Establishing a U.S. distribution and quality framework for 3D in vitro airway models

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ABSTRACT

Increasing regulatory and commercial emphasis on New Approach Methodologies (NAMs) for evaluating respiratory irritation and sensitization has created a growing need for advanced, human-relevant in vitro models. Epithelix 3D airway models offer physiologically relevant platforms for respiratory research and regulatory applications; however, their broader adoption in the United States has been constrained by international shipping, customs clearance, and the need to maintain tissue viability and functionality during transit.

To address these challenges, the Institute for In Vitro Sciences (IIVS) and Epithelix established a collaborative framework for the reliable U.S. distribution of these models. The framework combines post-production quality control (QC) testing with a tiered QC approach at IIVS to verify tissue integrity and functional performance upon receipt. It also incorporates comprehensive documentation to maintain traceability throughout the supply chain, from production through end use.

INTRODUCTION/TEST SYSTEM

Epithelix reconstructed human airway (RHuA) models are fully differentiated, air-liquid-interface cultures that reproduce key structural and functional features of native airway epithelium. Their long-term stability and compatibility with multiple exposure methods make them useful for respiratory toxicity, efficacy, and disease research.

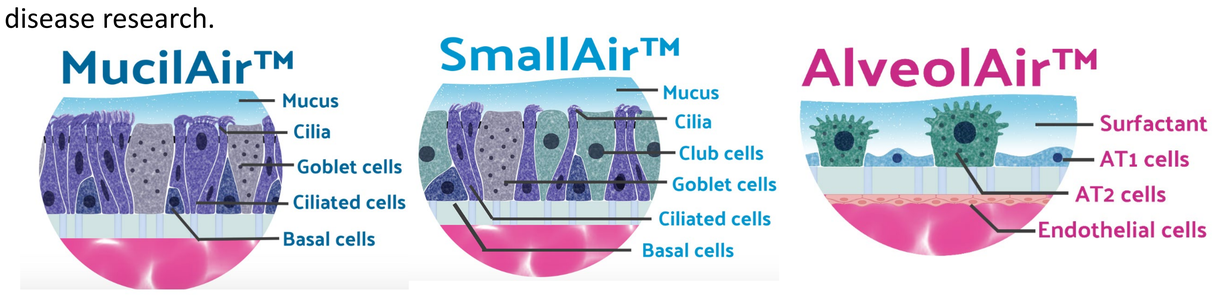


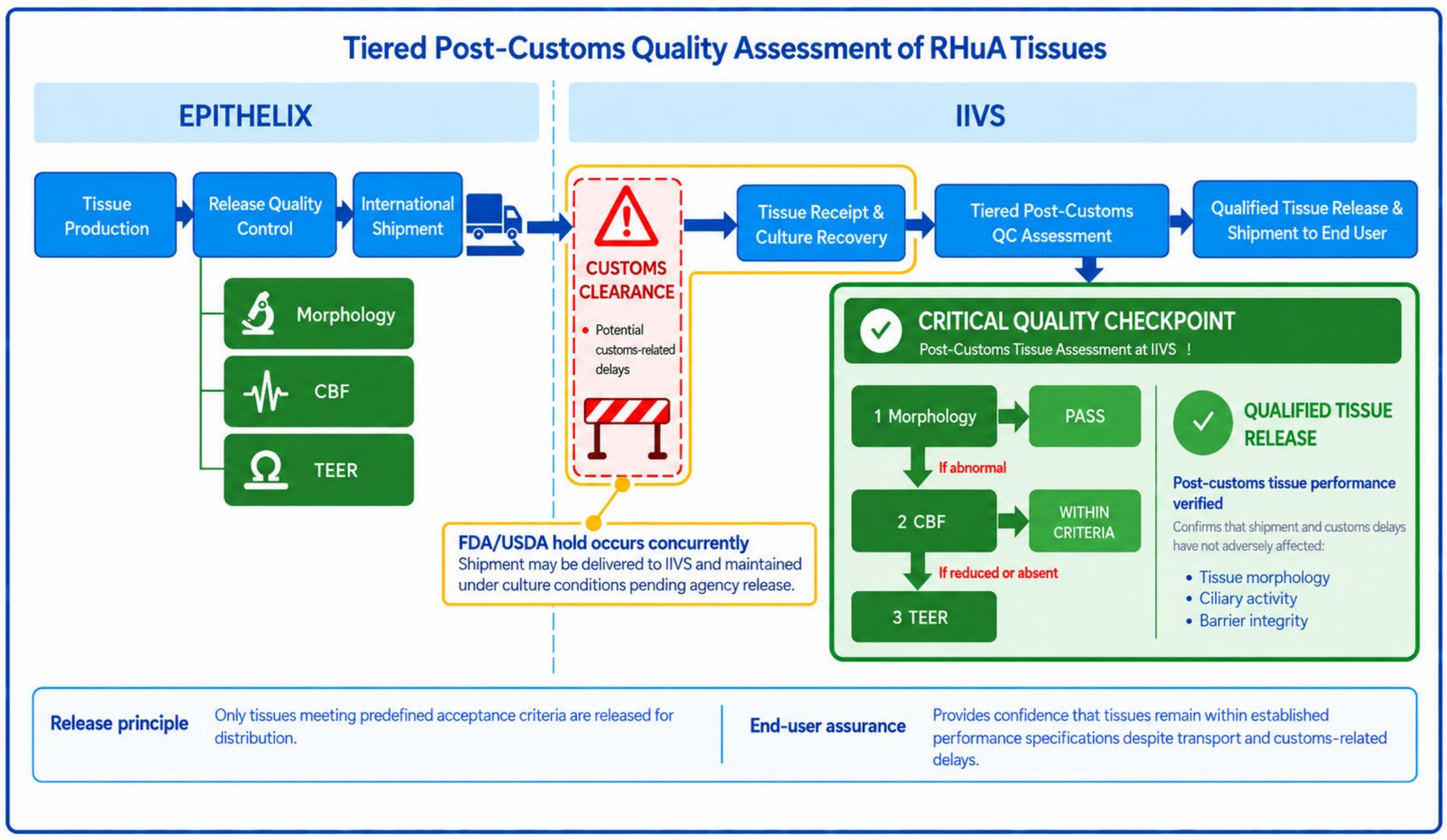
Figure 1. *Schematic representation of the MucilAir™, SmallAir™, and AlveolAir™ cross-sections.*

