From Developability to Commercial Readiness:

The New Reality of ICH Q1 Stability

Championing the missions that matter™

Elizabeth Grotemeyer, Biologics Analytical Services

January 29, 2025

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Agenda

01 Introduction: ICH Q1 Draft Guidance

02 Case Study:
Ensuring Sample Integrity During Shipment

03 Case Study:
Solvent Loss Revealed by Orthogonal Analysis

04 Case Study:
Container Compatibility for Reliable Data

05 Kansas City Biologics Analytical Services

06 Conclusion

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Introduction

ICH Q1 Draft Guidance

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Introduction: ICH Draft Q1 Guidelines

Key Takeaways

- Unified scope for biologics, vaccines, cell/gene therapies
- Lifecycle management and ongoing studies are now core
- Analytical rigor and real-world storage emphasized
- Excursion studies and forced degradation as development tools

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Introduction: ICH Draft Q1 Guidelines

Designing Biologics Stability Programs

Formulation and Process Understanding

- Define critical quality attributes (CQAs)
- Assess formulation/process variables
- Use stress/forced-degradation for product knowledge

Protocol Development

- Scientifically justified, risk-based design
- Real-world storage and handling conditions
- Validated, stability-indicating analytical methods

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Introduction: ICH Draft Q1 Guidelines

Designing Biologics Stability Programs

Batch Selection and Testing

- Representative lots (≈3, per guideline)
- Scaled manufacture and controlled sample handling
- Long-term, real-time, and accelerated studies
- Monitor potency, purity, safety with validated methods

Data Analysis & Program Review

- Statistical modeling for shelf-life/retest
- Interpret results to set storage/retest dates
- Periodic review and protocol adjustment as new data emerge

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Case Study: Ensuring Sample Integrity During Shipment

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Case Study: Ensuring Sample Integrity During Shipment

Study Design

Samples:
5 mL vial with 1 mL fill and bromobutyl stopper closure

Storage conditions:
Nominal and accelerated are both frozen conditions

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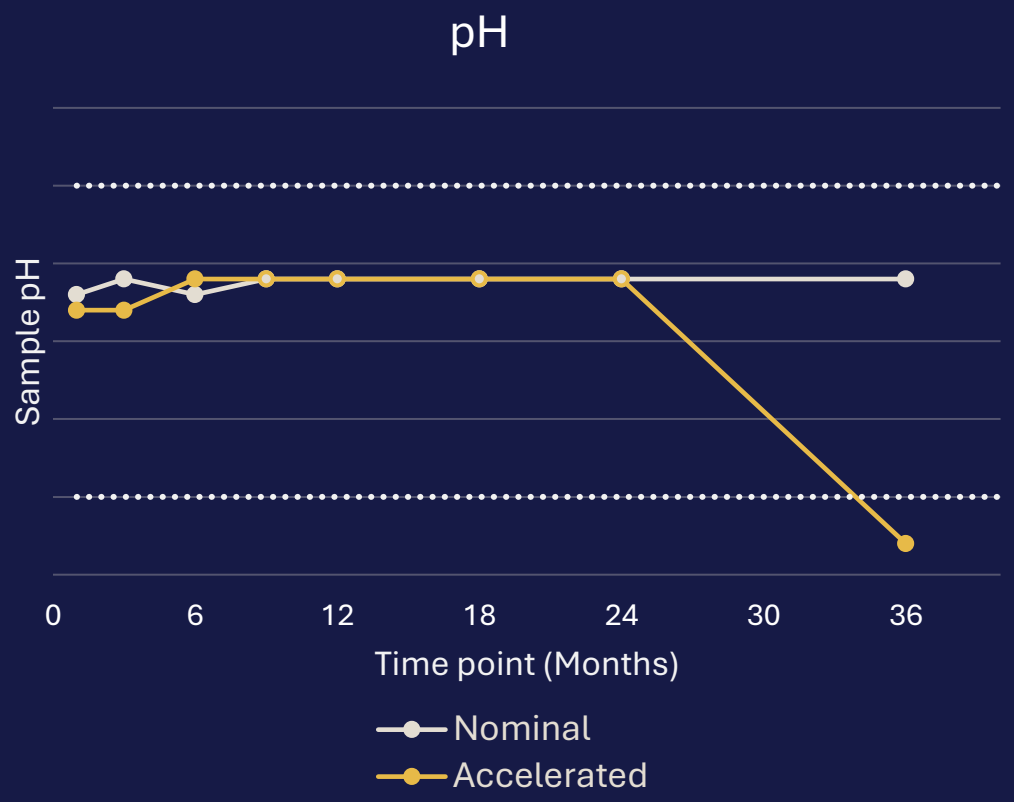
Case Study: Ensuring Sample Integrity During Shipment

36M Timepoint Results

Samples were randomly selected from the study, including both those originally taken at Catalent Kansas City and those that were shipped and added.

- pH was out of specification and out of trend for the accelerated condition
- Appearance showed an increase in opalescence in the accelerated condition but was still within specification



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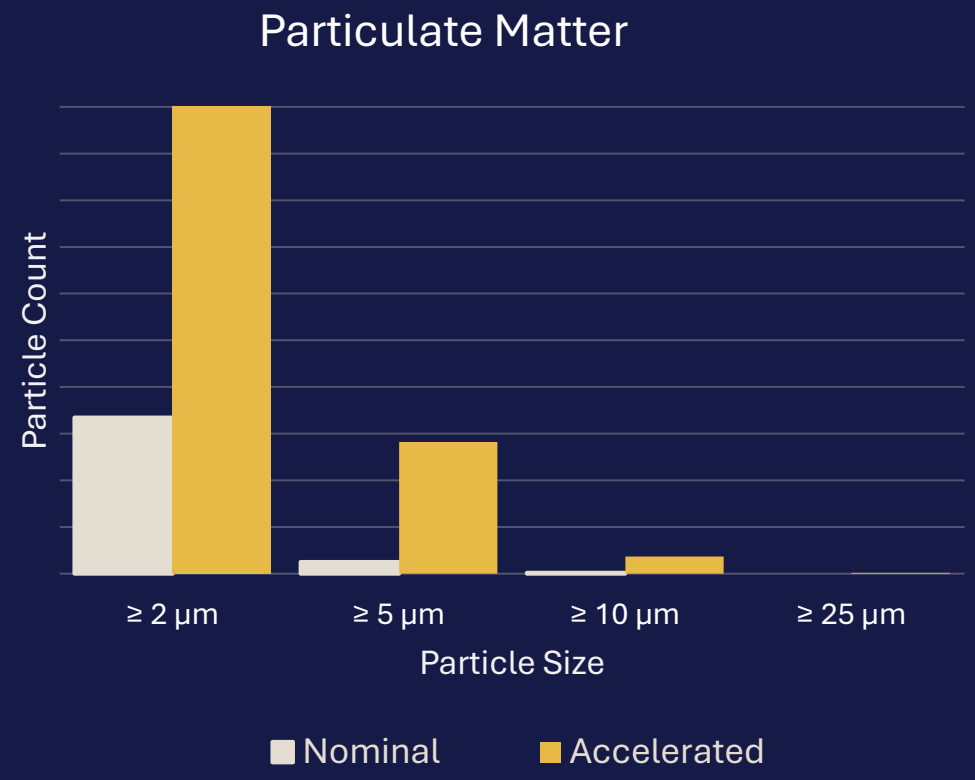
- Particulate matter showed a significant difference between the nominal and accelerated conditions



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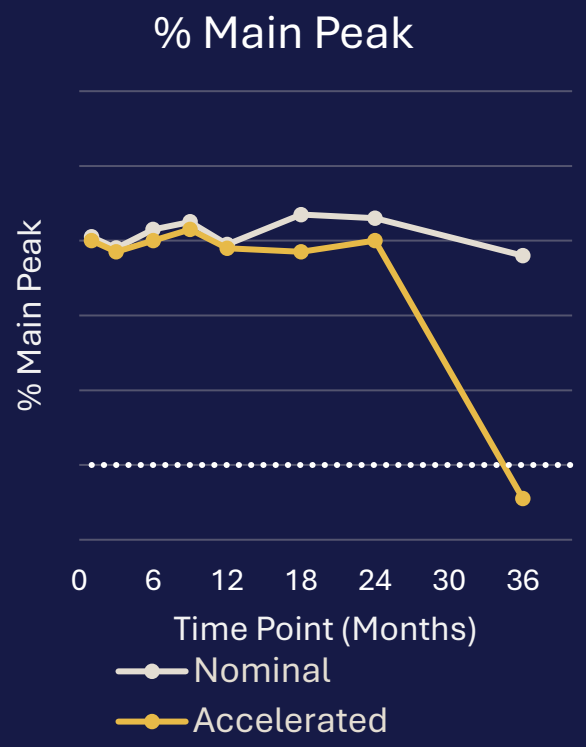
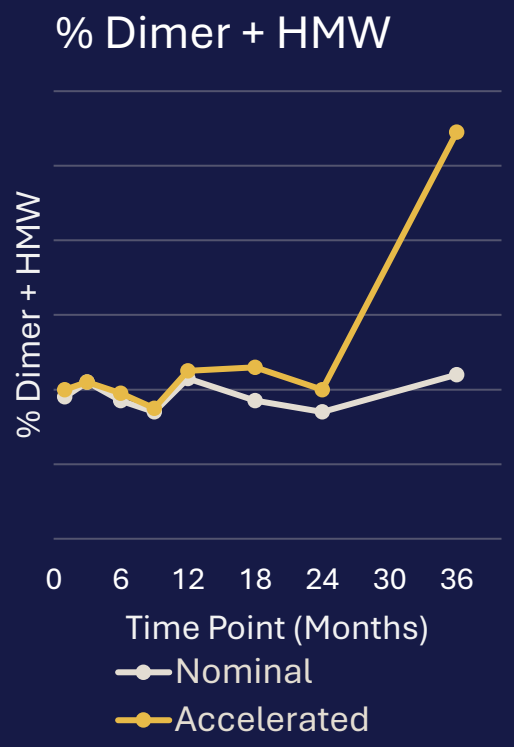
- Appearance showed an increase in opalescence in the accelerated condition but was still within specification
- Particulate matter showed a significant difference between the nominal and accelerated conditions
- SEC was out of specification for % main peak and showed a large increase in dimer and HMW species





