INTERNATIONAL CONSORTIUM for INNOVATION & QUALITY in PHARMACEUTICAL DEVELOPMENT

Microbial Challenge In-use Studies-

Industry efforts to harmonize strategies in collaboration with Health Authorities

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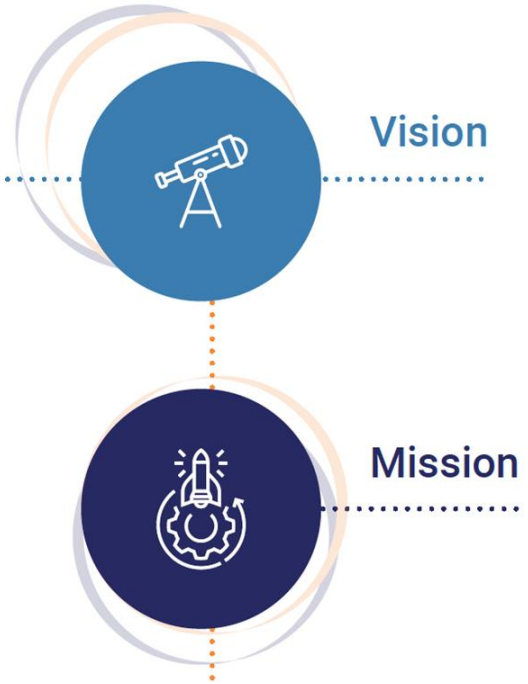
INTERNATIONAL CONSORTIUM for INNOVATION & QUALITY in PHARMACEUTICAL DEVELOPMENT

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.



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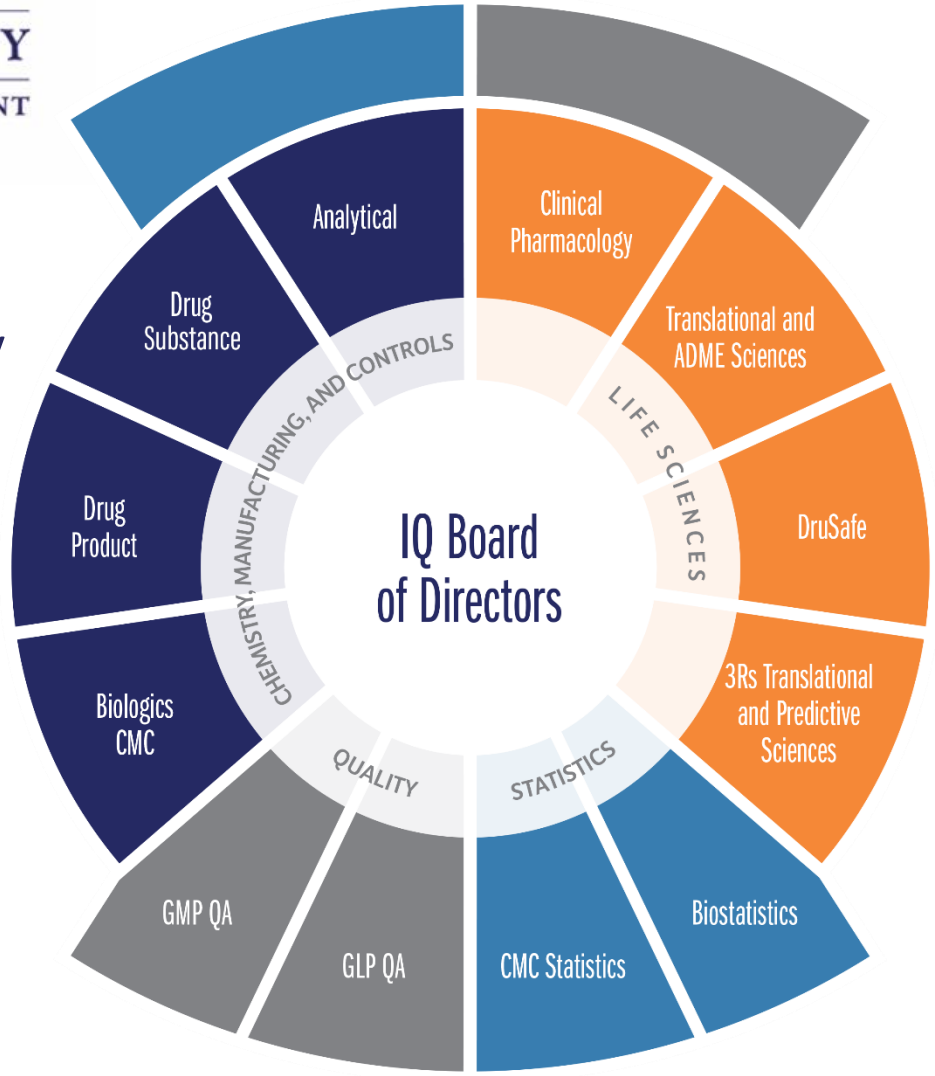

https://iqconsortium.org

Acknowledgements

IQ Micro in-use Working Group (WG) members

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Desired outcome: generate discussion on recommended strategies with industry and health authority representatives

- Background
- Work Group Purpose and Methodology
- Aligned strategies
  - Organism choice
  - Data interpretation and assigning in-use storage (hold) times
  - Assigning hold-times during clinical development (in-progress)
- Conclusions and next steps

Microbial challenge studies evaluate product's potential for growth proliferation

- Holding product after breach of sterility represents a risk
  - In-use storage time should be justified regardless of available data
  - Unjustified long in-use hold times pose unnecessary risks and may not be approved
- Label should include storage time for in-use solutions to ensure patient safety in the case of accidental contamination
  - Microbial stability is assessed in combination with physiochemical stability
  - Concepts included in ICH, CFR

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

Regulator expectations set by publications, information requests

- High-level study design defined by publications
  - Low inoculum level to simulate accidental contamination
  - Study should be at least 2x recommended storage period
  - Organisms should include USP<51> plus skin flora or nosocomial agents
  - Not more than 0.5log10 increase should be acceptance criteria
  - Growth trend should be considered when defining hold times
- Information requests further elucidate expectations
  - Definition of growth trend and data interpretation
  - Microbial data required to support in-use hold times >4 hrs at RT/2-8°C at **all** phases of development

Metcalfe, J.W. 2009. American Pharmaceutical Review, posted Feb. 1.

