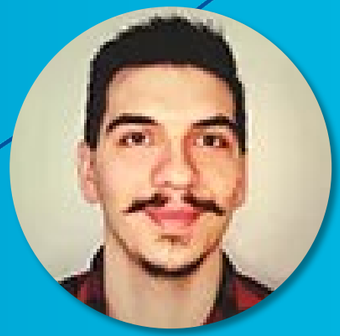
ISPE Pharma Best Practices Webinar Series

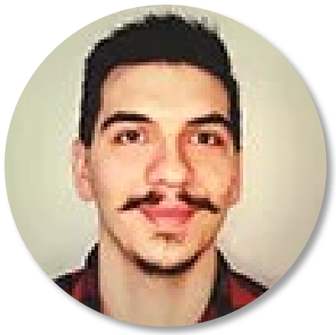
Acing an Audit: What to Do Before, During, and after an Inspection

SPEAKER



Joe Azzarella
Customer Success Engineer
Kneat Solutions

Speaker



Joe Azzarella
Customer Success Engineer
Kneat Solutions

Joe Azzarella is a Six Sigma Black Belt with 10+ years experience in lyophilization development, technology transfer, and process development for pharma and life sciences companies. An author of multiple papers and whitepapers, Joe has also guest lectured at Purdue University, appeared on webinars and podcasts, and currently works with Kneat Solutions to bring digital validation to life sciences leaders.

Overview

- What are audits and inspections?
- Typical inspection procedure
- Life after an inspection
- Acing the inspection experience
- Presenting the future (Industry 4.0 and beyond)
- Q&A – Discussion!

POLL #1

What is your audit experience?

- ❑ Never experienced an audit
- ❑ My company has been audited, but I was not directly involved
- ❑ My company has been audited, and I was part of the audit/inspection response team
- ❑ My company has been audited, and I am a key component (scribe, escort, etc.) of the audit response team
- ❑ My career is audit focused (I am an inspector/auditor, consultant, etc.)

What are Audits? What are Inspections?

Audits are:

- Generally, not legally consequential
- Review all aspects of an organization or service and can be more in depth about subject matter
- Conducted by internal auditors or third-party independent auditors
- Formally documented and information is shared

Inspections are:

- Legally consequential (jail time, arrests, etc.)
- Focused on a product or services being provided
- Conducted by government regulators
- Review limited to meeting requirements
- Documented and summarized in an inspection report (FDA Form 483)

Types of Audits and Inspections

Audits

- ISO/GxP
- Internal
- External (Contract Manufacturing, Client)

Inspections

- General/Surveillance
  - Monitor the manufacturing process and the quality products on the market. Intent is to assess compliance with manufacturing practices.
- For Cause
  - Initiated when the FDA has reason to believe that a facility has quality problems.
- Application Based
  - Context: These inspections are part of the application review process for new drugs, devices, or biologics.
  - Purpose: The FDA ensures the new product is manufactured in compliance with regulations and that submitted data are accurate and complete.

Inspection Lifecycle

Arrival and Credentials:

- The FDA inspector arrives at your facility and presents their credentials
- Inspector submits a “Notice of Inspection” (FDA Form 482)

Accompanying the Inspector:

- When the FDA inspector arrives, always have them accompanied by an informed representative of the organization
- This **escort** serves as a guide during the inspection, answering questions and providing access to relevant area
- Accompanying the inspector demonstrates cooperation and transparency

Inspection Procedures:

- The inspector will systematically review various aspects of your facility:
  - **Records**: They’ll examine production records, quality control data, SOPs, and other relevant documentation
  - **Processes**: They’ll observe manufacturing processes, sanitation practices, and adherence to regulations
  - **Samples**: The inspector may collect samples of raw materials, finished products, or environmental swabs
- Their goal is to **assess compliance** with regulations and identify any nonconformities