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Case Study: Ensuring Sample Integrity During Shipment

Investigation

Initial review

Sample tracking indicated that physical samples tested for pH and SEC were pulled from the additional samples

Samples for particulate matter testing included a mixture of samples from off-site and Catalent storage

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Hypothesis: Samples with out of specification results were from off-site storage

Performed pH and SEC testing on all remaining samples shipped from off-site and added to study and reference standard

All sample vials were out of specification for pH and SEC. Reference standard results were within specification

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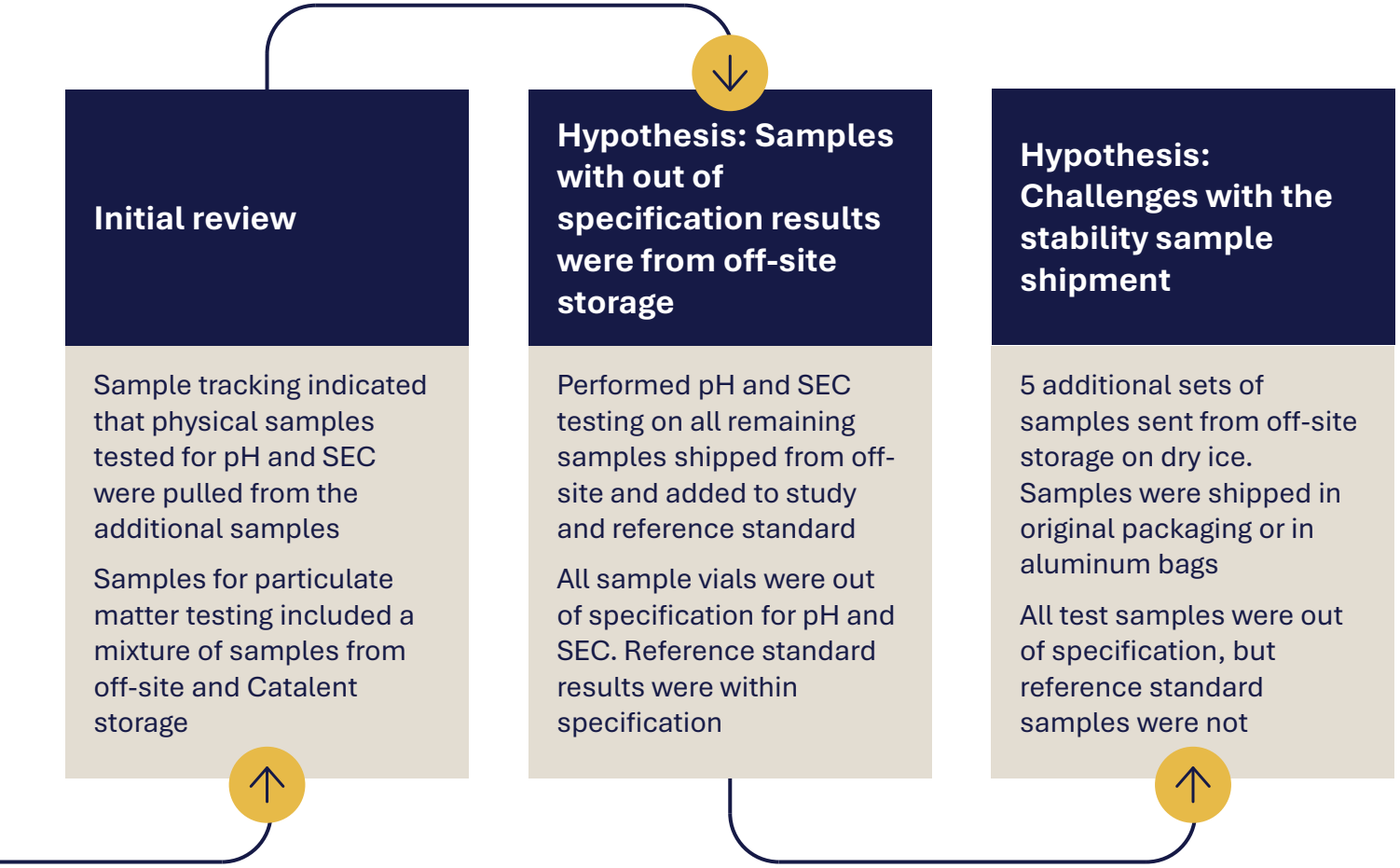
Case Study: Ensuring Sample Integrity During Shipment

Investigation



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Hypothesis: Challenges with the stability sample shipment

5 additional sets of samples sent from off-site storage on dry ice. Samples were shipped in original packaging or in aluminum bags

All test samples were out of specification, but reference standard samples were not

Hypothesis: Challenges with shipments from off-site storage

Client shipped additional samples from their reserves on dry ice. Samples were shipped in original packaging or in aluminum bags

All test samples were out of specification

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Hypothesis: Challenges with shipments from off-site storage

Client shipped additional samples from their reserves on dry ice. Samples were shipped in original packaging or in aluminum bags

All test samples were out of specification

Hypothesis: Shipment on dry ice resulted in compromised samples

Samples sent from off-site storage at refrigerated and ambient conditions

All test samples were within specification

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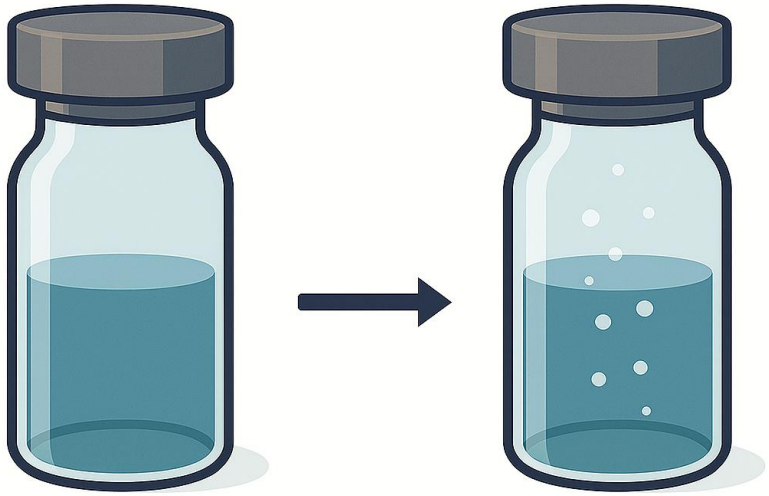
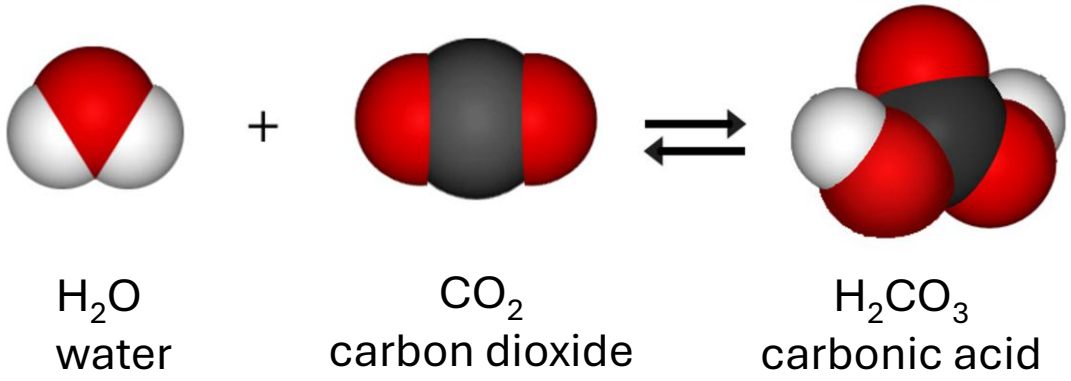
Case Study: Ensuring Sample Integrity During Shipment

Root Cause: CO_2 Intrusion due to Container Closure Failure



Dry Ice Temperatures Compromise Stopper Integrity

Bromobutyl stoppers experience changes in elasticity that compromise seal at temperatures below -60°C
Vial headspace condenses creating a vacuum



Carbon Dioxide Acidifies the Solution

Carbon dioxide in aqueous solution produces carbonic acid

Source: ACS.org

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Case Study: Ensuring Sample Integrity During Shipment

Conclusion

It is critical to consider shipping conditions when planning stability studies.