Purpose of IQ In-Use Microbial Stability WG

- Share industry experience and understand current practices
  - Survey sent to IQ Biologics LG member companies
  - 58 questions, 14 respondents
- Harmonize strategies on study execution and data interpretation for assigning in-use hold times
  - Supported by scientific rationale
- Align strategies with regulators

IQ WG End to End Deep Dive on Microbial Challenge In-use Studies

Overall 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?

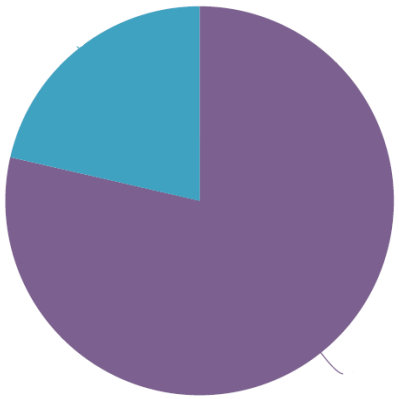
Interpretation of microbial growth and assignment of hold time

- 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?

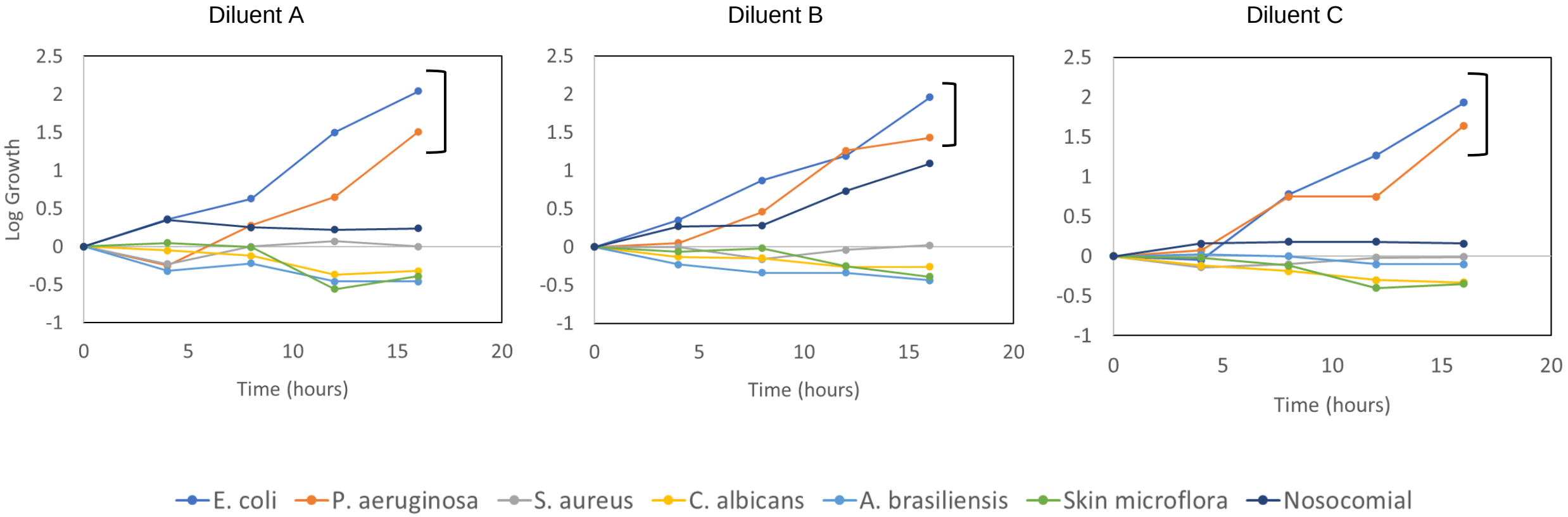
Selection of organisms varies by company



- For companies that add 1-2 organisms to USP<51>, different combinations are used
  - *Micrococcus luteus*
  - *Staphylococcus epidermidis*
  - *Acinetobacter baumannii*
  - *Klebsiella pneumoniae*
  - *Enterobacter cloacae*
  - *Streptococcus pyogenes*
- USP<51> microorganisms are listed as consistently fast-growing by multiple respondents
  - *E.g. E. coli* (10 of 13 responses)

USP<51> includes: *E. coli, P. aeruginosa, S. aureus, C. albicans, A. brasiliensis*

Case study: *E. coli, P. aeruginosa* consistently grow quickly in diluted dose solutions



Studies conducted at 25°C

No clear alignment on likely microorganism contaminants for biologics in literature

- Variability in types of organisms that might be present
  - Nosocomial agents present at bedside generally gram negative
  - Clean room organisms primarily gram positive – potential similarity to organisms found in pharmacy preparation hoods
- Literature references on contaminated products are not representative of biologics dose preparation
  - Non-biologics products (e.g., anesthetics, multi-use products, etc.)
  - Contamination occurred during surgery or at bedside
  - Identified organisms vary