Inspection Lifecycle

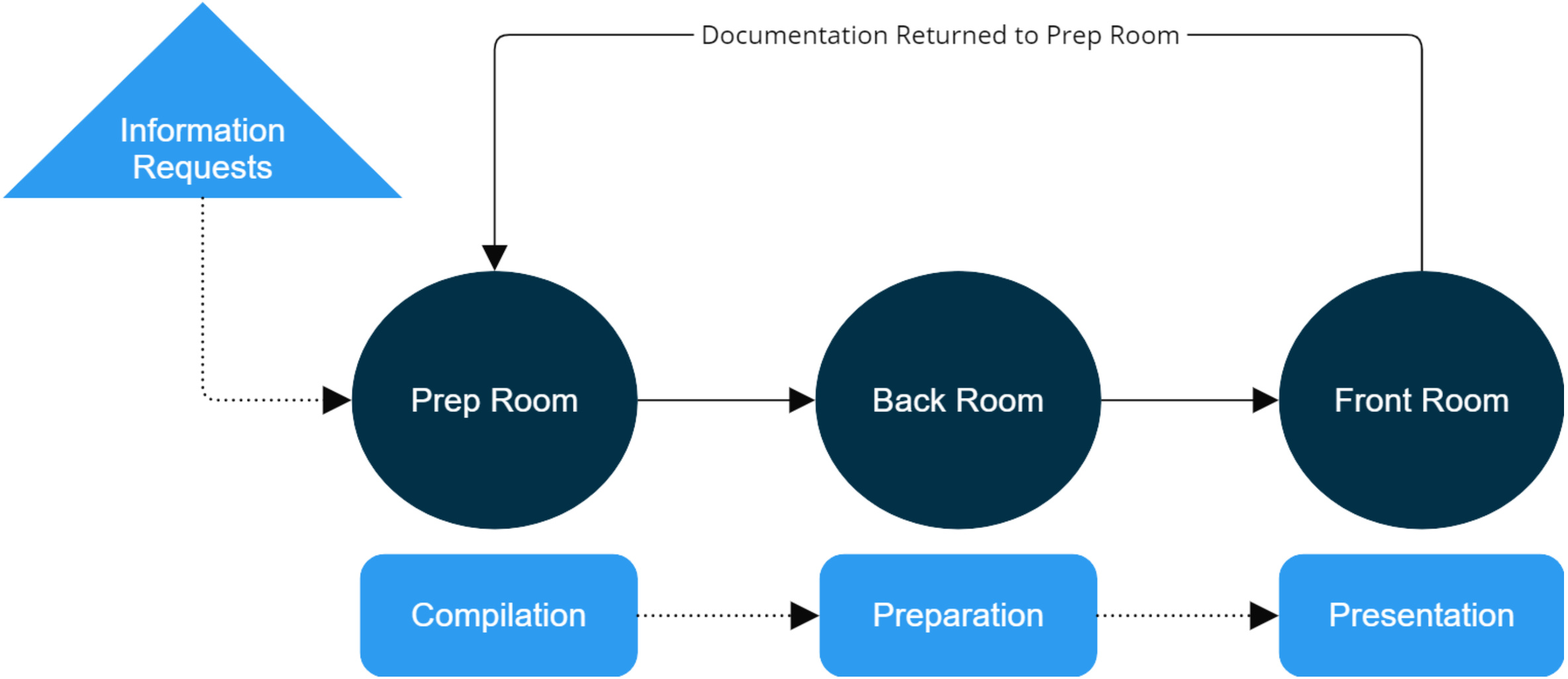
Closeout Meetings and Feedback:

- At the end of each day, there is a closeout meeting to determine what will be reviewed the following day
- At the end of the inspection, there is generally a final closeout meeting. At that time, any observed nonconformities are discussed with your firm's management.
  - You'll have an opportunity to ask questions, seek clarification, and provide context.
- During closeout, the inspector may provide one of three statuses. This may also be provided later by the FDA.
  - No Action Indicated (NAI): All is well and the organization is compliant with FDA requirements.
  - Voluntary Action Indicated (VAI): FDA has found objectionable conditions or practices, but these findings aren't serious enough to merit administrative or regulatory action.
  - Official Action Indicated (OAI): FDA has made official recommendations as the manufacturing organization isn't compliant with regulations. Corrective actions are required.
- Your firm can respond to the FDA 483 in writing, outlining corrective actions taken or planned (highly recommended!)
  - Timely and effective responses demonstrate commitment to compliance

Resolution and Questions:

- Disagreements are handled via the FDA's Office of the Ombudsman.