- Generally the concern is about protecting the samples from conditions outside the shipper but we must also consider if the samples require protection from conditions within the shipper as well

- Additional measures to isolate the samples from environmental conditions should always be considered
  - Aluminum bagging, light protective boxes, etc.

- Careful planning of all aspects of stability studies including sample shipment to the stability storage location are critical in determining a study's success

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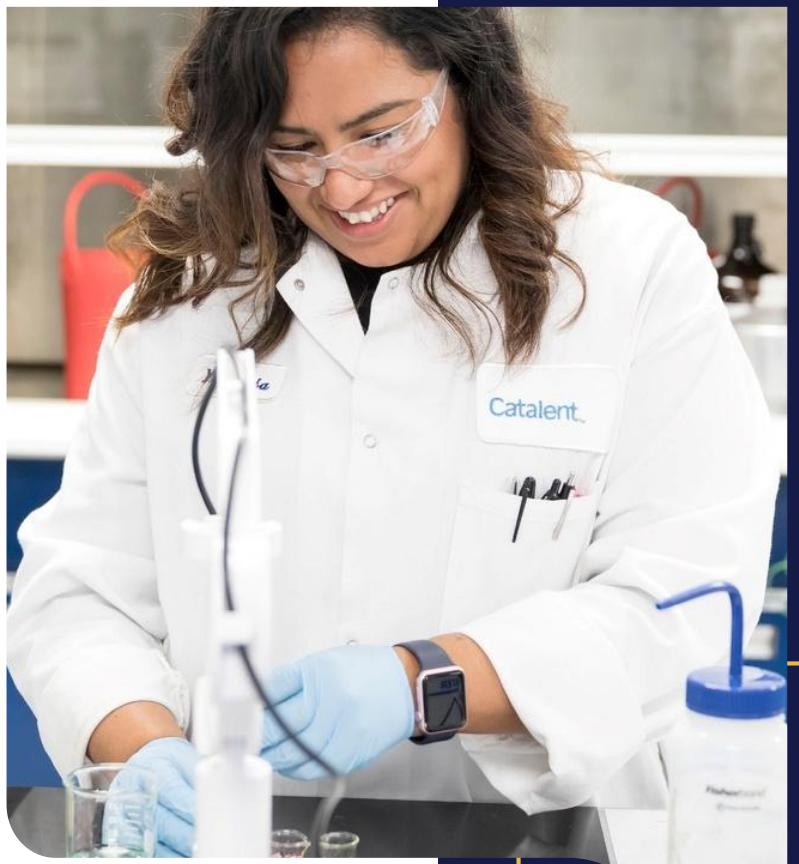

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Case Study: Solvent Loss Revealed by Orthogonal Analysis

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Case Study: Solvent Loss Revealed by Orthogonal Analysis

Two stability studies for drug substance were set down in **30 mL** bags with frozen nominal and **5°C/ambient** humidity accelerated conditions

For this study, the **5°C** storage was scheduled for **24M**

Previous studies for this material in **30 mL** bags terminated at the **6M** timepoint

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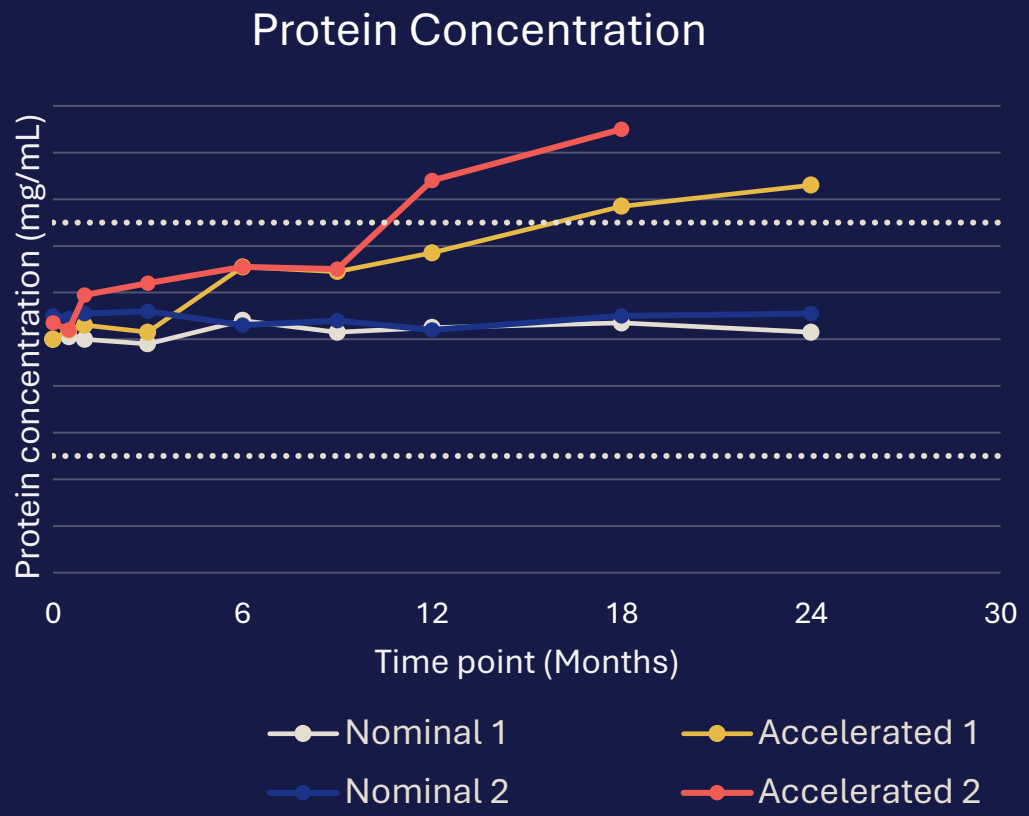
Case Study: Solvent Loss Revealed by Orthogonal Analysis

18M and 24M Time Point Results

Protein concentration was out of specification at 18M 5°C condition and later at the 24M time point



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Case Study: Solvent Loss Revealed by Orthogonal Analysis

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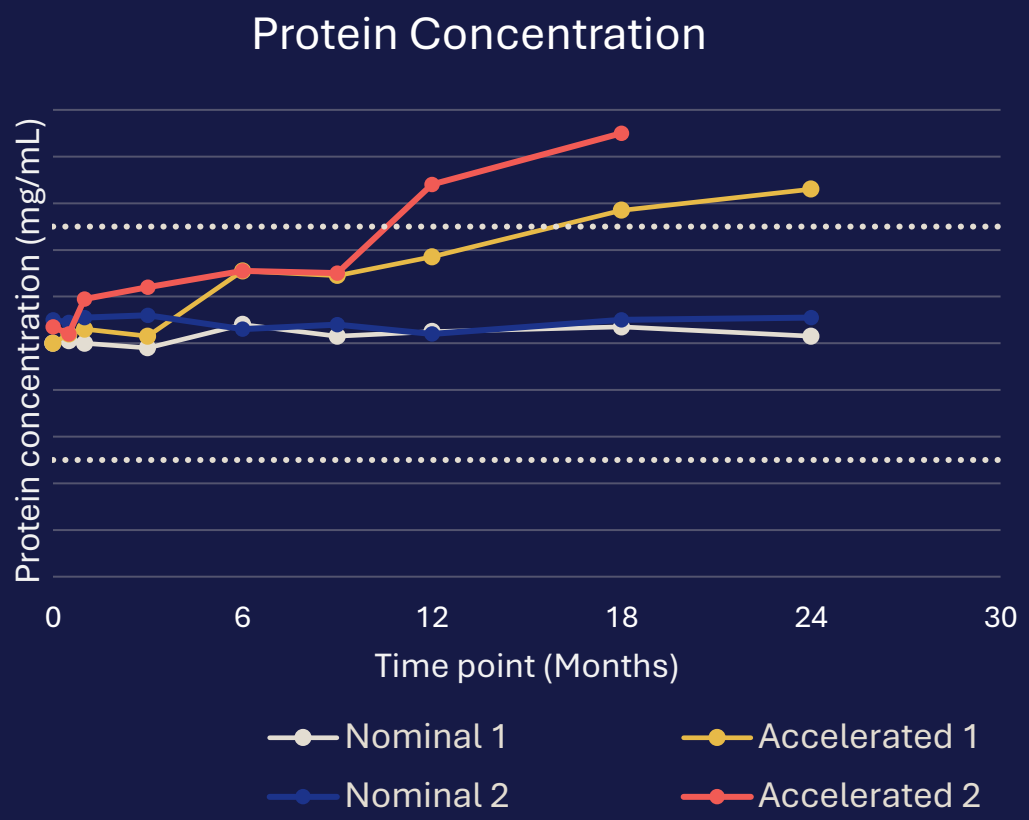