WG recommends USP<51> organisms only for microbial challenge studies

- USP<51> represents wide variety of organisms, often worst-case for growth
  - Includes gram positive, gram negative, etc.
  - Industry survey identified USP<51> (e.g., *E. coli*) to be consistently fast-growing
- Clinical contaminants not relevant to biologics
  - Biologics generally prepared in pharmacies, not bedside
  - Literature of contaminated products are non-biologic products
- No scientific justification to harmonize on specific nosocomial agents

Proposed "Decision Path" for interpretation of microbial data and hold time assignment- Background

- Created "Decision Path" to determine in-use hold time from microbial data
  - Based on publications from FDA leaders and Health Authority feedback
  - Incorporates FDA expectation to identify when exponential growth begins
  - Incorporates well recognized ≥ 0.5 log10 increase
- Identified scientifically justifiable definitions
  - Fast-growing microorganism is selected as worst case for defining hold time in decision path
  - Defining Log increase for no growth, upward trend and growth
    - Decision Path is divided into three tiers:
      1. "No growth" in microbial data is observed
      2. An "upward growth trend" is observed
      3. Microbial "growth" is observed
- Incorporates application of safety factor, if applicable
  - 2-fold safety factor when growth is observed
  - 1.5-fold safety factor or apply previous time point when no growth or upward growth trend is observed
- Establishing minimum hold time set at 4 hours (definition of "immediate" use)
- Robustness of microbial data, passing method suitability criteria, and acceptable data for controls need to be demonstrated before using Decision Path

Proposed "Decision Path" for interpretation of microbial data and hold time assignment

Summary of Decision path

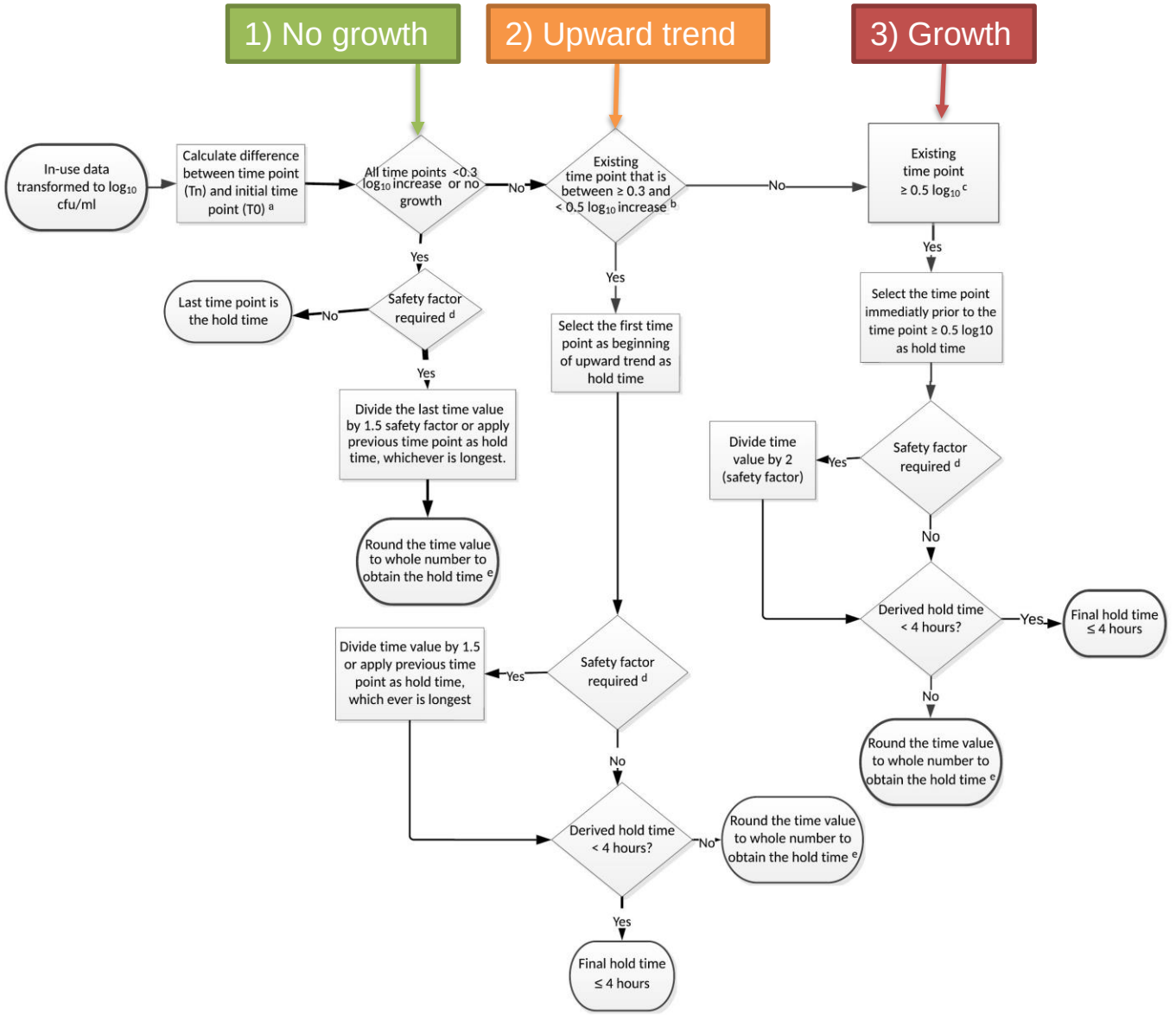
Input: Microbial data transformed to $\Delta\log_{10}$ CFU/mL from T0

Selection of time point based on tier 1, 2, or 3

Safety factor (if applicable) or selection of final existing time point

Considerations for 4 hours immediate use (if needed)

Output: In-use hold time



[a] Round the $\log_{10}$ value to one tenth decimal point for this evaluation.