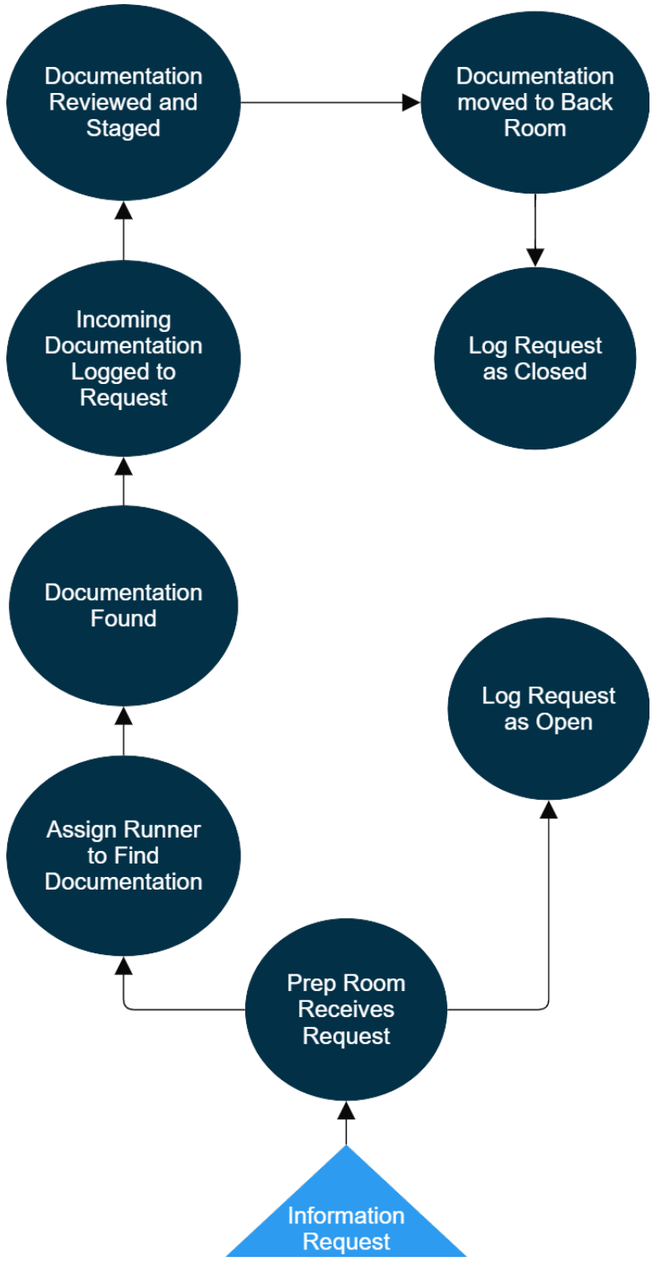
Information Movement During an Audit



Goal of the Prep Room

The goal of the Prep Room (also referred to as a War Room) is to provide the fastest and most effective communication, coordination, and document Compilation. Other activities include:

- Recording which documents are requested and tracking those requests
  - Remember, you can be cited for taking too long to find something!
- Reviewing / Staging documents
  - Confirm that the document request is correct and as a last chance to correct mistakes
- Tracing all documents entering and leaving the inspection room
  - Control of documentation is critical and represents your company's efficiency



Goal of the Back Room

The goal of the Back Room is to perform document staging and SME preparation.

