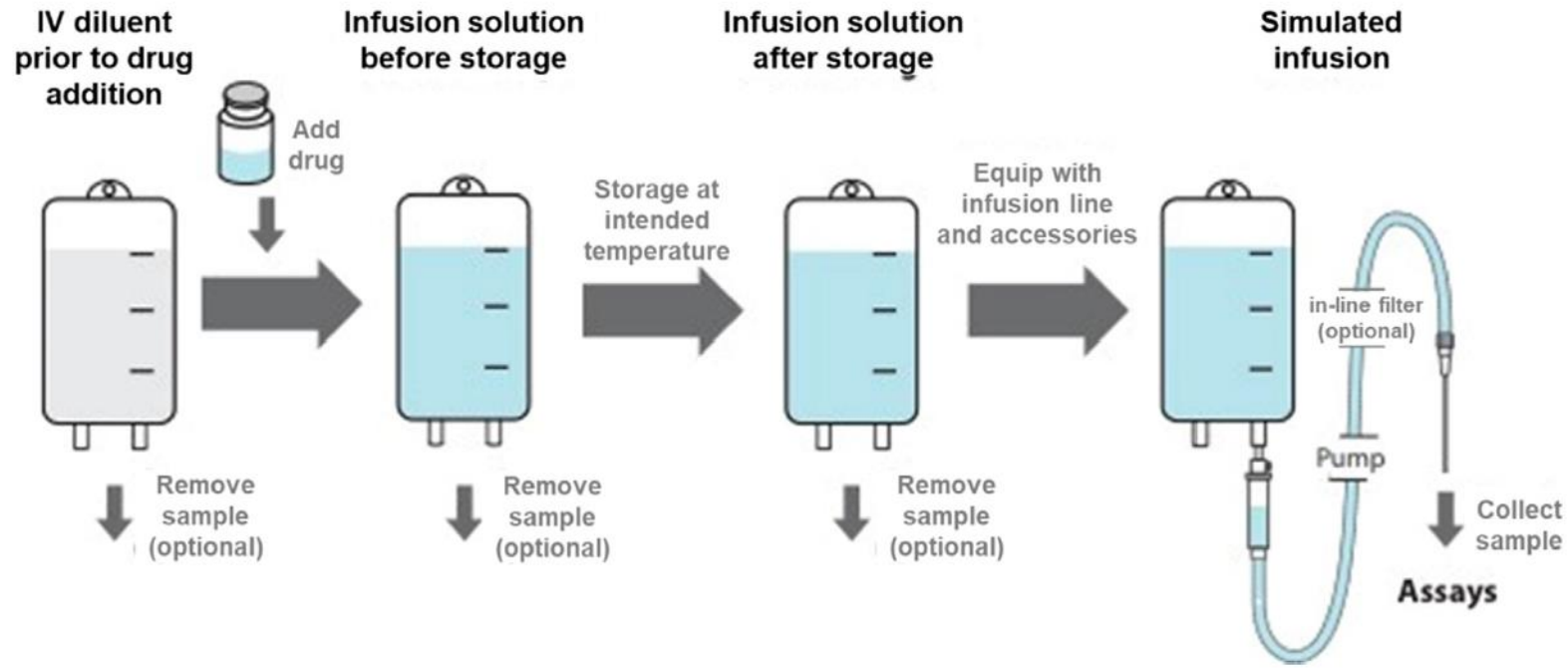
Commercial phase

- **Dose known**
- Test **wider range of materials & hold conditions**
- Data in **Marketing Application**
- Supports **commercial label**

See Table 3 in publication for more details

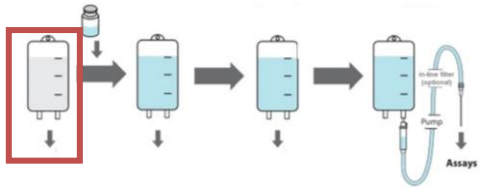
Case study: IV infusion compatibility

- Common route of administration, particularly in oncology settings (but not exclusively)
- One of the more complex cases for in use compatibility testing

