

Audit-Ready Gas Testing: Navigating USP, EP, and FDA Requirements

Ensuring compliance with key pharmaceutical gas testing standards

About the Presenter



- ▶ Charles 'Chad' Felter.
- ▶ Managing Partner at Gas Testing Analytical.
- ▶ 15+ years of experience in pharmaceutical utilities: gases, water, and environmental systems.
- ▶ Specialized in sampling, validation, and troubleshooting.
- ▶ Helping companies build audit-ready, compliant, and practical programs.

Session Agenda

- ▶ Overview of Pharmaceutical and Biopharmaceutical Gases and Their Applications
- ▶ Regulatory and Standards Frameworks for Process Gas Compliance
- ▶ Process Gas Testing Fundamentals and Best Practices
- ▶ Sampling: Best Sampling Practices
- ▶ Case Study: Investigating a Hydrocarbon Excursion in Process Gas
- ▶ Designing a Robust Gas Testing Program
- ▶ Troubleshooting Gas Testing Issues and Avoiding Common Pitfalls
- ▶ Cost Considerations when Implementing an Effective Gas Testing Program





Overview of Pharmaceutical and Biopharmaceutical Gases and Their Applications

TYPES OF GASES USED IN PHARMACEUTICAL AND BIOPHARMACEUTICAL PROCESSES

Common Pharmaceutical Gases

- Nitrogen
- Oxygen
- Carbon dioxide
- Air
- Argon, Helium, and specialty gases

Roles of Gases in Processing

- Gases serve critical functions during manufacturing and formulation:
- Inerting, Blanketing, and Sparging
- Operating pneumatic equipment
- Drying
- Environmental controls for cell culture, chemical synthesis, and breathing air
- Analytical techniques

PRIMARY USES OF GASES



Process Gases Usage

Process gases are essential in chemical reactions and formulation processes across various industries.

Pure Gases Applications

Pure gases support precise operations such as chromatography and other analytical techniques requiring high purity.

Utility Gases Functions

Utility gases assist in equipment operation and cleaning tasks, playing supportive but vital roles.

CRITICAL ROLES OF GASES IN PRODUCT QUALITY AND MANUFACTURING

Impact on Sterility

Gases play a crucial role in maintaining sterility during pharmaceutical manufacturing to prevent contamination during direct contact.

Ensuring Stability

Proper gas quality helps preserve product stability by avoiding reactions that degrade product integrity.

Safety and Validation

Validating gases from the source through distribution ensures safety and high product quality by preventing contamination risks.



Regulatory and Standards Frameworks for Process Gas Compliance



Overview of USP, EP, and JP Requirements

Pharmacopeia Standards

USP, EP, and JP set strict standards to ensure the quality and safety of process gases used in pharmaceuticals.

Testing Criteria Importance

These pharmacopeias define rigorous testing criteria to verify the purity and suitability of gases in manufacturing.

Global Regulatory Impact

USP, EP, and JP influence global pharmaceutical manufacturing practices by harmonizing quality requirements.

USP/EP/JP identification comparison

Gas	Compendia \ Test	USP		EP		JP	
		Technology	Spec	Technology	Spec	Technology	Spec
Oxygen	ID	Paramagnetic	Assay	Paramagnetic	Assay	Glowing splinter & GC	Reignites, peak time
Nitrogen	ID	Burning splinter	Extinguished	GC / burning or glowing splinter / Wet Chem	Peak time / extinguished / litmus	Burning splinter	extinguished
Carbon Dioxide	ID	Detector tube	CO2 tube fully reacts	IR, burning splinter, Wet Chem	Reference spectrum, extinguished, precipitate produced, then effervesces	Flaming splinter & Wet Chem	Extinguished / precipitate produced, then dissolved
Air	ID	Paramagnetic	Assay	Paramagnetic, splinter, wet chem	Assay, remains glowing, absorption	N/A	N/A

USP/EP/JP assay comparison

Gas	Compendia Test	USP		EP		JP	
		Technology	Spec	Technology	Spec	Technology	Spec
Oxygen	Assay	Paramagnetic	≥99.0%	Paramagnetic	≥99.5%	Wet Chem	≥99.5%
Nitrogen	Assay	GC	≥99.0%	GC	≥99.5%	GC	≥99.5%
Carbon Dioxide	Assay	Wet Chem	≥99.0%	IR	≥99.5%	Wet Chem	≥99.5%
Air	Assay	Paramagnetic	19.5%-23.5%	Paramagnetic	20.4%-21.4%	N/A	N/A