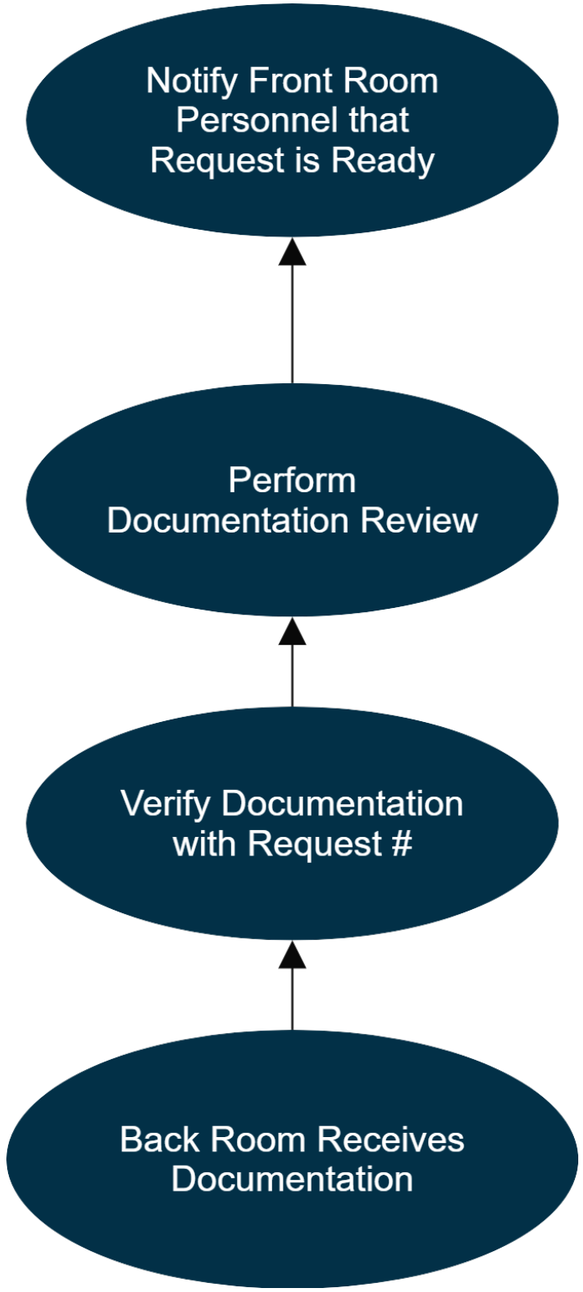
Typically, the Back Room is physically close to the Front Room for fast document movement.

Staging includes:

- Performing the **final** review of a document before presenting it to an inspector
  - Last chance to fix any potential mistakes
- Verifying the document meets a request
- Physically storing the document

SME preparation includes:

- Briefing the experts on the questions asked by the inspector
- Practicing the discussion between the SME and a mock inspector (QA compliance, consultant, etc.)
- Gauging the comfort of the SME
  - Do they have everything they need? Does the SME anticipate other documents will be required?