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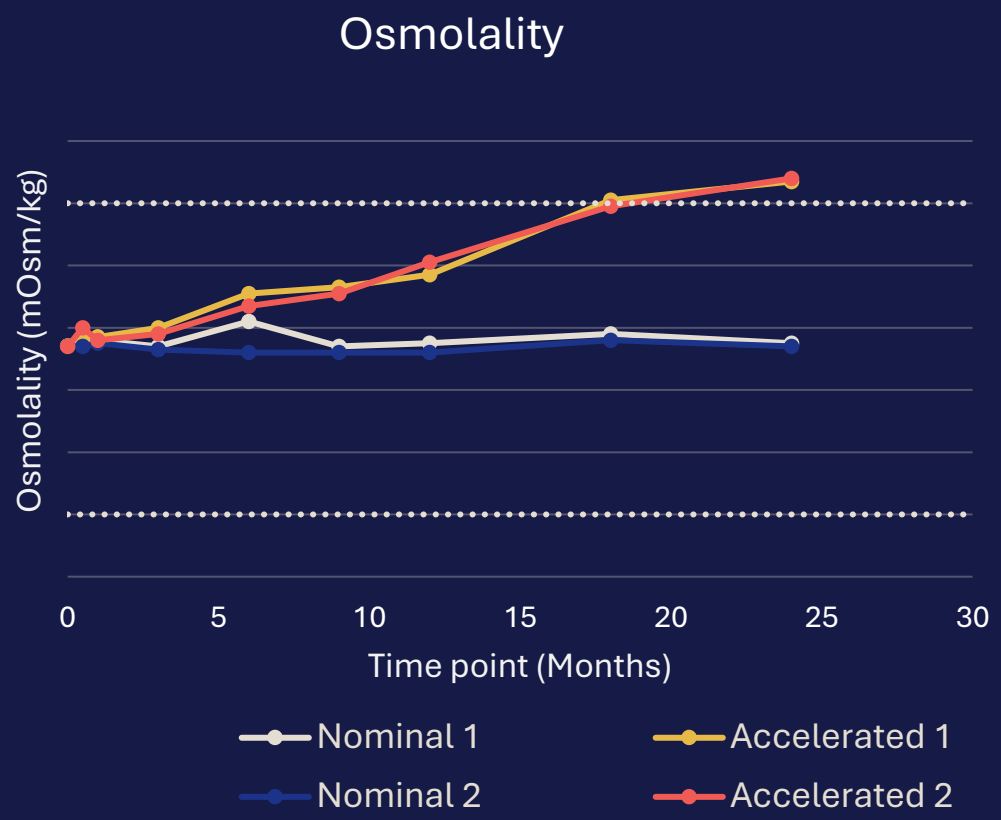
Case Study: Solvent Loss Revealed by Orthogonal Analysis

18M and 24M Time Point Results

- Protein concentration was out of specification at 18M 5°C condition and later at the 24M time point
- No changes in SEC eliminate possibility of aggregation resulting in increased UV absorption
- Osmolality also out of specification at 18M and 24M and demonstrated a clear, upward trend over lifetime of study in both lots



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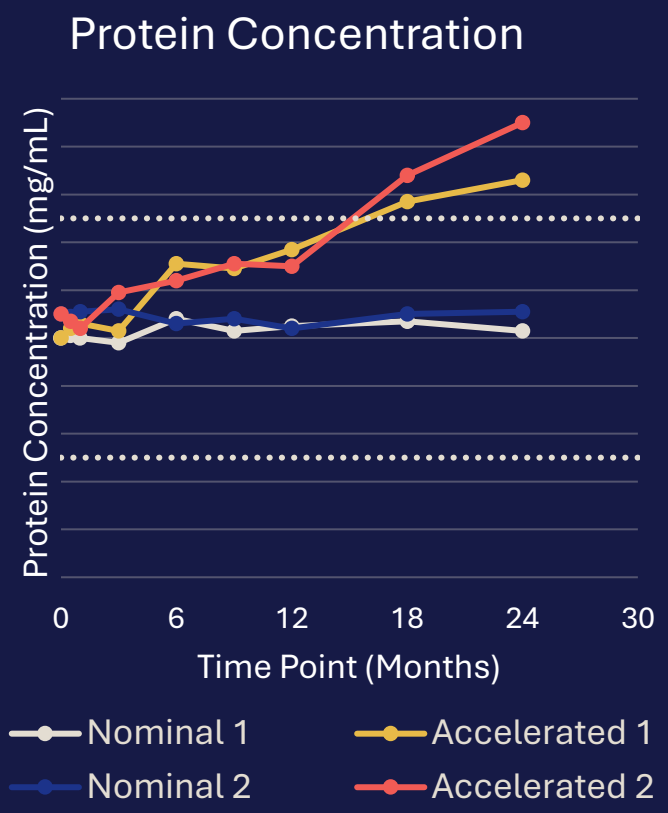
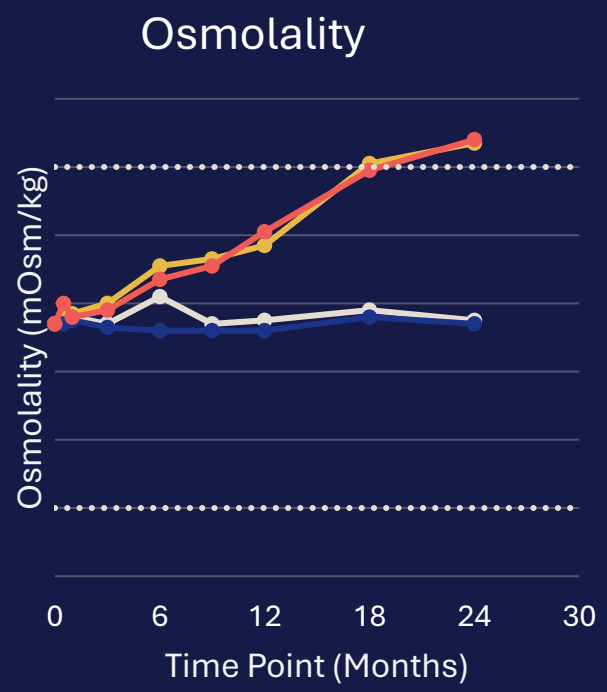
Case Study: Solvent Loss Revealed by Orthogonal Analysis

Conclusion

Clear upward trend of both lots over life-time of studies for both protein concentration and osmolality

Results are consistent with solvent loss through semipermeable bag wall





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Case Study: Solvent Loss Revealed by Orthogonal Analysis

Conclusion

- Solvent loss from semipermeable containers is possible at ambient humidity – in small volumes, this loss can result in significant changes in drug substance behavior

- Investigation was only possible due to inclusion of orthogonal methods in initial study design
  - Protein concentration and osmolality can both serve as indicators of solvent volume

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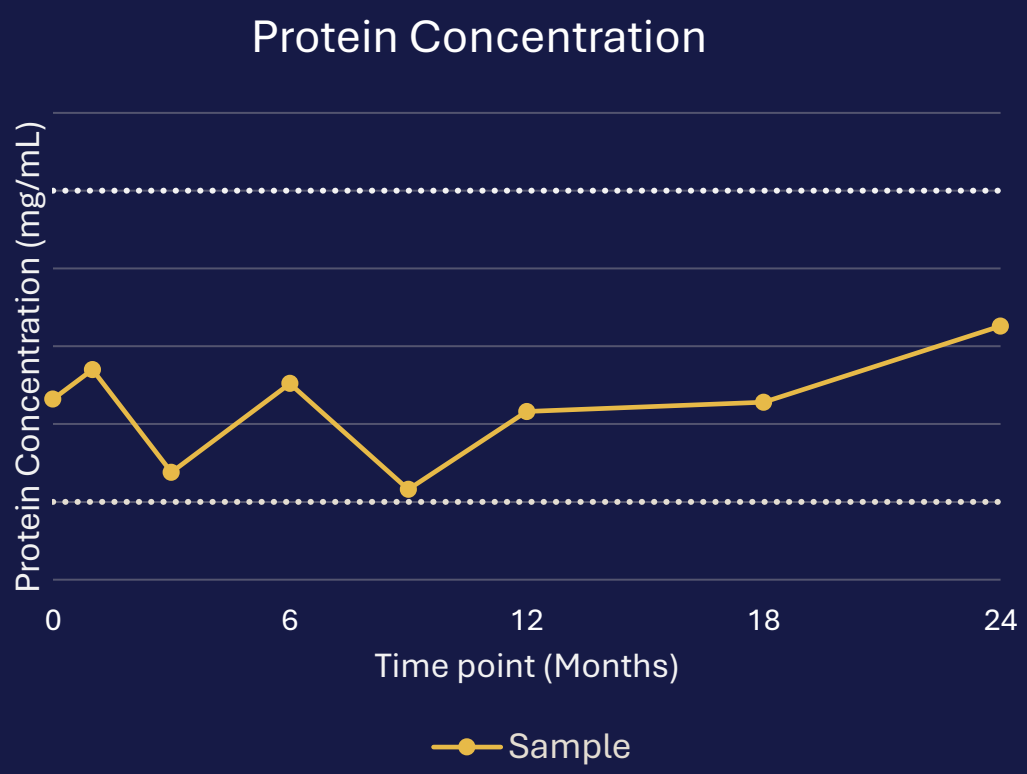
Case Study: Solvent Loss Revealed by Orthogonal Analysis

