INTERNATIONAL CONSORTIUM for INNOVATION & QUALITY in PHARMACEUTICAL DEVELOPMENT

How to Design and Perform in-use Stability and Compatibility Studies?

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on behalf of IQ working group 'Physicochemical In-Use Stability Testing'
CMC Strategy Forum North America, Washington DC, 22-JAN 2024

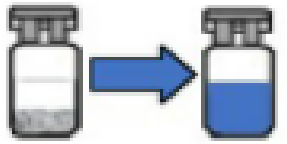
What is In-Use Compatibility?

Cover manipulations of Drug Product (DP) by the patient or health care provider from opening the sealed container for dose preparation through patient delivery

IV infusion

Subcutaneous injection

Reconstituted vial



Goals:

- Demonstrates accurate dosing (drug recovery) and product quality after contact with materials and manipulation expected during 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

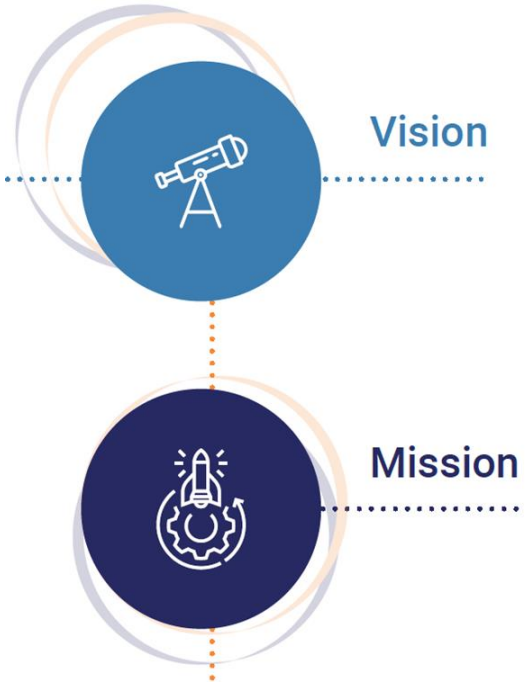
High-level expectations on in-use stability and compatibility to support labeling