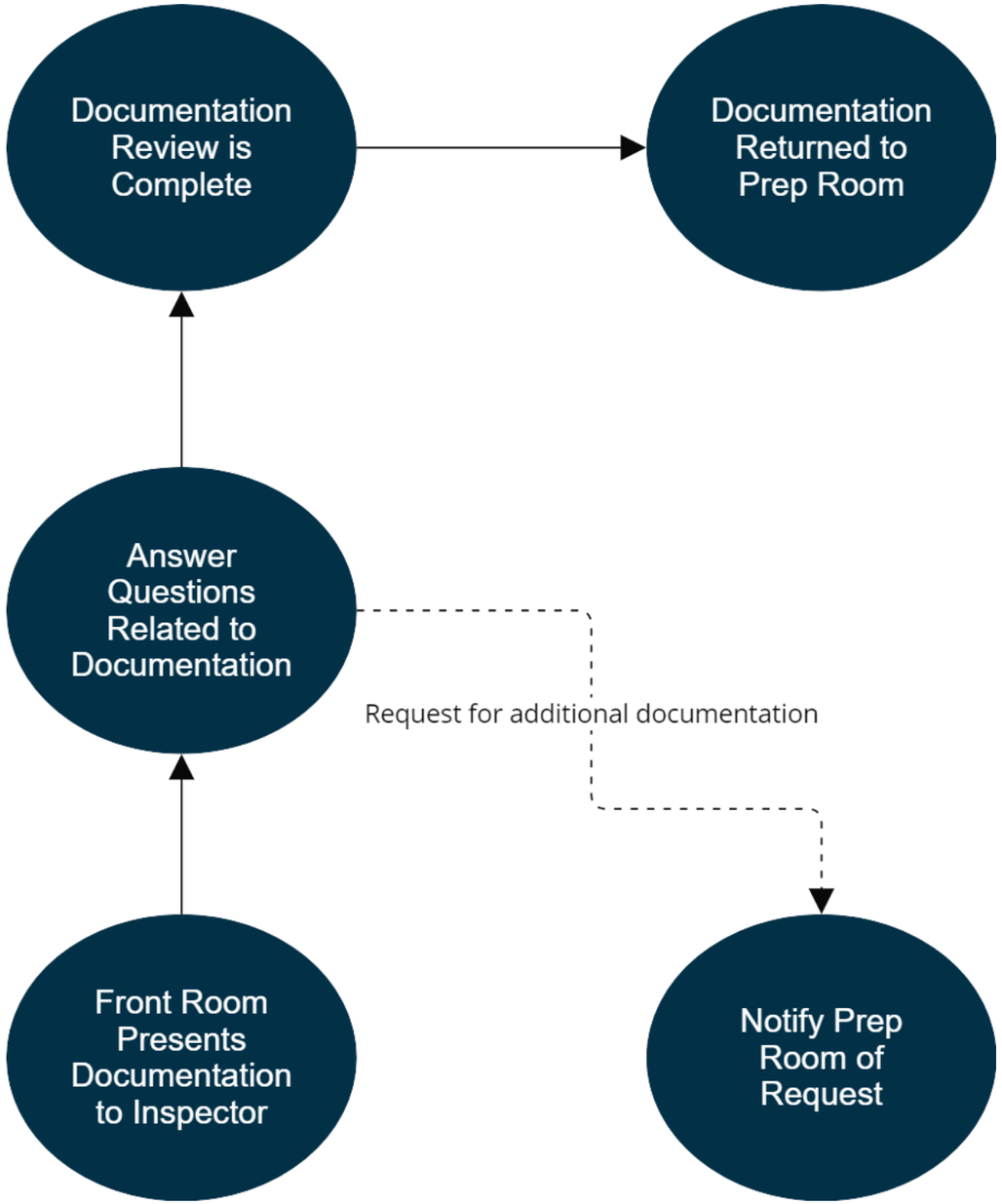
Goal of the Front Room

The Front Room is where the inspector resides when not actively moving throughout a facility.

Upper-level management, the escort, and scribe will primarily reside here.

Activities include:

- Recording which documentation is presented to inspectors
  - Some organizations may note which pages an inspector is reviewing, duration of time spent looking at documentation, etc.
- Answering questions
- Providing information back to the Prep Room
  - Document requests, inspector reactions, general information



Your Role in an Inspection

Escort

- Stays with the inspector for the entirety of the day
- Acts as first line response to questions
- Supports SMEs that are being questioned
- Assist inspectors by pointing out the sections in documents or in the facility to answer their questions

Scribe

- Acts as the ‘first mate’ to the escort
- Writes down everything as it happens. Document requests, samples taken, inspector comments, etc.
- The scribe is the primary communicator to the Prep Room

Your Role in an Inspection

Runners

- Finds documentation requested and provides it to the Prep Room personnel for staging

Prep Room Personnel:

- Acts as the central nervous system of the audit
- Receives information from the Scribe
- Coordinates the Runners
- Initially prepares the Subject Matter Experts
- Stages documentation before sending to the Inspector
- Ensures the organization is always prepared (Mock Audit Prep)

Subject Matter Experts (SME)