A second case

- Protein concentration shows high degree of variability between time points
  - No clear or obvious trend

- Variability is not reflected in other methods

Lack of orthogonality makes it difficult to make conclusions about the root cause in this case



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Case Study: Container Compatibility for Reliable Data

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Case Study:
Container Compatibility for Reliable Data

Introduction

Antibody drug conjugates must be evaluated for free payload content at release and over the shelf-life of the compound

For this ADC, free drug is evaluated using an RP-HPLC method

These methods are sensitive to interference from extractable and leachable compounds from storage vials.

Extractables:
Compounds released from product container closure, packaging, or delivery system under accelerated conditions

Leachables:
Compounds released from product container closure, packaging, or delivery systems under normal conditions

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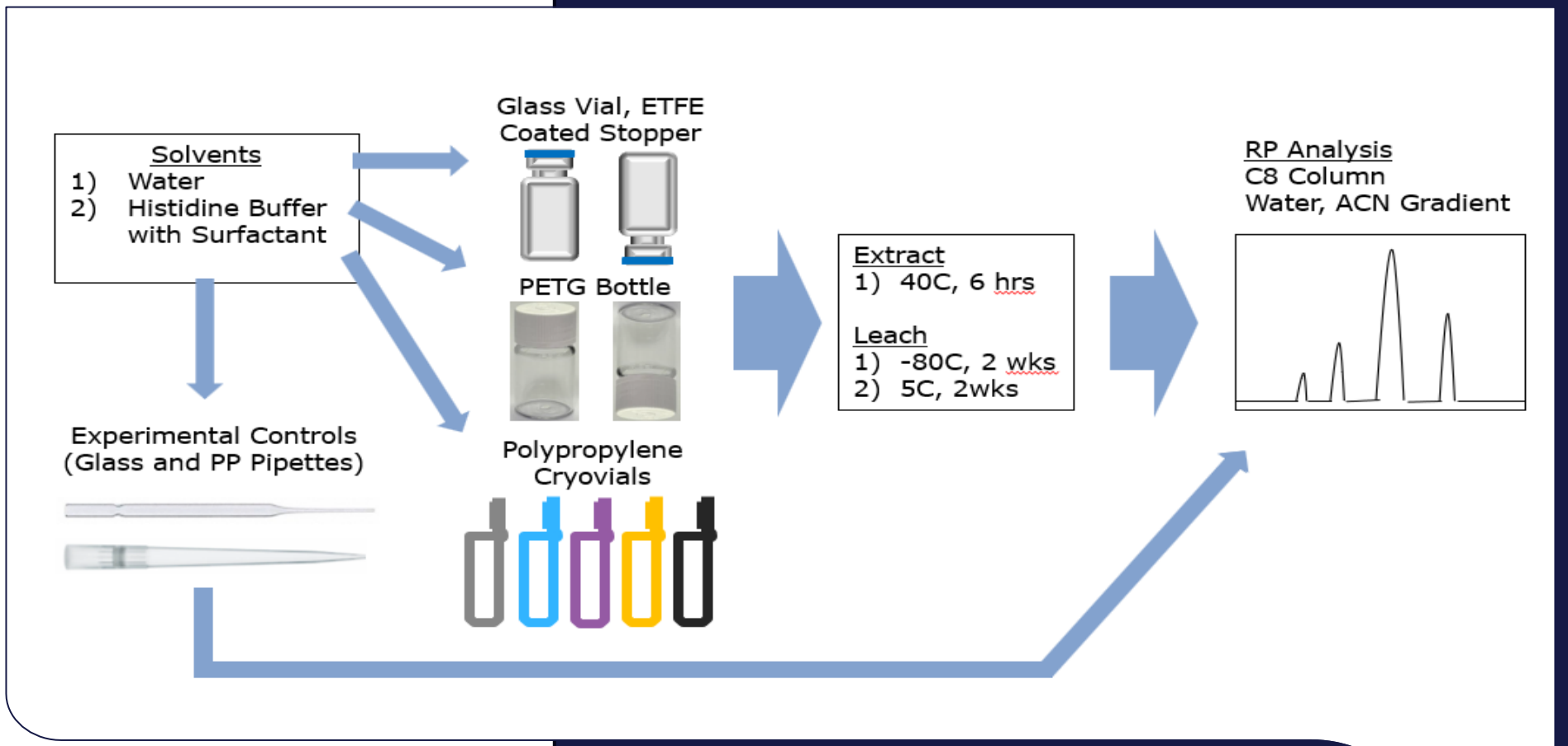
Case Study: Container Compatibility for Reliable Data

Study Design



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Case Study: Container Compatibility for Reliable Data

Study Results

Controls:

- **Pipettes:** No interfering signals
- **Glass vials:**
  No interfering signals in UPR or INV orientations
- **PETG vials:**
  No interfering signals in UPR or INV orientations

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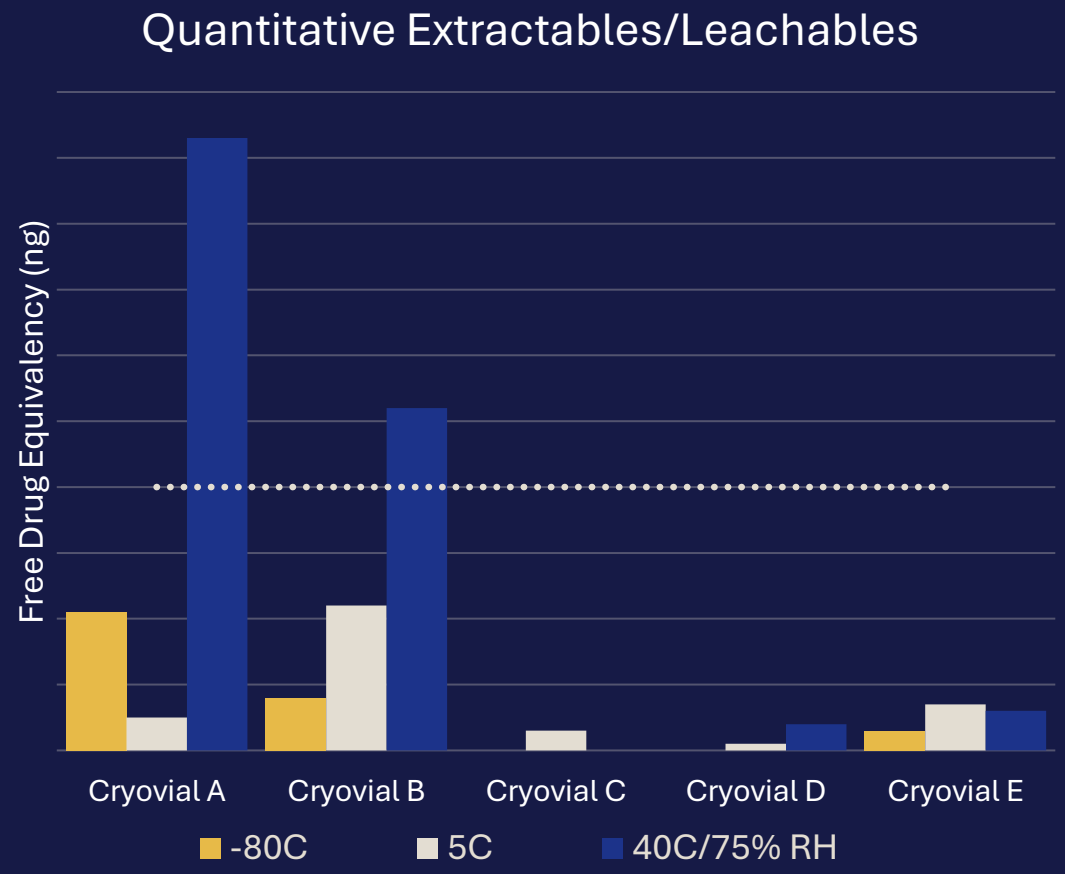
Cryovials:

