INTERNATIONAL CONSORTIUM for INNOVATION & QUALITY in PHARMACEUTICAL DEVELOPMENT

In-Use Studies Microbial Challenge Studies: Cross-industry efforts to harmonize strategies in collaboration with Health Authorities

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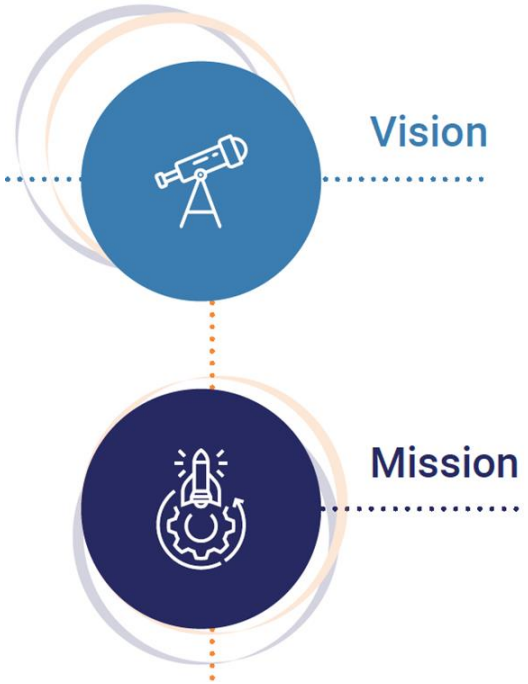
Presentation Overview

1. IQ Mission and Vision
2. Acknowledgements
3. Introduction to Microbial Challenge Studies
4. Introduction to IQ Microbial In-use Working Group
5. Highlighted Recommendations and Topics from Zamiri *et al*.
6. Next Steps

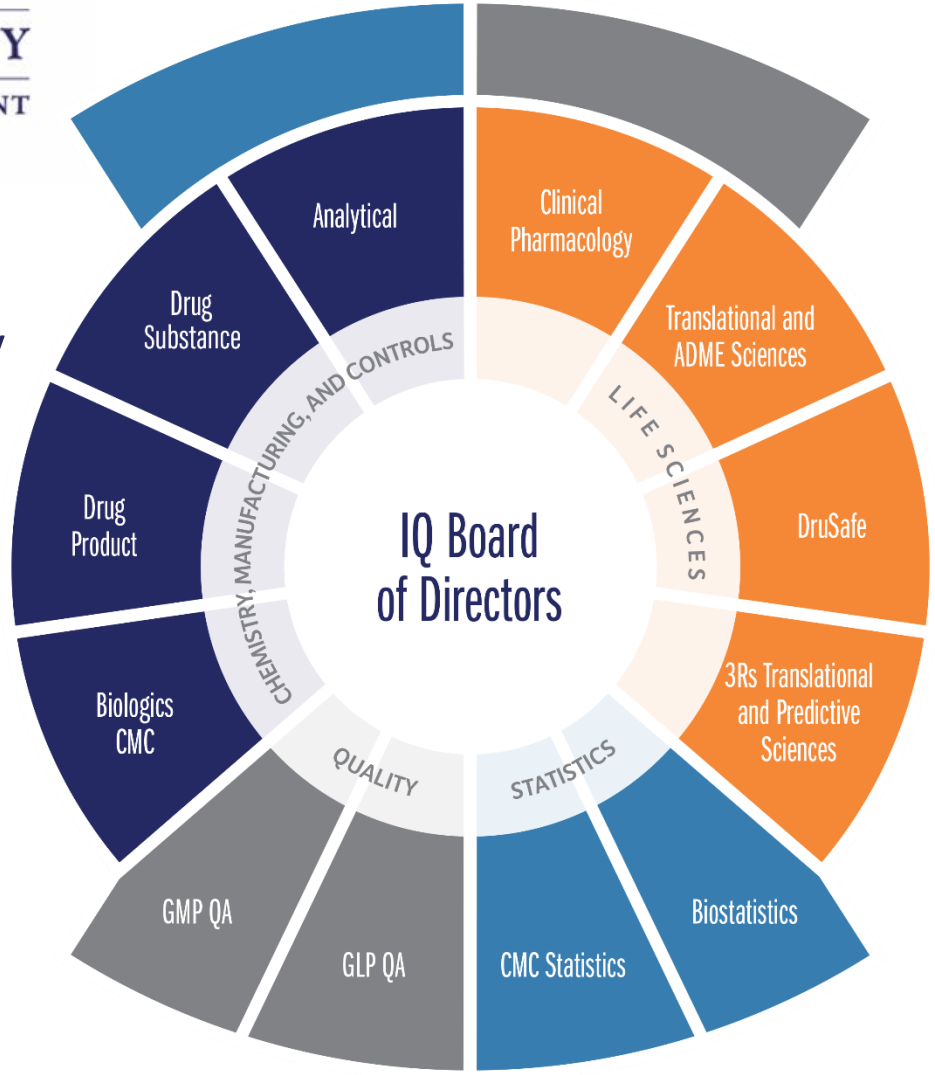
INTERNATIONAL CONSORTIUM for INNOVATION & QUALITY in PHARMACEUTICAL DEVELOPMENT

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

Acknowledgements

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Bolded names are authors on WG publication.