CHALLENGES

International shipping	Transport large tissue batches safely.
Customs clearance	Avoid delays and border clearance issues.
Transit unpredictability	Account for shipment disruptions and potential tissue loss.
Temperature control	Maintain stable conditions with temperature monitoring.

COLLABORATIVE FRAMEWORK

To be suitable for regulatory and research applications, these complex models must demonstrate consistent performance across multiple biological endpoints, including tissue viability, ciliary beating activity, and tight junction integrity. Maintaining this functionality requires controlled culture conditions and use within a defined window of optimal performance, making reliable handling and transport critical.



STANDARDIZATION AND DOCUMENTATION

In vitro test systems must reliably perform as expected when used in studies. GIVIMP recommends implementing quality controls (Chapter 2), standardizing procedures (Chapter 7), and retaining documentation on activities performed and standards followed (Chapter 10). IIVS meets the recommendations in GIVIMP for handling the 3D reconstructed human airway tissues.

GIVIMP-ALIGNED FRAMEWORK

- **Standardization**
  Epithelix procedures followed for receipt, culture transfer and reshipment.
- **Traceability**
  Personnel, media, equipment and procedural steps documented.
- **Data integrity**
  ALCOA+ principles applied to paper and electronic records.

INFORMATION PROVIDED TO END-USERS

GIVIMP chapter 1 discusses the responsibility *in vitro* test system providers have to share information on test system characterization, authenticity, and safe transport, use, and disposal. IIVS provides a package of this information to test system end users to satisfy the GIVIMP requirements of test system providers.

PILOT SHIPMENTS

To ensure the collaborative framework meets expectations, it was evaluated through a pilot shipment to a U.S.-based laboratory, where tissues underwent additional QC assessments to confirm model performance, including WST-8 viability assay, CBF activity, and TEER measurements.

Endpoint	Epithelix	IIVS	RTI International
Viability	■	■	■
TEER (>200 Ω·cm²)	■	■	■
CBF (>5 Hz)	■	■	■
Morphology	■	■	■

The authors gratefully acknowledge RTI International for participating as the U.S.-based laboratory in the pilot shipment and for evaluating tissue performance following distribution.

KEY OUTCOMES

- ✅ Established U.S. distribution framework
- ✅ GIVIMP-aligned documentation and traceability
- ✅ Tiered QC verification following shipment
- ✅ Successful pilot shipment demonstrating tissue functionality

SUMMARY

- Increasing regulatory and commercial emphasis on NAMs has created a growing need for advanced, human-relevant in vitro models.
- Epithelix 3D airway models offer physiologically relevant platforms for respiratory toxicity research and regulatory applications.
- Broader adoption in the United States has been constrained by international shipping, customs clearance, and the need to maintain tissue viability during transit.
- IIVS and Epithelix established a collaborative framework for the reliable distribution of these 3D airway models within the U.S.
- Key elements include post-production QC testing prior to shipment and a tiered QC approach at IIVS after international shipment to verify tissue integrity and performance.
- The effort included a pilot shipment to ensure the framework improves reliability and reduces risk to tissue quality, and culminated in reliable tissue availability in North America that meets Epithelix requirements for tissue QC.