USP/EP/JP impurities comparison

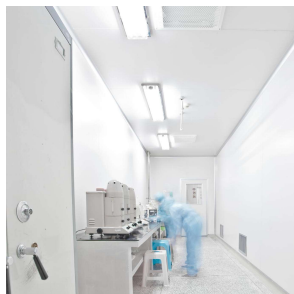
Gas	Compendia \ Test	USP		EP		JP	
		Technology	Spec	Technology	Spec	Technology	Spec
Oxygen	Impurities	Detector Tubes / Organoleptic	CO, CO2, Odor	Instrumentation	CO, CO2, H2O	Wet Chem & GC	pH, Oxidation, Chlorine, CO2, N2
Nitrogen	Impurities	Detector Tube, Assay, Organoleptic	CO, O2, odorless	Instrumentation / detector tubes	CO, CO2, O2, H2O	Wet Chem	CO2
Carbon Dioxide	Impurities	Detector tubes	CO, H2S, NO, NO2, SO2, H2O, NH3	Instrumentation / detector tubes	CO, H2S, NO, NO2, SO2, H2O	Wet Chem & GC	pH, reducing, CO, O2/N2
Air	Impurities	Detector Tubes, Mirror	CO2, CO, SO2, NO, NO2, H2O, Oil	Instrumentation / detector tubes	CO2, CO, SO2, NO, NO2, H2O, Oil	N/A	N/A

Key Elements of ISO 8573-1 and ISO 14644 for Gas Testing



ISO 8573-1 Purity Classes

Defines standards for purity levels in compressed air and gases ensuring quality and safety in industrial applications.



ISO 14644 Cleanroom Standards

Sets criteria for cleanroom environments affecting gas handling and contamination control in sensitive manufacturing.



Compliance and Product Integrity

Adhering to both standards ensures regulatory compliance and maintains the integrity of products using gases.

FDA Expectations

- ▶ **Critical Utility Classification**
FDA views process gases (N₂, O₂, CO₂, compressed air) as critical utilities – equivalent to water systems.
- ▶ **Validation & Qualification**
Gases must be qualified and validated to demonstrate consistency, purity, and suitability for use.
- ▶ **Pharmacopeial Compliance**
Testing must align with USP, EP, JP monographs where applicable. Off-spec results require documented investigation and remediation.
- ▶ **Quality System Integration**
Gas systems should be covered under change control, deviation management, and CAPA systems. Procedures must be documented in SOPs and training records.
- ▶ **Data Integrity & Documentation**
Sampling, testing, and trending data must be complete, accurate, attributable, and auditable (21 CFR Part 11 expectations apply).
- ▶ **Inspection Focus Areas**
Adequacy of sampling locations and purge protocols. Trending of gas testing results across facilities/points of use. Corrective actions for excursions and preventive controls.





Global Harmonization and Audit-Readiness Considerations

Global Standards Harmonization

Aligning standards internationally simplifies audits and enhances regulatory compliance efficiency.

Audit-Ready Documentation

Maintaining thorough and validated documentation ensures preparedness for audits at any time.

Consistent Testing Processes

Implementing standardized and validated testing procedures guarantees reliable and compliant results.

Gas Testing Fundamentals and Best Practices



Testing Parameters

Identification - Tests to identify the gas of interest

<https://www.youtube.com/watch?v=0VonvhSzhR4>

Purity - Tests to quantify the purity of the gas of interest

Impurities - Tests to ensure known, harmful, or otherwise at-risk impurities are below specified limits.

Oxygen
Moisture
Carbon Monoxide
Carbon Dioxide
Nitrogen Oxides
Hydrocarbons
Oil-mist

Sulfur dioxide
Hydrogen sulfide
Ammonia
Halogens
Particulates
Microbes



Testing Techniques (USP/EP/ISO)

Identification - Various physical, chemical or instrumentation

Purity -Chromatography and Paramagnetic analysis

Impurities - physical/chemical testing, instrumentation

Non-viable particulate testing

Viable testing



Sampling Plans and Best Sampling Practices

Designing an Effective Sampling Plan



Critical Sampling Points

Selecting key locations is essential to capture representative gas quality data accurately.