[b] Upward trend defined as first time point that is beween ≥ 0.3 and < 0.5 $\log_{10}$ units from initial time point (T0) **AND** consecutive time points maintain or continue upward **OR** no consecutive time point is available. If subsequent time points are again lower than 0.3 $\log_{10}$ units, the further procedure must be defined on a case-by-case basis.

[c] Growth defined as first time point at ≥0.5 $\log_{10}$ units from initial time point (T0) **AND** consecutive time points are indicative of growth. If subsequent time points are again lower than 0.5 $\log_{10}$, the further procedure must be defined on a case-by-case basis.

[d] Some Health Authorities require incorporation of a safety factor in the calculation of hold time (e.g. FDA).

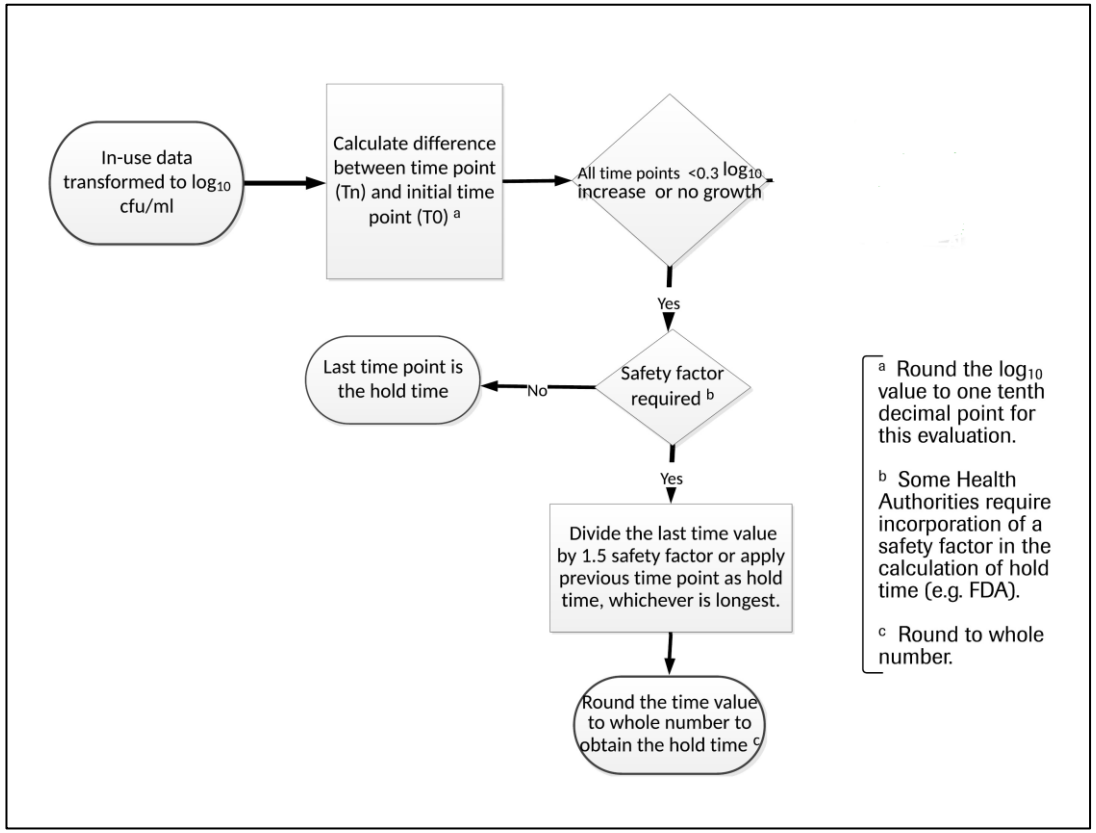
[e] Round to whole number.

The data from all time points are assessed holistically end to end, along with the corresonding controls for the determination of growth. If lab error is supsected, repeat testing may be warranted, as possible.

Example: A data set such as: T1: 0.0, T2: 0.1, T3: 0.5, T4: 0.2, T5: 0.4, T6: 0.6, T7: 0.2 should be evaluated as possible lab error and repeated, as possible.

Case 1 Example: No growth observed

	$\Delta\log_{10}$ CFU/mL from T0						
Time point	*E. coli*	*P. aeruginosa*	*S. aureus*	*C. albicans*	*A. brasiliensis*	*Additional 1*	*Additional 2*
T1	0.0	0.0	0.0	0.0	0.0	0.0	0.0
T2	-0.1	-0.1	0.1	0.1	0.2	-0.5	-0.1
T3	0.0	0.0	0.0	0.0	0.2	-0.8	-0.2
T4	-0.1	-0.1	0.0	0.0	0.1	-0.6	-0.1
T5	-0.5	-0.4	0.0	0.0	0.2	-1.2	-0.5
T6	-0.4	-0.4	-0.1	0.0	0.0	-0.9	-0.2
T7	-0.2	-0.8	0.1	0.0	0.0	-1.6	-0.1
T8	-0.2	-0.7	-0.2	0.0	0.1	-1.6	-0.2