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

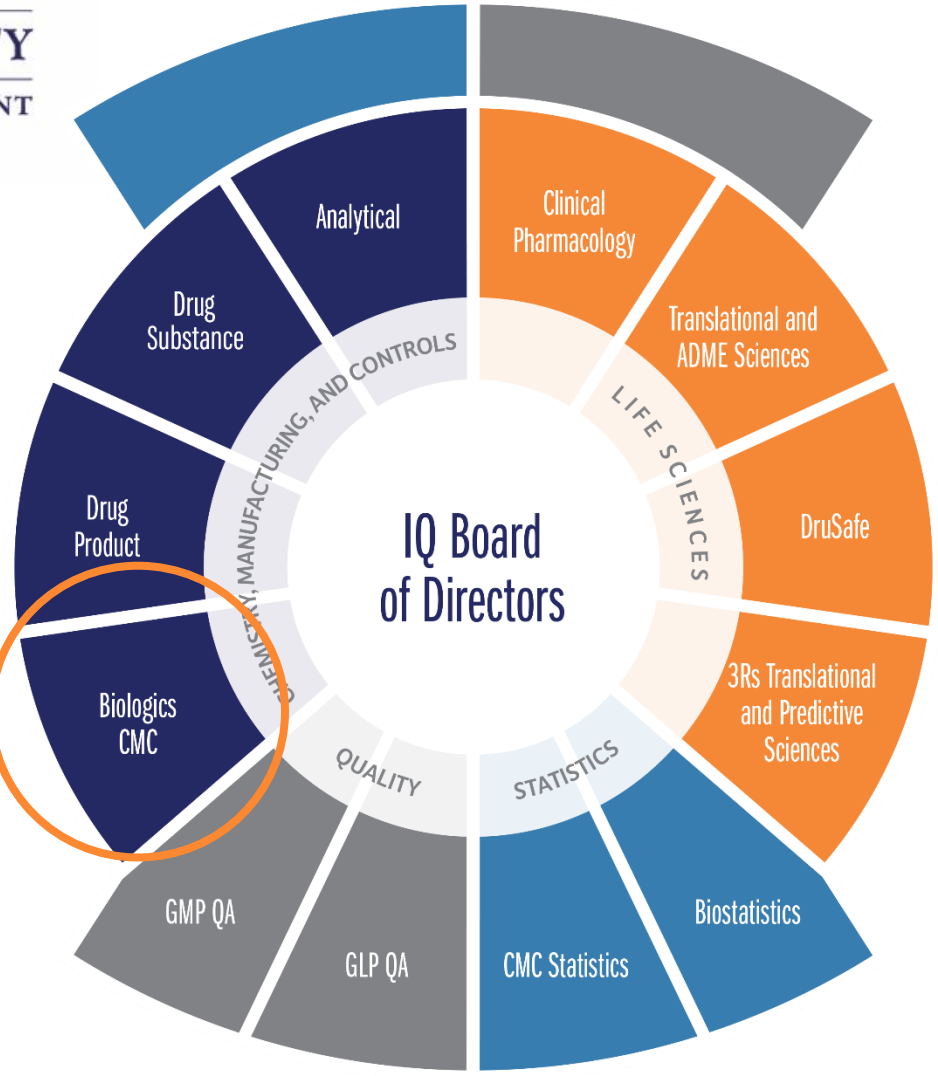
INTERNATIONAL CONSORTIUM for INNOVATION & QUALITY in PHARMACEUTICAL DEVELOPMENT

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

Contents lists available at ScienceDirect

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journal homepage: www.jpharmsci.org

Review

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

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Compatibility testing: Clinical development *vs.* commercial phase