Sampling Frequency

Determining optimal intervals for sampling ensures consistent and reliable data collection.



Sampling Volume and Timing

Appropriate volume and timing of samples impact the accuracy and representativeness of gas quality measurements.

Gas Sampling Approach

Avoiding Contamination

Specialized techniques are essential to prevent contamination during liquid nitrogen sampling processes.

Purge Protocols Importance

Established purge protocols ensure removal of residual gases, improving reliability and accuracy in gas analysis.

Ensuring Representative Samples

Sampling methods must guarantee that collected liquid nitrogen samples accurately represent the bulk material.

Maintaining Safety

Proper safety protocols and equipment are crucial for handling liquid nitrogen during sampling to protect personnel.



System Hardware: Sampling Ports, Connections and Fixtures

Sampling Port Placement

Strategically placed sampling ports enable accurate gas collection minimizing contamination during testing procedures.

Connections and fittings

Various fittings and connections are possible within a facility and between the variety of testing techniques available.



Case Study: Investigating a Hydrocarbon Excursion in Process Gas

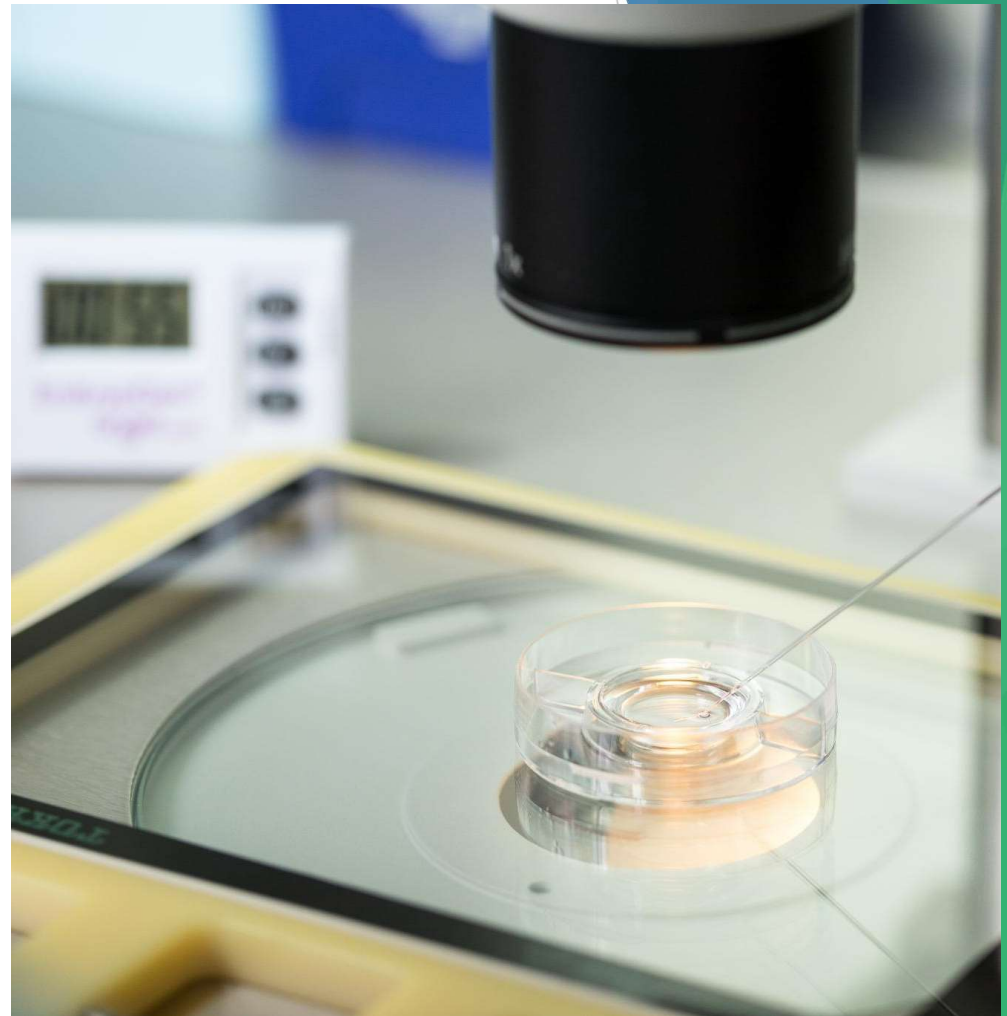
Incident Background and Discovery

Hydrocarbon Excursion Detection

Routine testing identified an unexpected hydrocarbon excursion requiring urgent attention.

