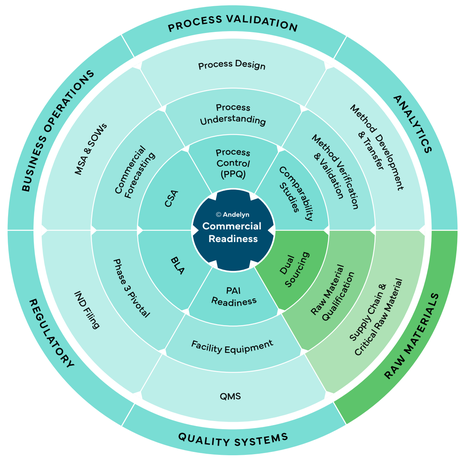
PPQ Ready Risk-Based Identity Testing for Ancillary Raw Materials in Gene Therapy Manufacturing

Carson Greco, William Fountain
Andelyn Biosciences

WHY RAW MATERIALS?



Raw Materials are one of the six pillars of Andelyn's Commercial Readiness framework. Within this pillar, establishing clear Specifications and Testing is critical — without them, PPQ cannot be achieved.

As materials move from early-phase use to commercial readiness, added testing is required to meet regulatory expectations. A risk-based approach helps ensure compliance while maintaining feasibility, scalability, and control.

WHAT IS REQUIRED?

- **Identity testing** required by FDA (21 CFR 211.84), ICH Q7, EMA, EP 2034
- **Risk-based reduction** allowed per ICH Q6A and USP <1043>
- **Orthogonal/performance testing** acceptable in limited cases (USP <1047>)
- **Biological/animal-derived materials** need added characterization (EP 5.2.12, USP <1043>)
- **Each lot** must be distinguishable from similar materials
- **Reduced testing** may be used after 3 full lots tested (ICH Q6A)

PPQ AND COMMERCIAL REQUIREMENTS

Ancillary raw materials play a critical role in gene therapy manufacturing by enabling key processes without becoming part of the final product. Ensuring the identity of these materials is essential to maintain product quality, safety, and compliance.

A robust identity strategy at the PPQ stage is essential to enable commercial success.

Table 1: PPQ vs Commercial Requirements – Adapted from ICH Q6A, Q9, and internal Andelyn Strategy

Aspect	PPQ Stage	Commercial Stage
Identity Testing	Must distinguish each raw material; **orthogonal** or **performance testing** acceptable if justified	**Fully validated** identity testing required for **all** materials
Test Method Validation	Methods may be in **development**; formal validation not always complete	All methods must be **validated and approved**
Reduced Testing & Regulatory Expectations	**Reduced testing** not typically acceptable unless justified; focus is on demonstrating process consistency	**Reduced testing allowed with historical data** (e.g., ≥3 lots, per **ICH Q6A**); must demonstrate long-term control

For PPQ readiness, it is acceptable to use testing that reasonably distinguishes each raw material from similarly appearing materials — provided there is a plan to implement more-specific identification methods.

Andelyn has determined through our own risk management procedures that most Ancillary Raw Materials are medium risk. None are classified as low risk, as all have the potential to affect the in-process product. High risk Ancillary Raw Materials are typically animal-derived.

RISK-BASED APPROACH

Raw Materials and Consumables are assessed per-client, per-product, and per-manufacturing phase. This ensures the risk mitigations align with product-specific requirements.

Risk is categorized using a framework based on ICH Q9, including hazard identification, risk analysis, and evaluation. High- and medium-risk materials trigger additional controls.

1. Materials are categorized into a risk group. Key attributes considered include:
   - Intended use in manufacturing and critical material attributes
   - Risk tier per USP <1043>
   - Supply chain complexity
   - Vendor qualification
   - Phase of manufacture and intended markets of finished product
2. Risk mitigations are selected based on material risk group and assessment.

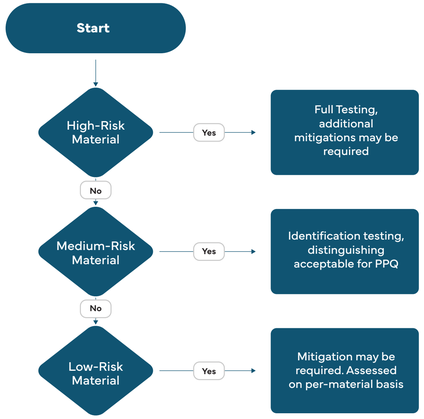
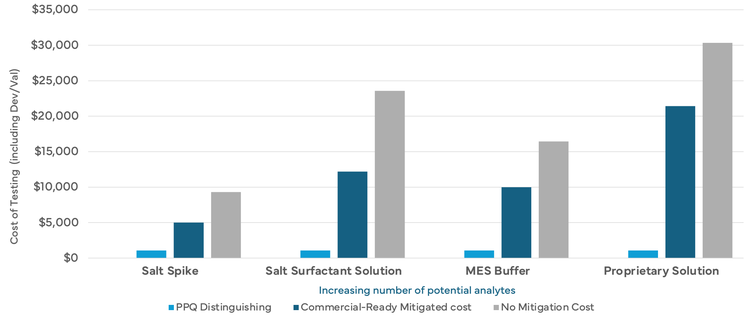


FIGURE 1: RISK-BASED TESTING DECISION TREE

RESULTS



Purchased custom-prepared solutions presented a challenge, as components may be identical across different concentrations. To resolve this, critical analytes were selected and identified through analytical testing (e.g., FTIR, NMR). While identity methods were under development, characterization tests (e.g., pH, conductivity) were utilized to distinguish between similar solutions. Orthogonal testing enabled differentiation while method development and validation were ongoing.

As the number of analytes increases, so does the cost of method development. A risk-based strategy mitigated these costs while ensuring materials could still be reliably distinguished and appropriately controlled.

ADDITIONAL OUTCOMES:

- **Amino acid analysis** for **complex formulations.**
- **Electrophoretic profiling** for **high-risk** (animal-derived) materials
- **CoA verification** testing for certain medium-risk materials while more specific identification tests were developed.

The outlined approach can lead to substantial cost savings, particularly for prepared solutions where full analyte identification would be cost-prohibitive and unnecessary based on risk. Risk-based testing provides a cost-conscious strategy to demonstrate material identity — benefiting both CDMO and client.

REFERENCES

- USP <1043> – Ancillary Materials for Cell, Gene, and Tissue-Engineered Products
- USP <1047> – Gene Therapy Products
- ICH Q9(R1) – Quality Risk Management
- ICH Q6A – Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances
- 21 CFR 211.84 – Testing and Approval or Rejection of Components, Drug Product Containers, and Closures

CONTACT

For inquires, contact:
andelynbusiness@andelynbiosciences.com