- Answer technical questions on a subject
- Not necessarily the most senior person, but the best presenter of information while being concise, confident, and calm in stressful situations
- Be friendly and courteous, but do not overshare

Consequences of a Poor Inspection

- Damage to organization and personal career
- Mandated recalls
  - https://www.fda.gov/drugs/drug-safety-and-availability/drug-recalls

Injunctions (Consent Decree)

- Legal action compelling a company to take corrective measures

- Criminal prosecution
  - https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/criminal-investigations/press-releases
  - Industry Ban

Improving the Audit Experience

‘Easy wins’ that everyone can do

- Be courteous
- Have a system / flow in place
- Know roles prior to the inspection

Mid Level wins

- Embrace digital methods and documentation
- Utilize current best practices (GxP, QbD via First Principles, etc.)

Top Tier wins

- Introduce Industry 4.0 to organization
- Embrace emerging technologies

Digital Documentation and Paperless Validation

One of the biggest upgrades an organization can make is to implement the transition to paperless validation and paperless operations.

Data Integrity Enhancement via Contemporaneous Recording

- Ensuring data integrity is paramount in our industry. Digital solutions provide electronic timestamps, virtually eliminating the risk of falsification. Audit trails and transparency align with the ALCOA+ principles.

Legibility and Accuracy

- Poor handwriting and documentation errors plague paper-based systems. Digital records remain legible, promoting compliance with Good Documentation Practices (GDP).

Enduring Records

- Paper fades, gets lost, or meets unfortunate coffee spills. Digital data stands the test of time.

Efficient Audits and Inspections

- Being able to create digital binders and collections of commonly asked topics from inspectors has been shown to reduce preparation time by up to 90%.

Digital Validation at Its Finest

3.1.1 Calibration Verification

Test Information:

Test ID	Test Description	Acceptance Criteria	Specification Reference	Risk Assessment Reference
IQ - WI-FZ-123-EVENT-02-TC-001	To verify the calibration certification for any instruments/devices used for the installation of the Asset # WI-FZ-123 showing that the instrument is calibrated to national standards.	Calibration certification exists for instruments/devices used for the installation of Asset # WI-FZ-123 showing that the instrument is calibrated to national standards. Documentary evidence attached to this protocol.	URS - WI-FZ-123-EVENT-01 (1.0 Dev) 3 #URS-001	N/A

Execution Note: If an Expected Result is not met, notify the Validation Department and initiate a deviation utilizing the comments and deviations table below the execution table.

Operating Procedures

#	Procedure	Expected Result	Actual Result	Pass/Fail	Signature
1	Verify that a calibration schedule is established for all devices to be calibrated. Verify that a calibration certification exists for any instruments/devices used for the installation of the Asset # WI-FZ-123 showing that the instrument is calibrated to national standards. Attach documentary evidence to this protocol.	Documentary evidence that a calibration certification exists for any instruments/devices used for the installation of Asset # WI-FZ-123 showing that the instrument is calibrated to national standards. Documentary evidence attached to this protocol.	Trend is great. SCRN-3.1.1-T2-R1-C4.1	Pass	**Amy Wilhite (amy.wilhite)** Row Sign. 30-Mar-2023 19:44:33 (UTC)