Microbial challenge studies evaluate potential for microbial growth

- Holding product after breach of sterility represents a risk, in-use storage time should be justified
- Label should include storage time for in-use solutions to ensure patient safety, microbial stability is assessed in combination with physiochemical stability (concepts included in ICH, CFR)
- Large, resource heavy studies that are challenging due to inherent variability
- Regulator expectations set by publications and IRs

ICH Q1A R2	Stability testing of the drug product after constitution or dilution, if applicable, should be conducted to provide information for the **labeling on the preparation, storage condition, and in-use period of the constituted or diluted product**.
ICH Q8 R2*	Where relevant, **microbial challenge** testing under testing conditions that, as far as possible, **simulate patient use** should be performed during development and documented in this section.

*Antimicrobial effectiveness testing

ICH Q9, Q8, Q1A, Q5C
21 CFR 201.57, 211.137, 211.166

IQ In-Use Microbial Stability WG purpose is to share experience, develop industry position, and engage and harmonize with regulators.

- WG published a position paper with the FDA in October 2023 which covers:
  - Cross-industry practices; survey responses from 14 IQ Biologics LG member companies
  - Global regulatory expectations
  - Harmonized strategies on study design, execution, and data interpretation
  - Considerations for the use of platform data, long infusion times, USP <797>, and others

Best Practices for Microbial Challenge In–use Studies to Evaluate the Microbial Growth Potential of Parenteral Biological Products; Industry and Regulatory Considerations

Camellia Zamiri, Danielle L. Leiske, Patricia F. Hughes, et al.

PDA Journal of Pharmaceutical Science and Technology **2023**,
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IQ WG End to End Deep Dive on Microbial Challenge In-use Studies

Regulatory considerations and strategy

- Product specific or general approach?
- How are in-use hold times established in early phase?

Experimental design and execution

- Where is study performed?
- How many batches?
- What conc. of product?
- Commercially prepared ready to use inoculum or in-house suspension?
- What type of microorganisms in addition to USP<51>?
- What is the min countable inoculum?
- How are CFU counted during microbial studies? and why?
- What is definition of replicates?
- How is method suitability performed?
- What are the time points and temperatures?
- What type of container is used??
- Is admin time included?
- Are studies performed separately or cumulatively?
- Are all diluents used?

Interpretation of microbial growth and assignment of hold time

- How is log difference calculated?
- What is considered the start of exponential growth?
- How in-use hold time is defined?
- What safety factor is used to determine safe in-use time?
- Is a trend line used?
- What are the rounding rules?

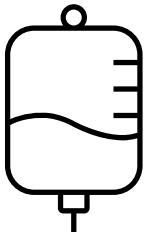
Country specific HA requirements

- What countries require microbial in-use studies?
- What are country specific requirements for micro in-use studies?

Regulatory considerations and strategy

Microbial challenge study requirement for IND stage products

- Around 2019, FDA began to require microbial data to support in-use hold times > 4 hrs at RT/2-8°C at **all** phases of development, when they had previous allowed 4 hours at RT and 24 hours at 2-8ºC without microbial challenge data
- Through collaboration between the FDA and the WG, the requirement changed and is currently:
  - **For biological products at IND stage:**
    - Microbial challenge studies are required to support in-use storage times beyond 4 hours at room temperature and beyond 24 hours at 2-8ºC."
  - **For BLA approval:**
    - Microbial challenge studies are required for assigned in-use hold times longer than 4 hours at 2-8°C or room temperature



Regulatory considerations and strategy

Use of platform data to support clinical in-use times

- One strategy to support in-use hold time during clinical trials is through the utilization of data from similar products/formulations or platform data that covers a defined space of formulation matrices.
- To apply this approach, the investigational drug and formulation need to be:
  - Similar to the protein type evaluated in the platform data
  - Similar to the protein concentration ranges evaluated in the platform data
  - Within the range of the formulation/solution matrices of the data including pH, osmolality, excipient composition (e.g. surfactant and sugars) and concentration, and diluent type (if applicable).
- Use of platform data with similar temperatures and in-use conditions to the investigational product under evaluation is recommended.
- Any differences between the investigational product and historical data should be scientifically justified.