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**

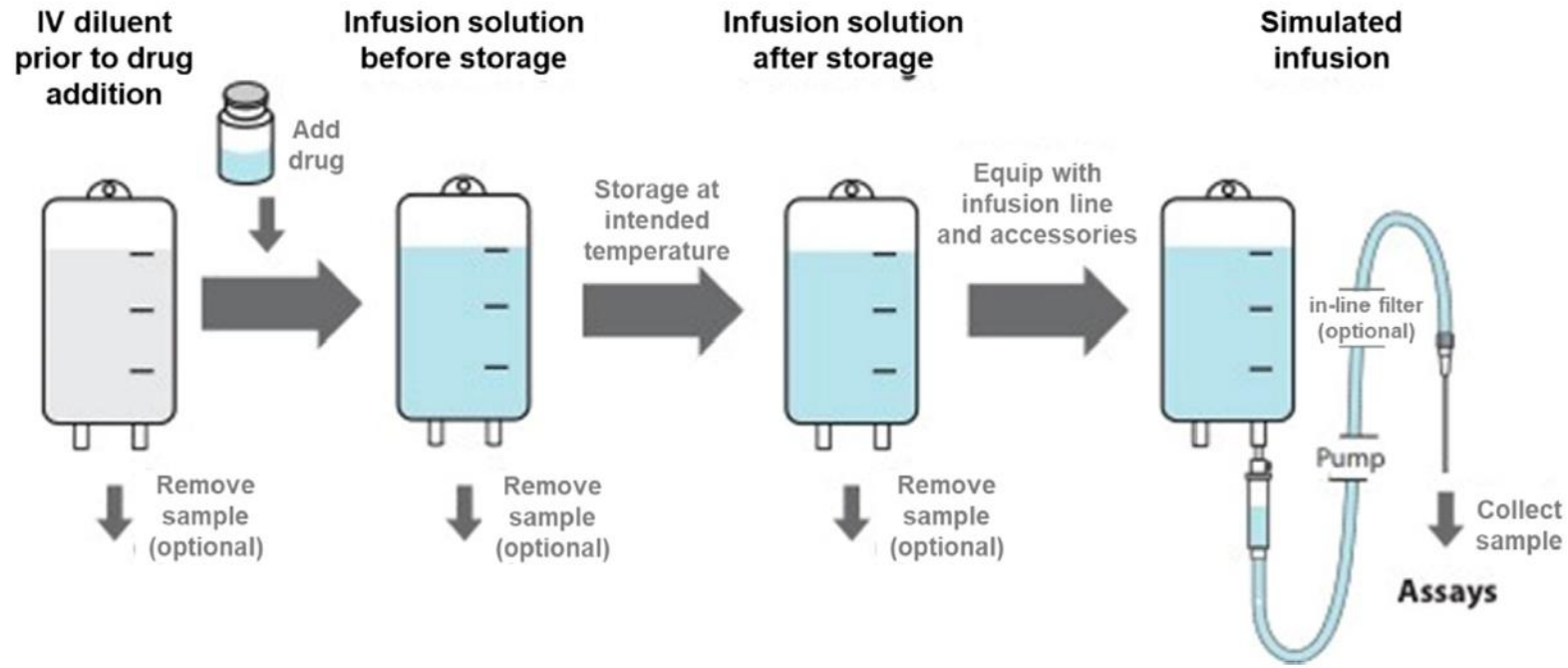
Commercial phase

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

See Table 3 in publication for more details

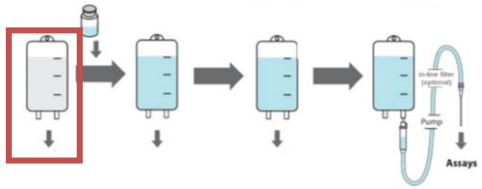
Case study: IV infusion compatibility

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

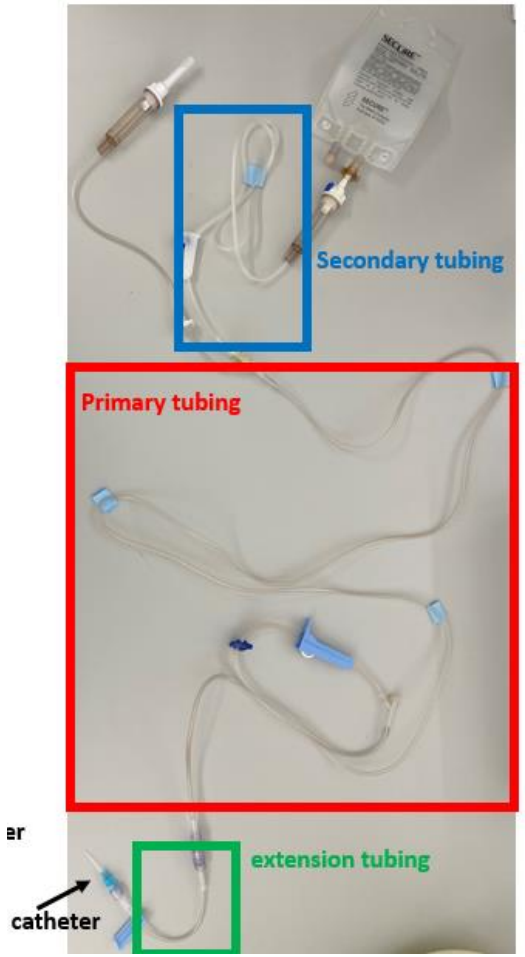


Testing all combinations impractical → Use science-based rationale, prior knowledge

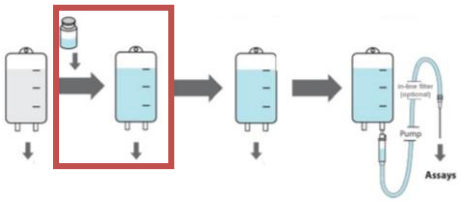
Materials and Diluents



- **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

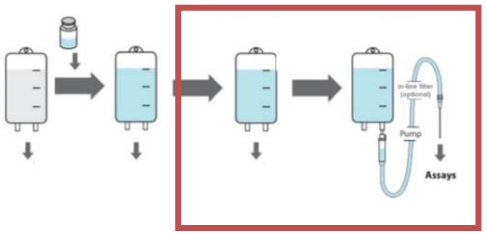


Selecting Drug Product



- **Representative formulation, manufacturing process**
  - Significant changes in either formulation or process require a new study
  - Unrelated changes (e.g., vial fill volume for a liquid SKU) do not require a new study
- **Concentration**
  - ***Clinical Team sets doses; Scientists 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)
- **Number of DP Lots**
  - 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**