Immediate Investigation Initiated

The detection triggered a prompt investigation to safeguard product quality and ensure compliance.



Fishbone Diagram: Root Cause Analysis Visual

Fishbone (Ishikawa) Diagram - Root Causes of Hydrocarbon Excursions in Compressed Air

Equipment Failure Causes

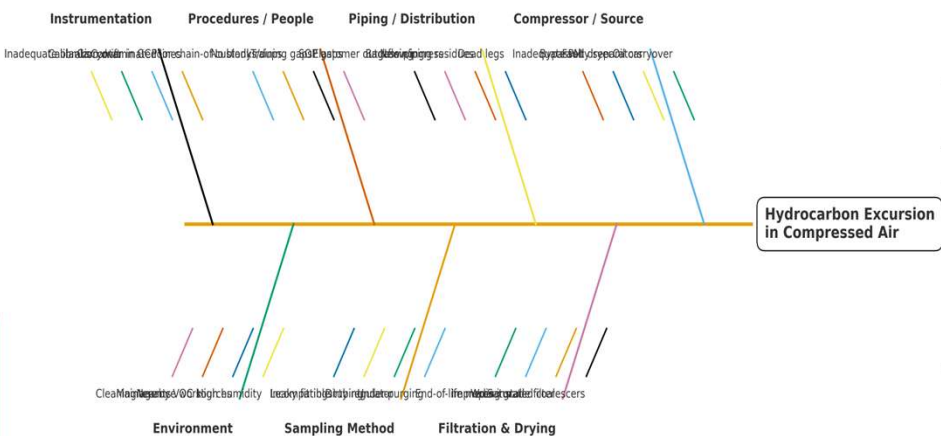
Identifying equipment failure helps uncover mechanical issues affecting process outcomes.

Contamination Sources

Mapping contamination sources reveals origins of quality and safety problems.

Procedural Lapses

Procedural lapses highlight human or process errors contributing to root problems.



Corrective Actions and Remediation Steps



Equipment Adjustment

Intake for the compressor was relocated

Filter changes

Any residual contamination removed, new filters ensure purge is effective

System purge

Once the new intake was established and intake air was verified as appropriate, the system was purged to remove residual contamination.

Updated Protocols

Establishing updated protocols resolved the discrepancy and ensured future detection of an issue in the event of recurrence.

Lessons Learned and Best Practice Takeaways

Design

Consistent monitoring helps detect issues early, ensuring process gas integrity and system safety.

Proactive Monitoring

Detecting issues early can ensure process gas integrity and system safety.

Clear Communication

Effective communication among teams enables quick responses and reduces errors in process management.