- Vials A and B show significant interference in the region of the Free Drug signal
- Vial E shows some interference
- Vial C and Vial D show very little interference



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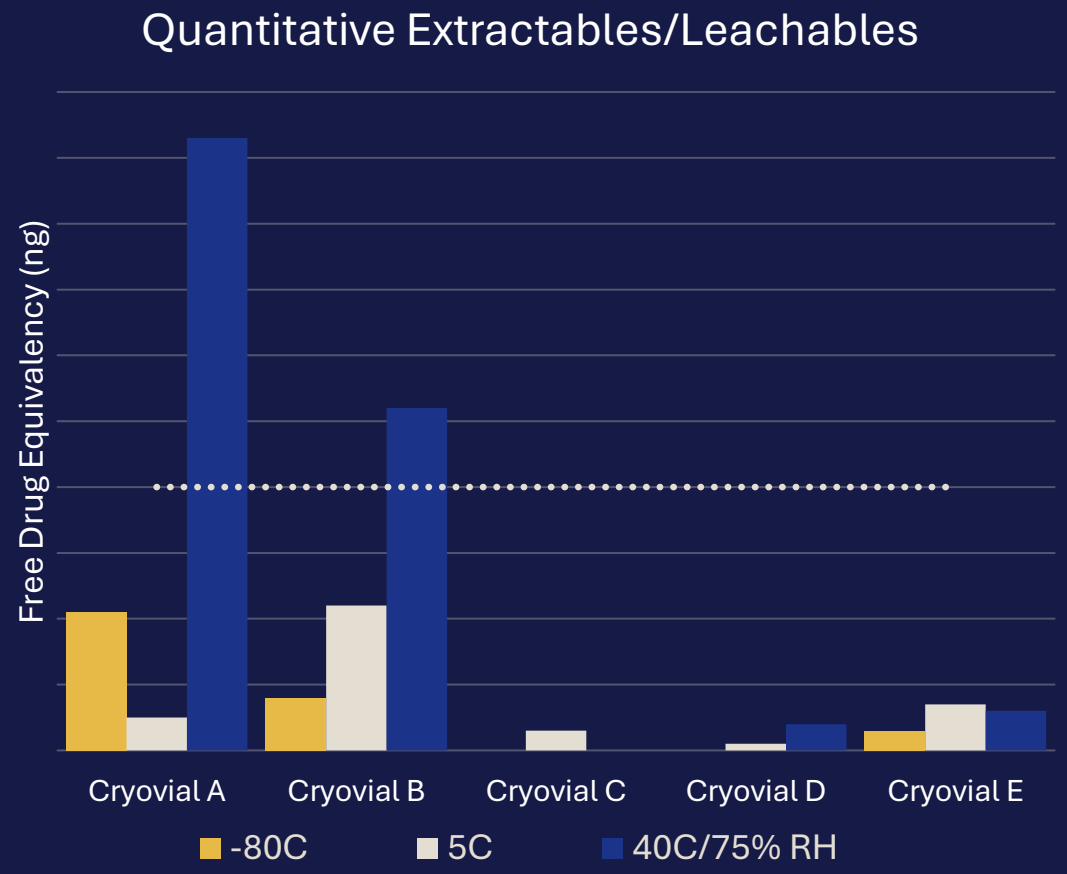

Cryovial C was chosen for subaliquoting of stability samples for free drug analysis

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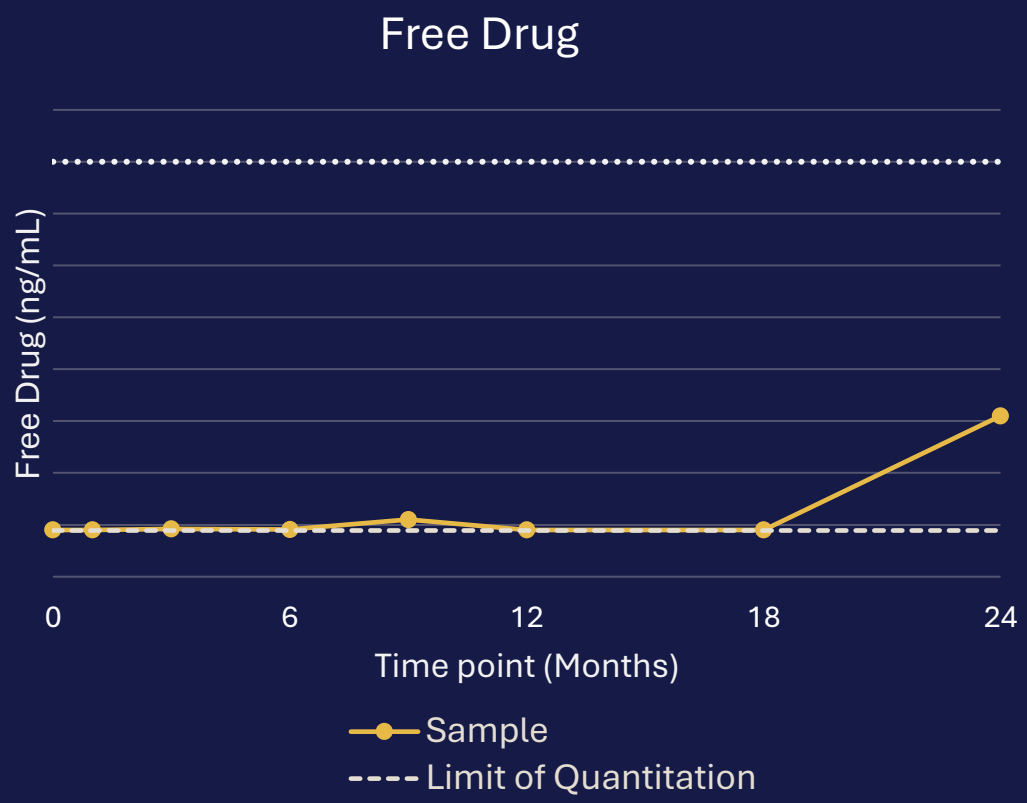
Case Study: Container Compatibility for Reliable Data

24M Timepoint Results

- Atypical peak in the chromatogram contributed ~85% to the calculated free drug concentration
- No atypical peak in reference standard control sample
- Calculated free drug is also atypical but within specification



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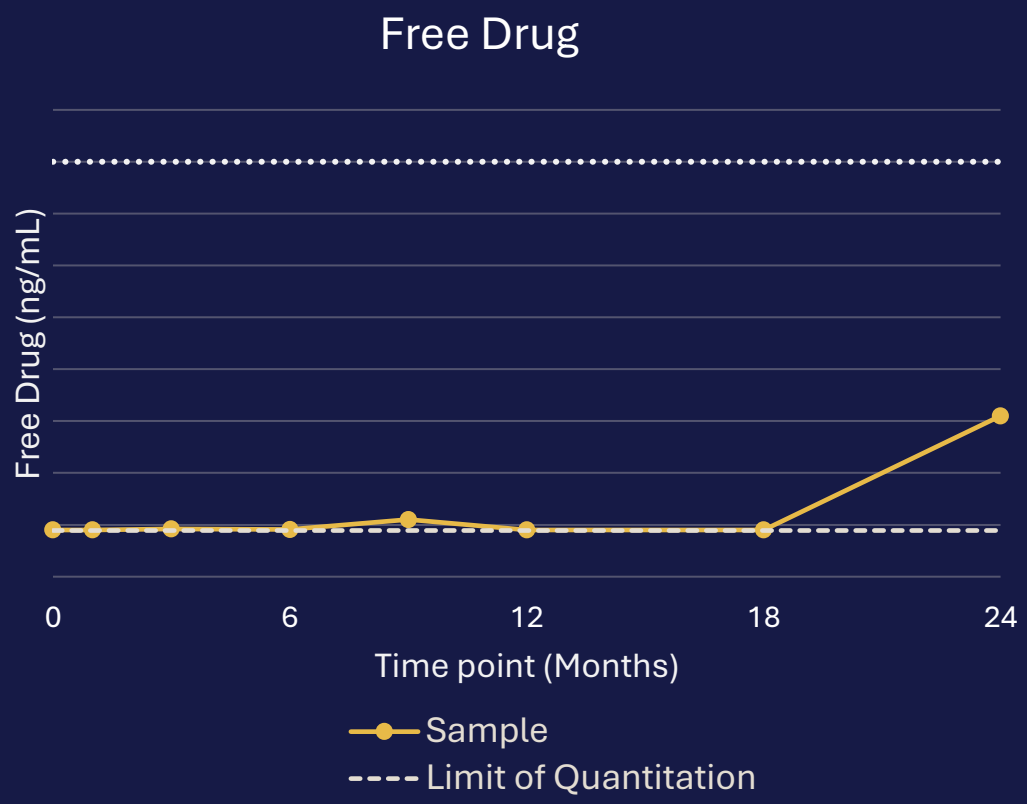