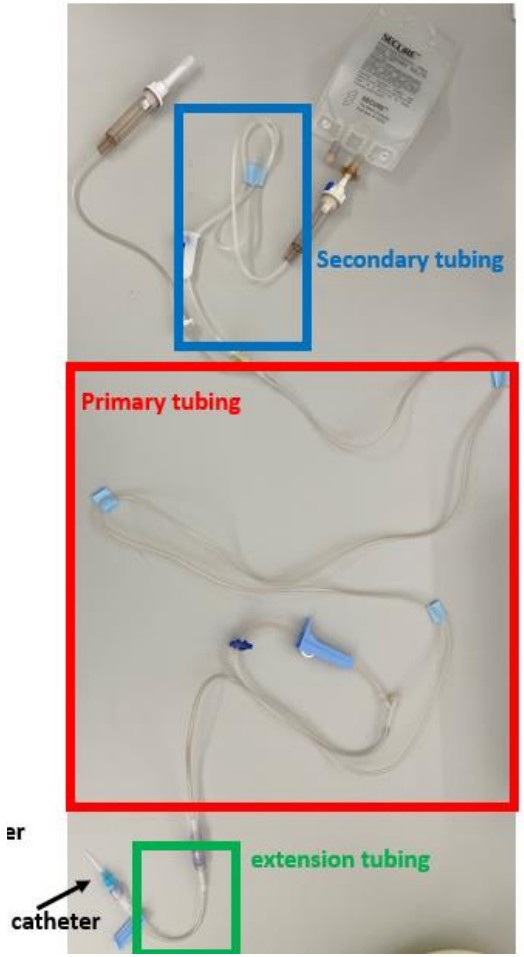


Testing all combinations impractical → Use science-based rationale, prior knowledge

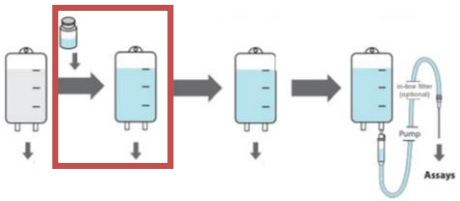
Materials and Diluents



- **Diluent:** Saline most common, 5% dextrose common alternate (risk of glycation)
  - Test diluent compatibility first! Small scale, simple container
- **Representative materials:** Test & recommend a type of material of contact (MOC), not specific suppliers or brands
  - **IV bags**: PVC, PO, EVA
  - **IV lines**: PVC, PE, PB
  - **In-line filters**: +/-, 0.2 um, PES vs. PS
  - **Catheters**: FEP, PU
- **Matrixing approach:** Testing all combinations is impractical

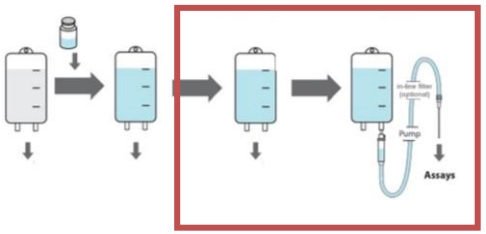


Selecting Drug Product



- **Representative formulation, manufacturing process**
  - Significant changes in either formulation or process require a new study
  - Unrelated changes (i.e. vial fill volume for a liquid SKU) do not require a new study
- **Concentration**
  - ***Clinical Development sets doses; Scientist test concentrations (dose/volume)***
  - Must equal or bracket the concentration administered to patients (wide in early phase, narrow in late phase)
  - Pre-filled IV bags typically ~10% overfilled
  - IV bag prep variations (i.e. withdraw diluent or not)
- **DP Lot number**
  - 1 lot in early stage; A few regions have asked for 2 lots at commercialization, but far from universal
- **End of Shelf Life (EOSL)**
  - Typically, not available, particularly in early development
  - Not universally required or tested

Incubation conditions, infusion



- **Temperature:**
  - Administration at ambient (i.e. room) temperature, short term storage at 2-8°C and
    - Climate zones I & II: 25°C
    - Climate zones III & IV: 30°C
- **Storage Times:**
  - Common strategies 2-8°C (24 h) → 30°C (4-24 h)