Regulatory considerations and strategy

Long infusion times

- The mechanism of action of some medicines necessitates infusions over extended periods of time, which may increase risk of microbial growth.
- There is currently no clear or aligned definition amongst industry or regulators for when an infusion time is considered “long.”
- It is recommended that companies conduct an overall risk assessment including product’s growth potential, type of product, risk of contamination (based on preparation complexity and expected clinical facilities), risk reduction factors, patient population, and HCP oversight of patients in case of any adverse events.
- For example, if a product is infused over 4 hours but found to be rapidly growth promoting (e.g., growth observed in 8 hours), a 4 hour infusion time with 4 hour storage at room temperature would present a high risk for microbial growth and risk reduction factors should be considered.

Regulatory considerations and strategy

Long infusion times

- For a product infused over extended period of time (e.g., >~ 12 hours), the infusion duration should be included as part of the microbial challenge in-use study design at room temperature to understand the risk during **storage and infusion**.
- Additional examples of risk reduction factors that may be considered:
  - Allowing only refrigerated storage
  - Use of a sterile in-line filter – note: not all in-line filters that are used in clinics are validated for microbial retention and use of the in-line filter may require an assessment of risk regarding loss of drug product potency due to adsorption to the filter and impact to overall product quality following filtration
  - Changing infusion bags
  - Use of a preservative if accepted by health authorities

Study design and execution

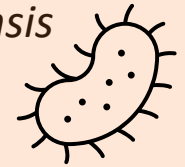
WG recommends only testing the 5 microorganisms listed in USP<51> for microbial challenge studies.

- Rationale:

1. They represent a broad range of organisms that could be present, often the worst-case for growth based on survey feedback.
2. They represent nosocomial agents (*C. albicans*, *E. coli*, *S. aureus*, and *P. aeruginosa* and skin flora (*Staphylococcus spp*.).
3. Literature from clinical cases on contaminated products show large variety of microorganisms isolated and, to the authors' knowledge, reported contaminated products are not relevant to single dose biological products (differences in product type (e.g. anesthetics, multi-use products) or preparation, as contamination mainly occurred during surgery or at patient bedside).
4. The use of USP <51> organisms as an industry approach will allow harmonization and enable a consistent approach on assignment of in-use hold time among different products from different manufacturers.

USP <51> Organisms

1. *Aspergillus brasiliensis*
2. *Candida albicans*
3. *Escherichia coli*
4. *Pseudomonas aeruginosa*
5. *Staphylococcus aureus*



Study design and execution

WG recommends several controls which are needed to ensure the integrity of the study.

Method suitability: Verification of the method of microbial recovery from the reconstituted and/or diluted solutions, acceptable percent recovery of each test strain is 50% - 200% (USP <61>)

Inoculum Count Verification: inoculum control performed for each organism to verify the inoculum level at the initial timepoint

Positive Control: identical containers to test sample (same volume, same diluent, etc.) are inoculated with each microorganism **with no active product** using the same inoculation procedure

Negative controls: prepared **with active product** and not inoculated with microorganisms, no growth should be observed

Sterility (plate) controls: prepared with plated media to confirm that no outside contamination has affected the study at the time of enumeration, no growth should be observed

- Studies can use inoculum count verification and/or positive control
- Positive controls do not need to be carried through the duration of the study but they can be.
- Matrices are often nutrient-deficient and microbes may not grow or survive.

Study design and execution

WG recommends separate studies for each temperature condition.

- Recommended microbial challenge study temperatures:

2-8°C for refrigerated storage	20-25°C (USP controlled room temperature) for the U.S. and zone 1 and 2 countries	Other temperatures may be appropriate (e.g., zone 4 conditions) to include as separate arms, determined on a case-by-case basis

- Cumulative temperature studies (e.g. storage of inoculated test containers at 2-8°C and then moved to 20-25°C) are not recommended (different approach than for physicochemical stability):
  - Data can be difficult to interpret due to microorganisms adapting or dying under refrigerated conditions and impacts true growth potential under warmer conditions
  - Separate temperature study conditions will provide “worst-case” conditions and enable better evaluation of data
- A cumulative study may be considered, however, it is recommended to ensure microbial growth rates at all temperatures are consistent with single temperature growth rates.

Interpretation of microbial growth and assignment of hold time

WG recommends decision tree for determining in-use time.