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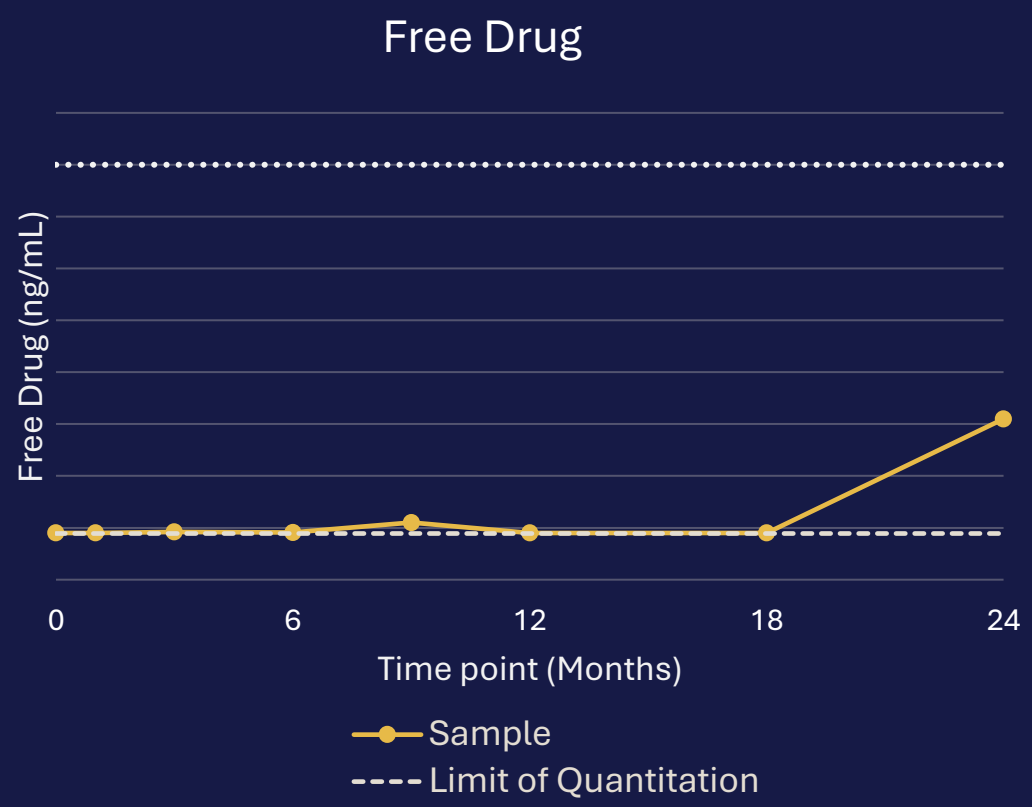
- Sample was re-analyzed from parent PETG vial: Atypical peak was not present



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Case Study: Container Compatibility for Reliable Data

Investigation Results

- Between 18M and 24M timepoints, a new lot of cryovial C was received for use in the labs

- Re-evaluation of cryovial C in formulation buffer showed a peak consistent with the atypical peak present in the initial sample analysis

- Peak was different than those observed in the initial cryovial evaluation

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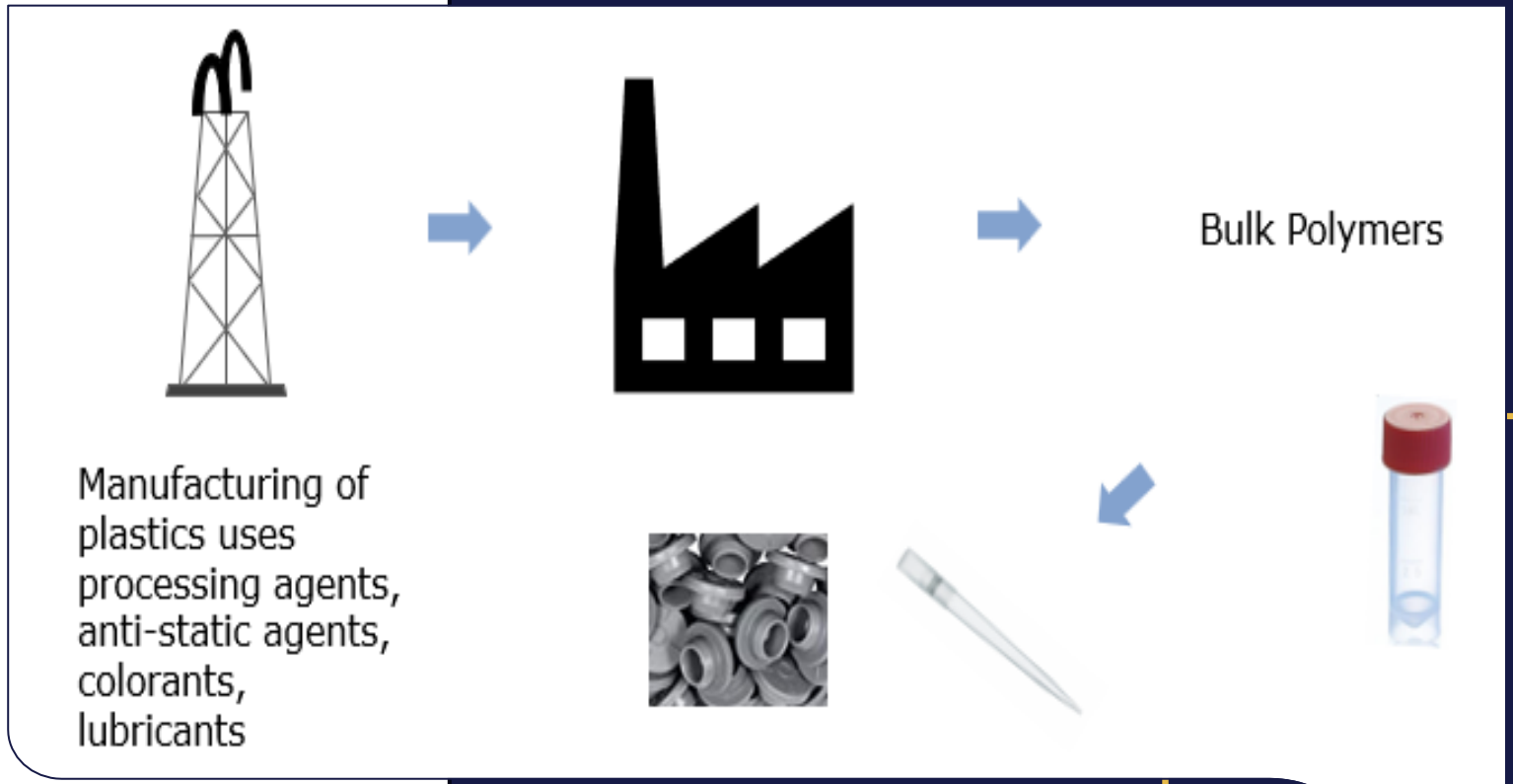

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Case Study: Container Compatibility for Reliable Data

Conclusion

- Glass or PETG are the safest choice for free drug but may not be practical for frozen samples
- When cryovials are required, it is important to make choices based on the specific method to be performed
- Even with careful planning, it is still possible to see unexpected results in long-term stability studies

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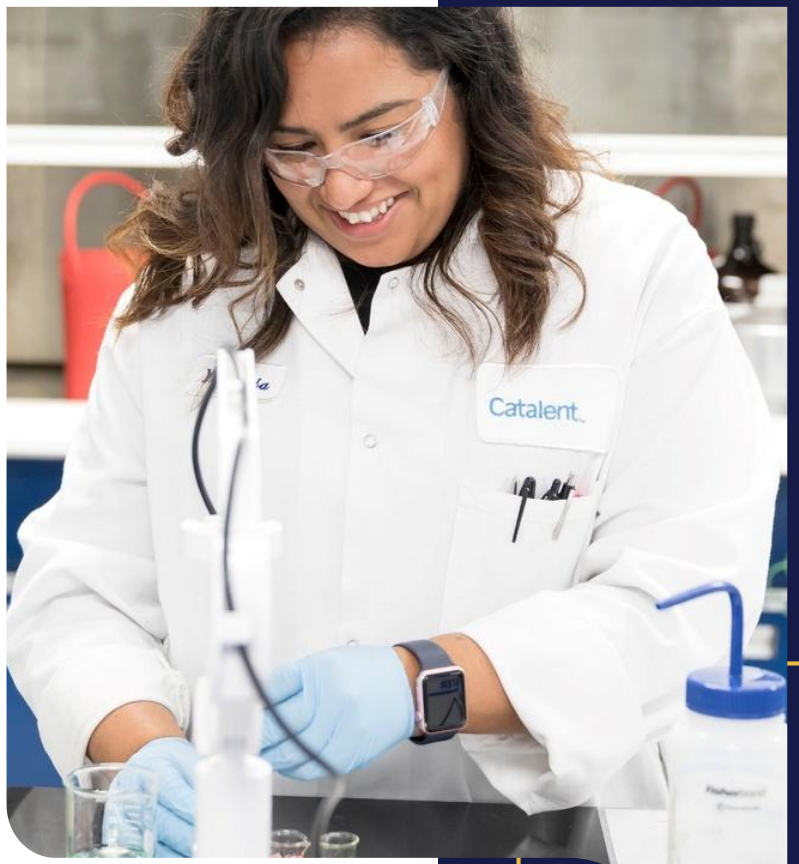