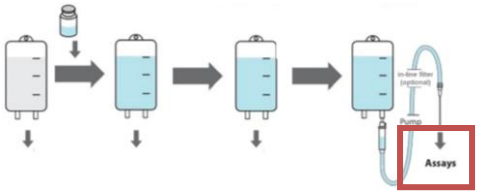
    Intermediate time points → Kinetic data

    → 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

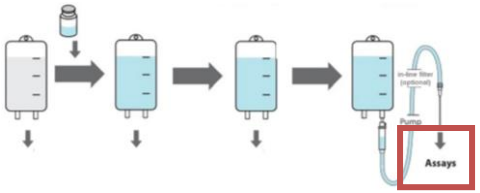
    Some companies use controlled light chambers (NOT ICH photostability conditions)

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 after dilution)
- **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 methodology
    - 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;
    confirm assay performance prior to study execution after dilution of DP to clinical dosing levels
- 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

Common practices for in-use stability study design

	Clinical development	Marketing application / commercialization
Administration components	Chose 1 or 2 most relevant MOCs	Choose relevant MOCs based on the intended commercial market
IV diluent	Normal Saline (0.9% NaCl) or 5% dextrose/glucose (check risk for glycation of the product)	Normal Saline (0.9% NaCl) and 5% dextrose/glucose; include solutions depending on the market needs
In-line/add-on filter	0.2 or 0.22 µm neutral/charged PES	Choose relevant MOC of filter based on the market or product needs
Drug product tested	One drug product batch (from representative process)	One representative drug product batch; file as Post Approval Supplement a second batch aged drug product (near the end of shelf-life)
Dose solution concentration	Bracket minimal and maximum concentrations to support early clinical stages	Bracket concentration range to support market application
In-use study condition (e.g., temperature, duration)	– Support maximum anticipated hold time – Refrigerated and 30 °C with ambient light exposure – Sample at begin and end-of-hold-time. May optionally include 1-2 intermediate time points for thermal and/or photo sensitive molecules or as fallback samples – Simulate administration infusion at worst-case infusion rate; simulate transportation agitation	Like early-stage clinical development, except that testing conditions need to be adjusted to support market application and label claims. Test longest anticipated hold time to support global marketing

Quality attributes and acceptance criteria for in-use stability study

Quality attribute to be tested	Recommended acceptance criteria
API content and recovery (e.g., assay by UV absorption)	Within ±10% of intended or starting content (for highly diluted potent product: consider assay performance)
Potency or bioactivity	To be defined for each product, depending on assay performance and product knowledge
Purity (e.g., size variants, charge variants, or other specific purity attribute)	Purity changes are acceptable when within specification. New product-related variants or impurities must be identified and investigated / assessed.
Subvisible particles	For subvisible particles in size ranges ≥10 µm and ≥25 µm: Assess whether there is a meaningful trend of change. In case of unexpected high particle counts or increasing trends: Further investigate, possibly involve multiple complementary techniques, using placebos or different sampling strategies.
Visible particles	Absence of visible particles due to contact with administration components and diluents
Color, clarity	No meaningful changes compared to initial values

Proposed questions for alignment

on “Common practices for in-use stability study design”

- How many batches of a product need to be tested for in-use study?
- Do in-use studies need to be repeated after manufacturing process changes, when comparability was shown?
- What are suitable acceptance criteria when testing hold times or administration component?
- What are acceptable approaches for bridging
  - between different product presentations (different fill volume)?
  - between different ‘materials of construction’?

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