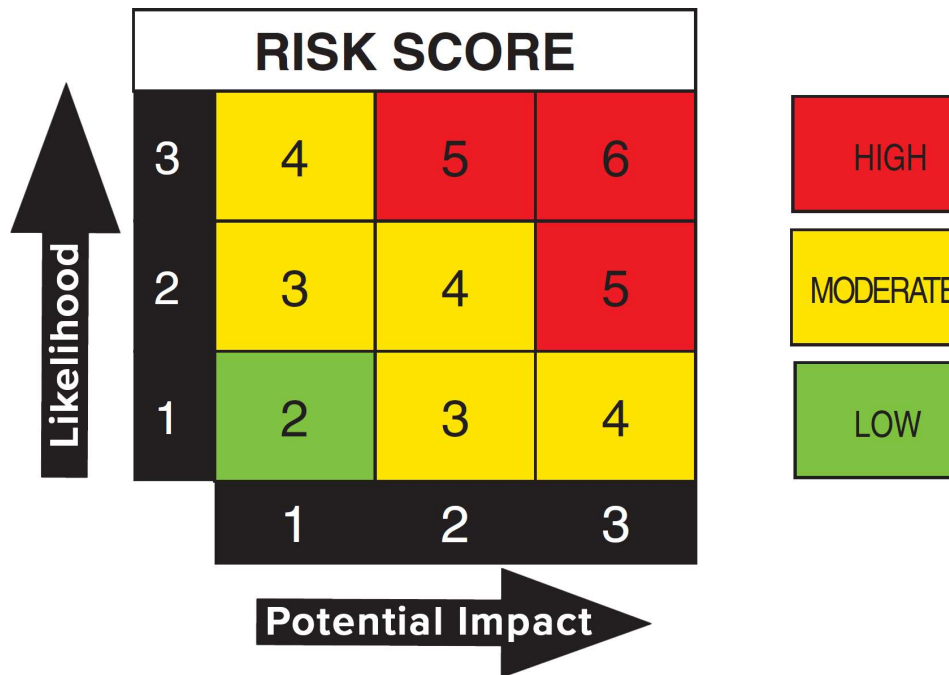
Robust and Thorough Procedures

Well-defined procedures ensure consistent operations and help maintain safety and quality standards.



Designing a Robust Gas Testing Program

Risk Ranking and Prioritization of Process Gases



Risk-Based Prioritization

Ranking process gases by risk enables targeted testing and efficient resource allocation.

Effective Resource Allocation

Focusing efforts on high-risk gases ensures better management of safety and compliance.

Comprehensive Sampling Plan Strategies

Detailed Sampling Locations

Specifying exact sampling locations ensures targeted and representative data collection for analysis.

Sampling Frequency

Defining sampling frequency helps maintain consistent data intervals and improves trend detection.

Standardized Procedures

Establishing clear procedures enhances reliability and repeatability of sampling results across trials.



Validation and Ongoing Verification Protocols

Importance of Regular Qualification

Regular routine monitoring and periodic system qualification ensure consistent performance.

Ongoing Equipment Verification

Continuous verification of equipment ensures tools remain fit for purpose and maintain measurement precision over time.



Equipment Calibration, Maintenance, and Audit-Readiness



Importance of Calibration

Regular calibration ensures sampling and analytical equipment provides accurate and reliable data for decision-making.

Routine Maintenance

Scheduled maintenance prevents equipment failures and prolongs the lifespan of analytical instruments.

Audit Preparation

Proper calibration and maintenance practices ensure readiness for audits and compliance with quality standards.

Documentation Essentials and Compliance Traceability

Clear Documentation

Accurate and detailed records ensure all testing activities are traceable and verifiable.

Accountability Support

Proper documentation maintains accountability across all testing phases and personnel.

Compliance Assurance

Detailed records facilitate compliance during inspections and audits by regulatory bodies.



Troubleshooting Gas Testing Issues and Avoiding Common Pitfalls

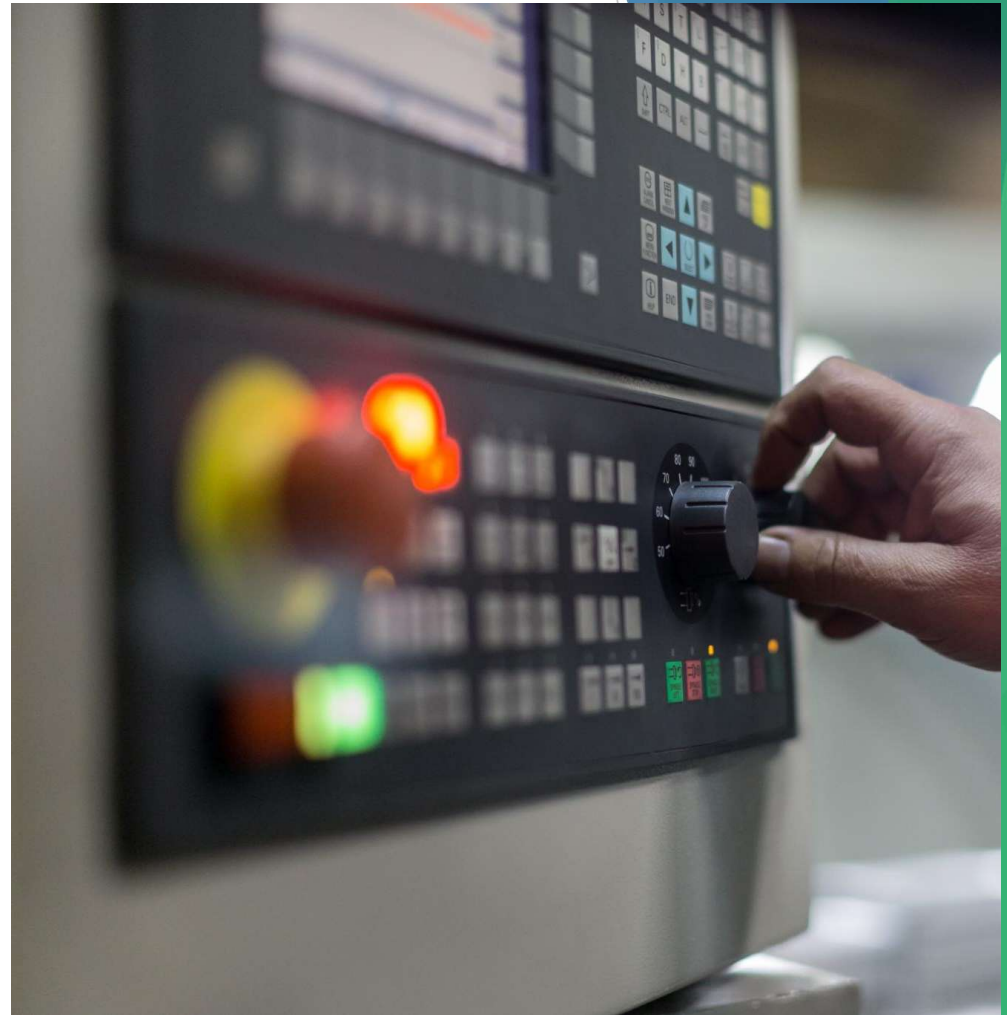
Recognizing Troubleshooting Patterns and Failure Modes