No upward trend or growth was observed throughout the duration of the study for all evaluated microorganisms

No SF: Last time point is hold time: T8

With SF: Divide T8 by 1.5 SF or set T7 as hold time, whichever is longest hold time

Simulated example: T8=24 hours and T7= 12 hours; **Hold time: 16 hours** (1.5 SF)

SF: Safety Factor

Case 2 Example: Upward growth trend observed

	Δlog_{10} CFU/mL from T0
Time point	*E coli*
T1	0.0
T2	-0.6
T3	0.0
T4	0.2
T5	**0.3**
T6	0.3
T7	0.8
T8	1.1
T9	1.8

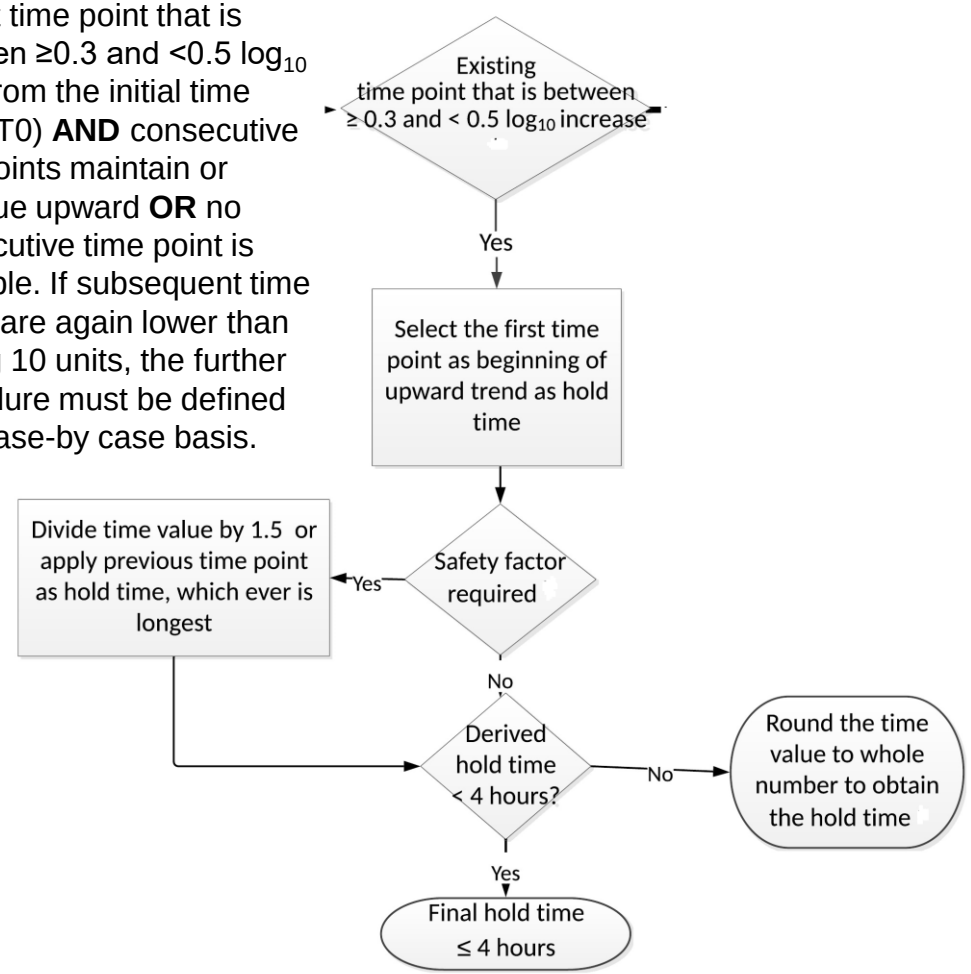
T5: First time point with upward trend

No SF: Set T5 as hold time

With SF: Divide T5 by 1.5 SF or set T4 as hold time, whichever is longest hold time

Simulated example: T5=24 hours and T4=16 hours; **Hold time: 16 hours** (T4 time point or 1.5 SF)

Note: Upward trend defined as first time point that is between ≥0.3 and <0.5 log_{10} units from the initial time point (T0) **AND** consecutive time points maintain or continue upward **OR** no consecutive time point is available. If subsequent time points are again lower than 0.3 log 10 units, the further procedure must be defined on a case-by case basis.