- A decision tree was developed for the determination of in-use hold time based on scientifically justifiable rules and recommendations from health authority publications and IRs during regulatory filings (see Figure 4 in IQ best practices paper)
- Three tiers:

Tier 1:
no microbial growth is observed (all time points are < 0.3 log10 increase from T0), apply 1.5X safety factor or use second to last timepoint, whichever is longest

Tier 2:
upward microbial growth trend is observed (existing time point that is between ≥0.3 and ≤ 0.5 log10 increase), apply 1.5X safety factor or use previous timepoint, whichever is longest

Tier 3:
microbial log growth is observed (existing time point is > 0.5 log10 increase), select previous timepoint and apply 2X safety factor

- Note: Some countries do not require a safety factor.

Next steps

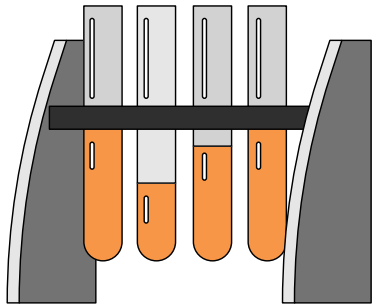
Support for 2-8°C in-use time for clinical stage

- WG is preparing template response text for FDA IRs stating NMT 4 hours at 2-8 ° C
- WG is preparing a data survey that will be sent to IQ member companies to collect 2-8 ° C data to support clinical in-use time of 24 hours at 2-8 ° C or longer

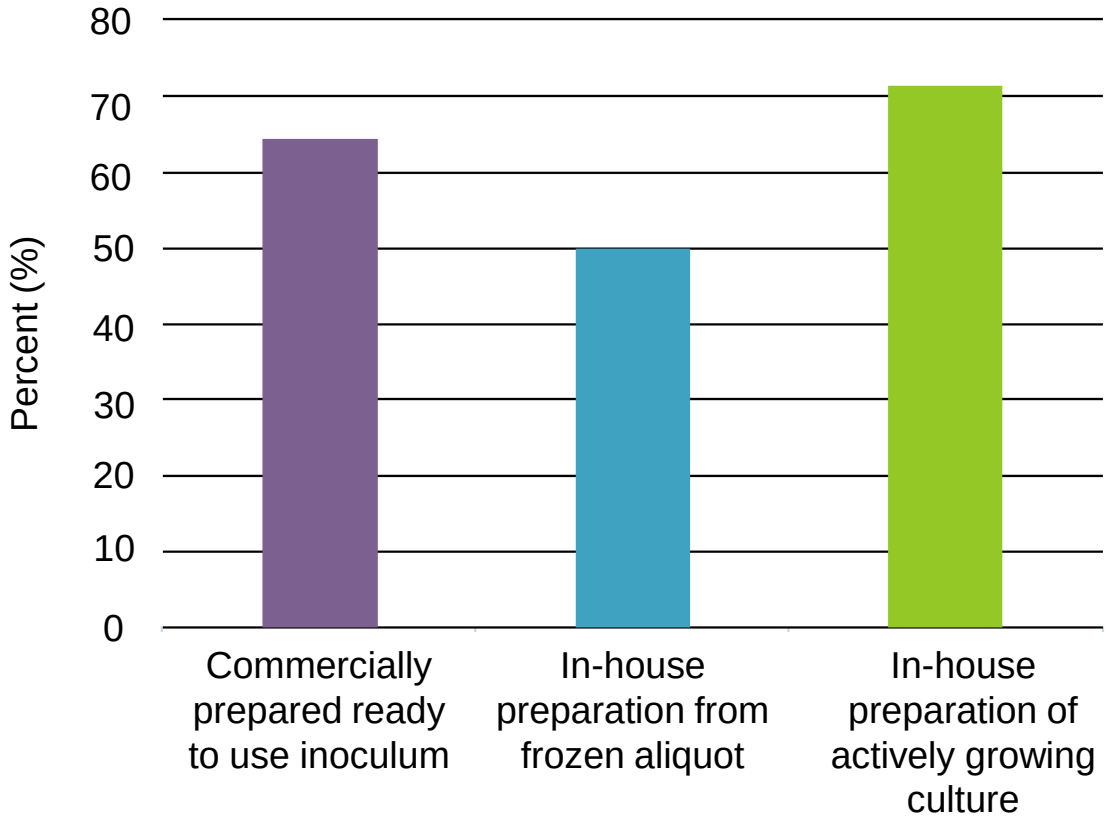
Next steps

Impact of inoculum source on growth

- Wide range of survey responses
- WG could not come to a recommendation due to a lack of data
- **WG is conducting studies to better understand the impact of inoculum source on growth**



Survey questions: Does your organization utilize commercially prepared ready to use inoculum (e.g. rehydrated preserved microorganism kits such as Bioball, EZ-Accu Shot, Quanti-Cult Plus, etc.) or make the suspensions in-house? Select all that apply.



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