Recurring Issue Identification

Detecting frequent problems like contamination and equipment failures is essential for effective troubleshooting.

Root Cause Analysis

Understanding failure modes helps in addressing the underlying causes of technical issues efficiently.



Audit-Ready Checklist for Gas Testing Program

Comprehensive Coverage

The checklist ensures all critical aspects of gas testing programs are thoroughly reviewed and addressed.

Regulatory Documentation

Proper documentation is prepared to meet regulatory audit requirements and demonstrate compliance.

Audit-Ready Checklist for Gas Testing Programs

- ✓ Risk Assessment & Mapping – documented use points and risk ranking
- ✓ Sampling SOPs – written, trained, and controlled procedures
- ✓ Validated Methods & Equipment – USP/EP aligned, qualified hardware
- ✓ QC Checks & Controls – blanks, duplicates, calibrations included
- ✓ Data Integrity (ALCOA+) – attributable, accurate, original, accessible
- ✓ Change Control & CAPA – deviations managed, corrective actions tracked
- ✓ Trending & Review – data reviewed, trended, and escalated
- ✓ Remediation Playbook – predefined investigation and response steps

Ensuring Data Integrity in Gas Testing



Accurate Data Collection

Ensuring gas testing data is collected precisely to support reliable analysis and reporting.

Validated Systems

Using systems that are validated to guarantee data consistency and compliance with standards.

Proper Documentation

Maintaining detailed, secure documentation to meet regulatory and audit requirements.

Cost Considerations: Implementing an Effective Gas Testing Program and

Cost Considerations and Budgeting for Compliance

Financial Implications

Recognizing the costs involved in gas testing is essential to ensure effective compliance management.

Balancing Compliance and Budget

Balancing regulatory compliance requirements with budget limitations ensures sustainable safety practices.



Testing Models Comparison

In-House Testing	Sample & Ship to Third Party	Third-Party Collection & Testing
High costs for capital and labor, minimal per-test costs	Moderate cost; some equipment + lab fees, less labor and capital intensive	No capital and labor costs, higher per-test costs, all-inclusive
Maximum control & scheduling flexibility	Moderate control; dependent on sampling SOPs	Less flexible without white-glove vendors; dependent on vendor scheduling
Highest burden: equipment, validation, training, compliance documentation	Shared compliance: internal sampling + lab accreditation	Strongest compliance assurance; ISO/FDA-aligned docs

Conclusion

Importance of Gas Testing

Process gas testing ensures pharmaceutical product quality and regulatory compliance throughout production.

Standards and Programs

Implementing established standards and robust testing programs strengthens quality assurance processes.

Audit Readiness

Proactively addressing challenges helps maintain audit readiness and safeguard product integrity.