SF: Safety Factor

Case 3 Example: Growth observed

	Δlog_{10} CFU/mL from T0
Time point	*E coli*
T1	0.0
T2	0.0
T3	0.6
T4	0.8
T5	1.1

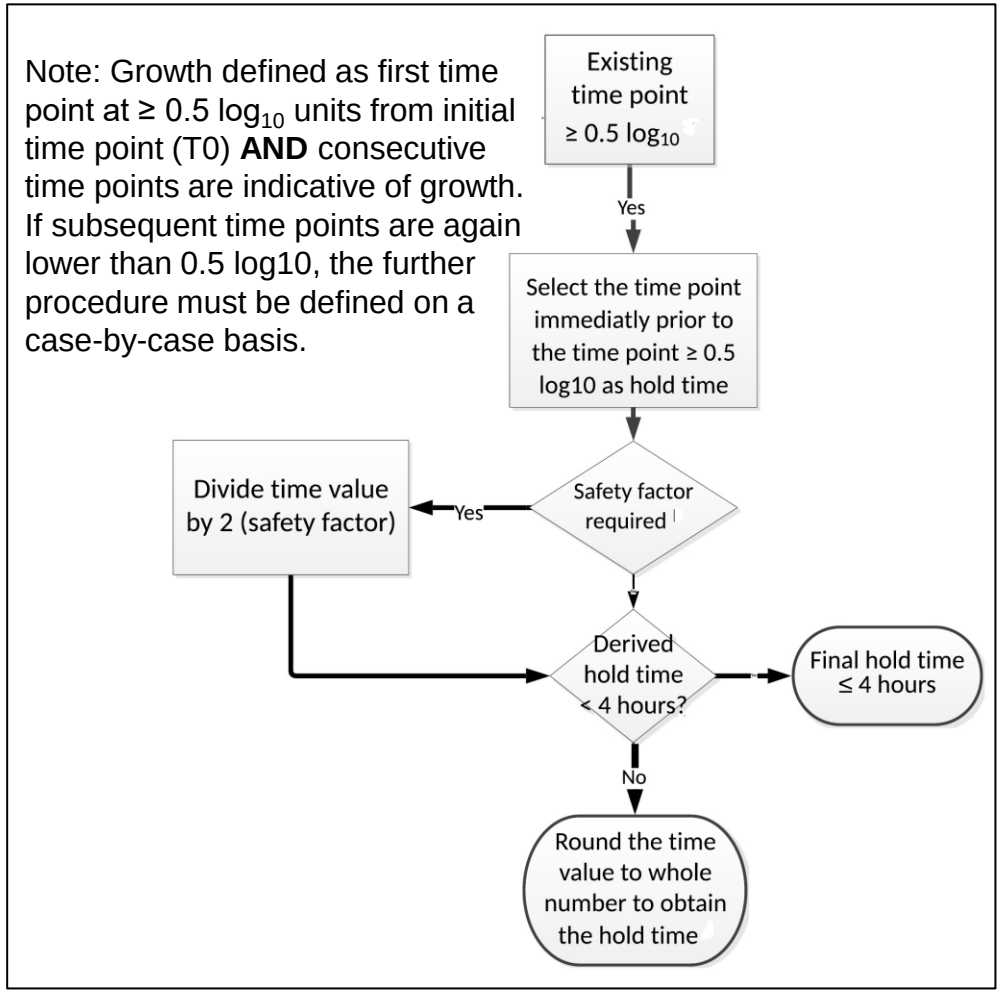
Select the time point prior to T3 that growth observed: T2

No SF: Set T2 as hold time

With SF: Divide T2 by 2 SF

Simulated example: T3=12 hours, T2=8 hours; hold time: 4 hours (2 SF)

Note: Growth defined as first time point at ≥ 0.5 log_{10} units from initial time point (T0) **AND** consecutive time points are indicative of growth. If subsequent time points are again lower than 0.5 log10, the further procedure must be defined on a case-by-case basis.



SF: Safety Factor

The need for alignment and partnership to support biologics in-use hold times at clinical sites

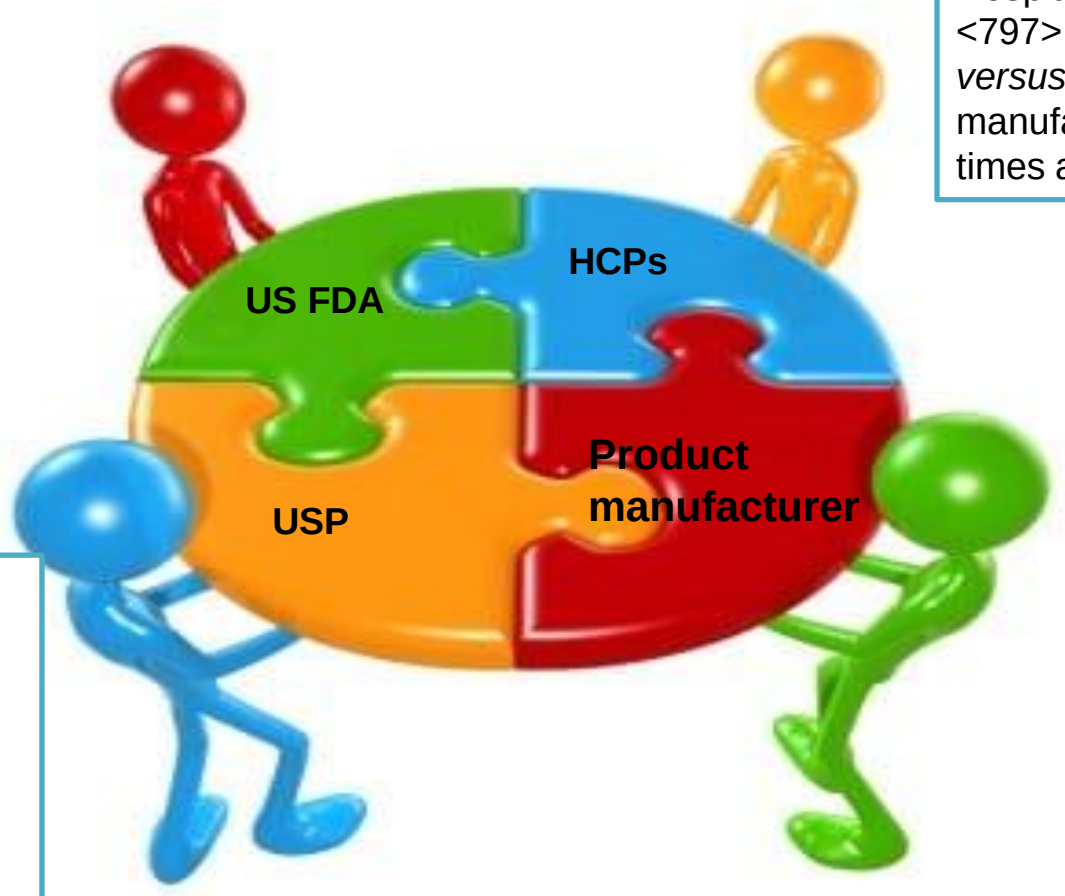
Survey question: How does your organization support in-use storage times for clinical sites?