    30°C (4 h) → 2-8°C (16-24 h) → 30°C (4 h)

    May test beyond target hold time as safety margin
- Time points:
  - Immediately after dose preparation (**T0**) and **after infusion**

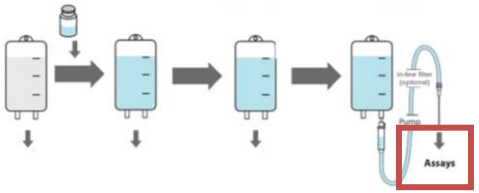
    Intermediate time points → Kinetic data

    → Fall back position
- Infusion:
  - Infusion pump or gravity. Control flow rate/time.

    Common to test both fast (shear stress) and slow (material contact/adsorption) infusion rates
- Light exposure:
  - Expose to ambient lab or biosafety cabinet lighting

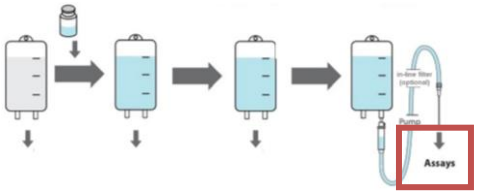
    Some companies use controlled light chambers (NOT ICH photostability conditions)

Analytics



- Analytical methods do not need to be GMP-validated, but need to be **fit for purpose**
  - I.e. linear conc. range, matrix interference for the diluted DP (in saline or dextrose)
  - Best practice: Test physical stability methods immediately, other assays within 24 h
  - Test sample stability in advance (Sample stability at 2-8C or frozen cannot be assumed)
- **Protein Content and Recovery:** Key to ensuring correct dosing to patients
  - Account for bag overfill/variability. Don't assume labelled volume (i.e. 100 mL). Measure weight and density.
  - Clinically acceptable recovery (at end of infusion): typically 90% - 95%
- Subvisible and visible particles
  - USP <787> provides guidance on Subvisible particles
    - 10 µm, 25 µm for small (</= 100 mL) vs. large (>100 mL) containers
  - Visible Particles – free of visible particles is ideal, but not always achievable
  - Appropriate lab techniques critical to avoid introducing environmental particles.
    - Ex. use of biosafety cabinet, avoid siliconized syringes for samples
  - Mitigations: Use of inline filter (must be tested), reformulation, alternate diluent, alternate MOC

Analytics



- Purity
  - **Physical stability**. Size-exclusion UPLC/HPLC to monitor aggregation
  - Chemical stability. More frequently tested in later development stages.
    - Longer expiry (> 24-48 h), risk of glycation, program-specific knowledge about chemical liability
  - DP concentration, sample matrix may affect assay performance
- Potency or bioactivity
  - Less sensitive to changes than purity assays, not always performed, esp. in early stages
    - However, if can be performed at lower concentrations, may be useful when concentrations are below LOD for purity assays

Translation into recommendations

- **Communication with Regulatory Agencies**
  - Data presented in P.2.6 sections at both Clinical trial (IND/CTA) and Marketing Application (MA) stages
  - **Data must support conditions recommended in clinical or commercial instructions**
  - Data may be broader than recommended in a particular region, to support global filings
- **Communication with clinical sites**
  - Detailed preparation instructions (reconstitution, IV bag dosing, etc.), allowed materials, clinical hold times and conditions

    Pharmacy Manual (PM) Investigation Product Instruction Manual (IPIM)

    Investigator's Brochure (IB) Clinical Protocol (CP)
- **Commercial labels**
  - Summarized version of preparation instructions, allowed materials, expiry

    Product Insert (PI)

    Summary of Product Characteristic (SmPC)

Conclusions

- In-use stability and compatibility studies are critical to demonstrate product quality during preparation, handling and administration
- Minimal guidance on Biologics in-use stability testing
- Lack of written and harmonized guidance/expectations causes challenges for global submissions
- IQ WG has written a review paper describing industry experience & recommendations for best practices

Blümel et al. (2023) Current Industry Best Practice on in-use Stability and Comparability Studies for Biological Products. **J. Pharm. Sci. 112(9):2332-2346**

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