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Kansas City Biologics Analytics Services

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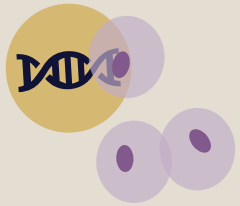
A Powerful Offering Stemming Across Modalities

mAbs &
Bispecific Abs

Pegylated Peptides

Bioconjugates &
ADCs

Recombinant,
Fusion Proteins



Gene & Cell Therapies

Nucleic Acids

Supports All Modalities

Discovery | Preclinical | Phase I | Phase II | Phase III | Commercial

- Developability & pre-formulation studies
- Comparability studies
- Extended molecule and product characterization
- Method development
- Phase-appropriate method qualification
- Phase-appropriate method validation
- Compendial method verification
- Stability studies
- Material and impurity characterization and identification
- GMP release testing

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Capabilities at a Glance

Method Establishment	• Method development, evaluation, and optimization • Method transfer, qualification, phase-appropriate validation, method validation remediation
Mass Spectrometry	• State-of-the-art mass spectrometry core with high-resolution LC/MS; GC/MS and ICP/MS; Protein metrics software for data processing • Size & charge variant characterization including fraction collection for impurity ID
Extended Characterization	• Secondary & higher order structural characterization using orthogonal approach • Size & charge variant characterization • Forced degradation study; comparability study
Bioassay/Cell-Based Potency	• Binding potency: ELISA, AlphaLISA™, surface plasmon resonance, Octet®, etc. • Relative potency: infectivity, cytotoxicity, mRNA transcription, neutralization, etc. • Cell banking/storage
Release & Stability Study & Storage	• Release testing; specialized expertise in temperature excursion, photostability • -150˚C to 60˚C, RH 25% to 90%, and customizable chamber conditions • In accordance with ICH/WHO/ASEAN guidelines

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Biophysical/Biochemical Characterization

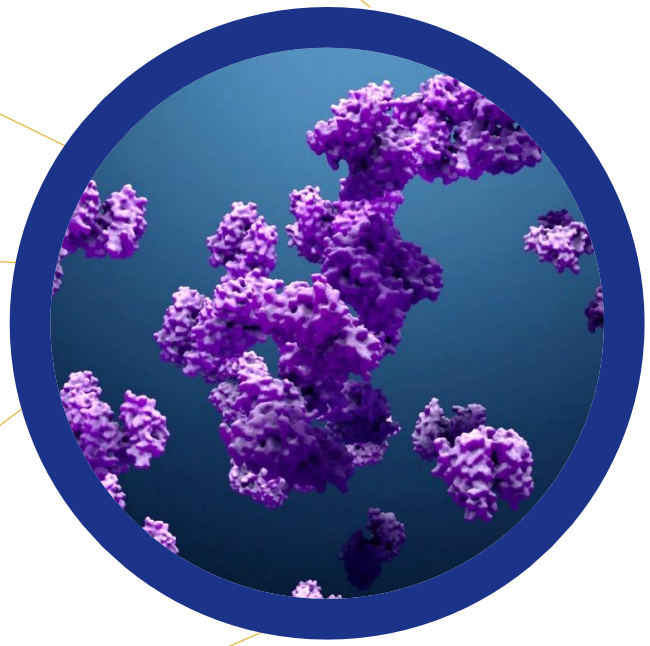
Orthogonal approach for a holistic understanding of your molecule

Mass Specs
Peptide mapping, intact mass, glycan mapping, PTM, size & charge variants, toxin conjugation sites; residual solvent, elemental impurities

Chromatography
Drug-antibody ratio, free drug, isoform & variant analysis, peptide & glycan mapping, polysorbate, sizing/aggregation, AAA & extinction coefficient

Electrophoresis
Purity/Fragmentation analysis, isoform analysis, glycan profiling, AAV protein purity and capsid ratio

Higher order structure
Secondary/Tertiary conformation, thermal stability/transitions, protein binding kinetics, aggregation and sizing



Compendial testing
CCI, sub-visible particles, extractable volume, content uniformity, UV concentration, appearance (EP, USP), color, clarity, reconstitution time, pH, moisture content, viscosity

Process Development Support
In-Process impurities, in-use studies, comparability studies, forced degradation and photostability, formulation development, aggregation, functional testing; lab scale aliquoting services

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Developability Overview

De-risking Asset Development

Physicochemical Properties (Predictive Stability)

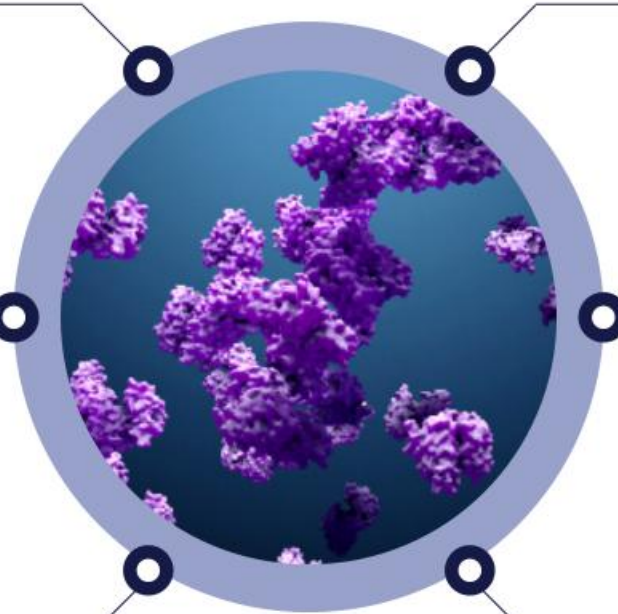
- Solubility
- Colloidal and Conformational Stability
- In Silico Modeling (Hotspot analysis and more)

Manufacturability

- Expression Titer and Cell Line Stability
- Purification Efficiency
- Compatibility with Platform Processes

Immunogenicity Risk

- In Silico Modeling
- Physicochemical Properties (above)
- Tox studies → AI/ML, Organ-on-a-Chip



Formulation Compatibility

- Suitability in Common Excipients
- Storage Stability
- Viscosity and Delivery Consideration

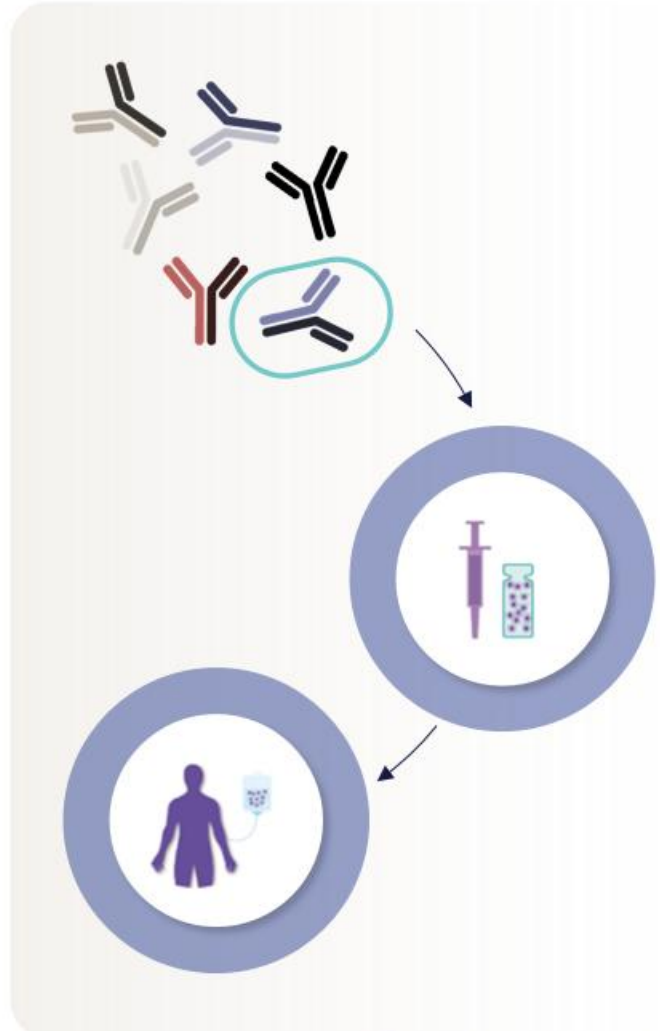
Analytical

- Forced Degradation
- Platform Analytical Method Compatibility
- Characterization Complexity

Binding Specificity

- Candidate Selection
- Formulation Studies

FDA **Apr 10, 2025:**
Roadmap to Reducing Animal Testing in Preclinical Safety Studies



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