Response	Percent
Rely solely on immediate use time (i.e. 4 hours for both RT and 2-8°C)	12.5%
Rely on physicochemical stability data only to support hold times longer than 4hrs	25.0%
Rely on physicochemical stability data and historical microbial data from other products to support times longer than 4hrs	37.5%
Rely on physicochemical stability data and Leverage USP Pharmaceutical Compounding — Sterile Preparations to support hold times longer than 4hrs	50.0%
Other – collecting data to create historical micro data to support longer times; 24 hrs at 2-8ºC/4 hr at RT	37.5%

The need for alignment and partnership to support biologics in-use storage times at clinical sites

FDA

- "**Compounding Does Not** include mixing, **reconstituting**, or similar acts that are performed in accordance with the directions **contained in approved labeling provided by the product's manufacturer** and other manufacturer directions consistent with that labeling"
- The BUDs provided in <797> do not apply to BLA products.
- Microbial data required for in-use storage times longer than **4 hours** at RT/2-8°C



Hospitals practice of using USP <797> storage periods (BUD) *versus* recommended product manufacturers in-use storage times are variable

USP<797> (2008*)

- CSP include any of the following:

1. Compounded biologics…
2. **Manufactured sterile products that are either prepared strictly according to the instructions appearing in manufacturers' approved labeling** (product package inserts) or prepared differently than published in such labeling.

- CSP microbial contamination risk levels and storage periods

1. Low risk: 48hrs at CRT/14 days at cold temp.
2. Mid risk: 30 hrs at CRT/9 days at cold temp.
3. High risk: 24 hrs at CRT/3 days at cold temp.

*USP is updating the status of Pharmaceutical Compounding – Sterile Preparations based on the Appeals Panel decision. The currently official , last revised in 2008, remains official. Note: The categories of CSPs and practices both in scope and out-of-scope of USP <797> are revised in updated Chapter.

BUD: Beyond Use Date, CSP: Compounding Sterile preparation, CRT: Controlled Room Temperature

Conclusion and Next Steps

- The outcome of microbial challenge studies has significant impact on product label in-use hold times, essential for HCPs to allow time for dose preparation and timely administration
- The industry practice is quite variable and multiple areas of collaboration to harmonize strategies have been identified

Next Steps

- IQ position paper on harmonized approaches for microbial challenge studies is under preparation in collaboration with industry and US FDA representative
- Proposal for a workshop to socialize the strategies with health authorities with participants from industry, global HAs, and USP is under discussion
- Future work to clarify the USP <797> requirements from pharmacy practice

Acknowledgement

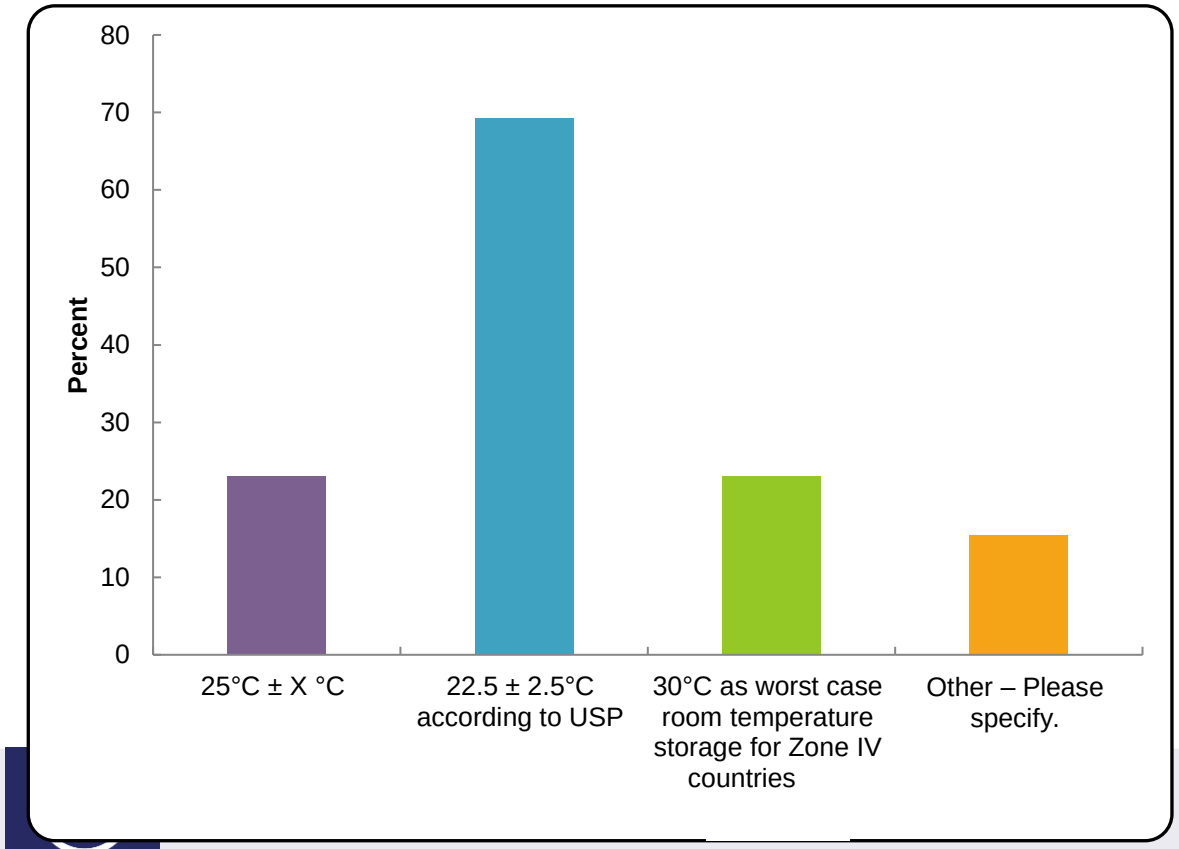
This presentation was developed with the support of the International Consortium for Innovation and Quality in Pharmaceutical Development (IQ, www.iqconsortium.org). IQ is a not-for-profit organization of pharmaceutical and biotechnology companies with a mission of advancing science and technology to augment the capability of member companies to develop transformational solutions that benefit patients, regulators and the broader research and development community.

Backup Slides

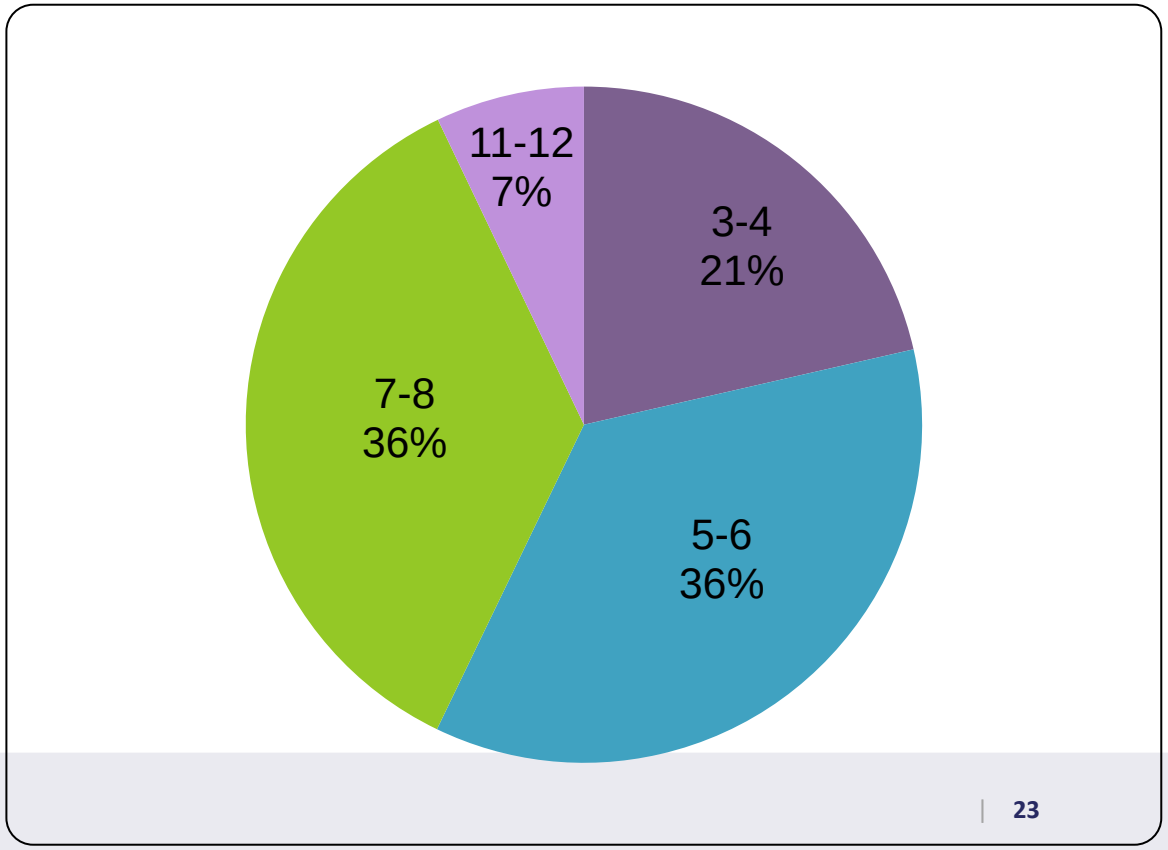
Temperatures and Time points

- Industry practice is variable on study duration, number of time points, and temp.

Survey question: What temperature do you perform microbial challenge in-use studies to assess in-use hold time at room temperature?



Survey question: Determination of time points: as part of your microbial challenge study design, how many measured time points do you test at room temperature condition?



Proposed Recommendations for Temperatures and Time Points

- Selection of temp and time points are based on product TPP and potential for microbial growth
- Temperatures
  - Commonly used temp: 2-8°C to support cold storage and 22.5±2.5°C (USP<51>) to support RT storage
  - Country specific requirements (ICH Zone IV) and specific applications (e.g. neonatal) should be considered on a case-by-case basis
- Time points
  - Study duration: 2X the expected storage in label claim
  - When growth is expected, more frequent time points are desired
  - RT time points: Min 4 time points in addition to T0 (e.g. T0, 4, 8, 12, 24 hours)
    - Note: Less than 2 hours frequency is not practical for execution of microbial in-use studies
  - 2-8°C time points: 4 to 5 time points is a good practice (e.g. 0, 24, 48, 72 hours)
    - More frequent time point before 24 hours If product has potential for growth