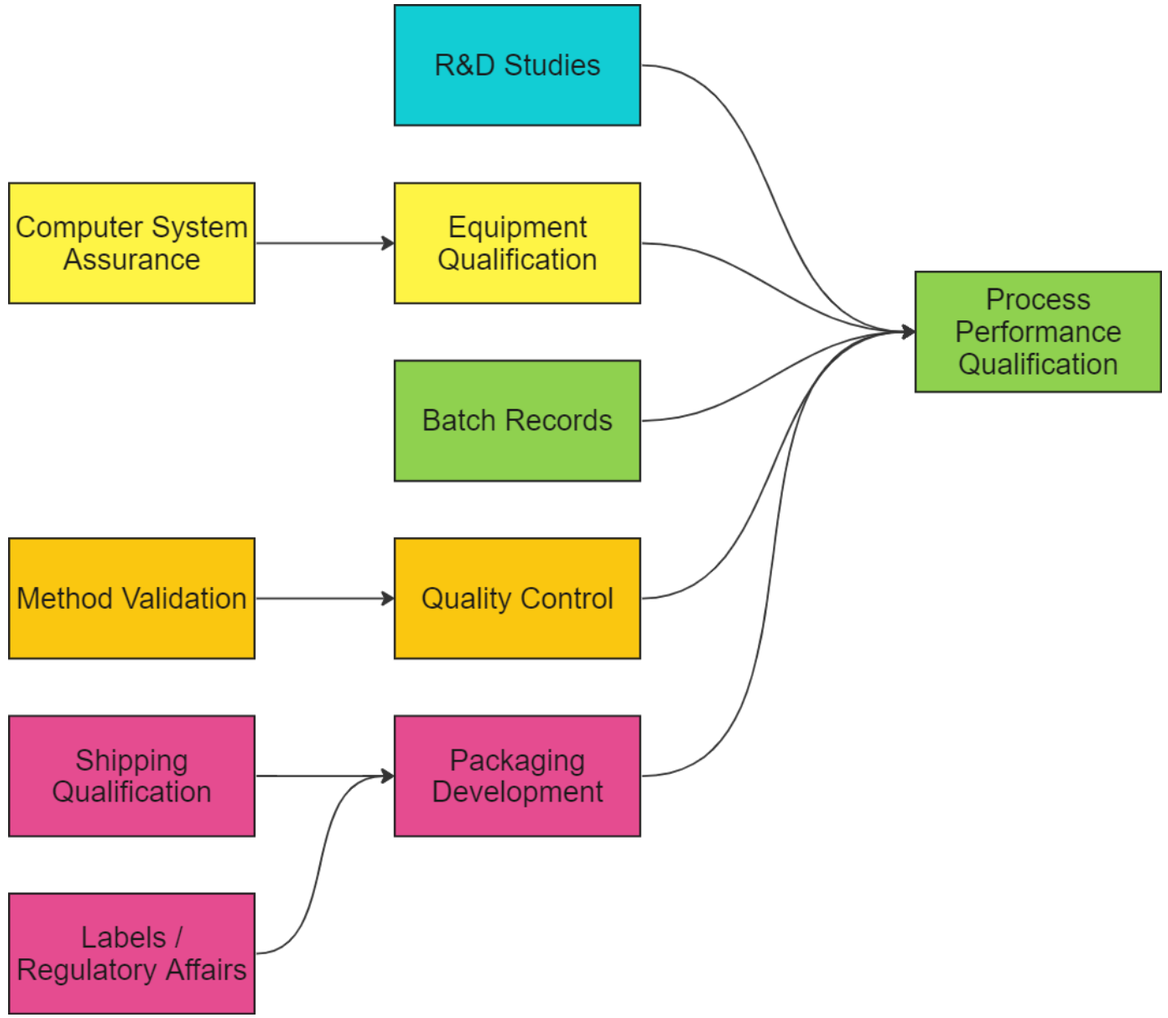
Test Summary

Overall Pass/Fail	Comments & Deviations
Pass	IQ - WI-FZ-123-EVENT-02-ISS-01
Signed by: Joe Azzarella (joe.azzarella) Table Sign, 23-Feb-2024 16:32:16 (UTC)	

Digitalizing the Validation Process

Digitalizing includes improvements!

- Simply taking all existing documentation and making it searchable digitally is not enough.
- Find a solution that allows documentation across different segments within an organization to cross reference/tag one another.
- For disciplines like Technology Transfer and Process Validation, the capability to acquire information and refer to it across different disciplines, sites, and external sources is critical.



Process Analytical Technology Considerations for Digital Validation

Process Analytical Technologies

- Ranging from as simple as temperature sensors to as complex as in-line samplers and computational flow dynamics.

PAT Integration: Seamlessly incorporate PAT technologies into digital validation systems

- Capture real-time process data.
- Enable continuous monitoring and analysis.

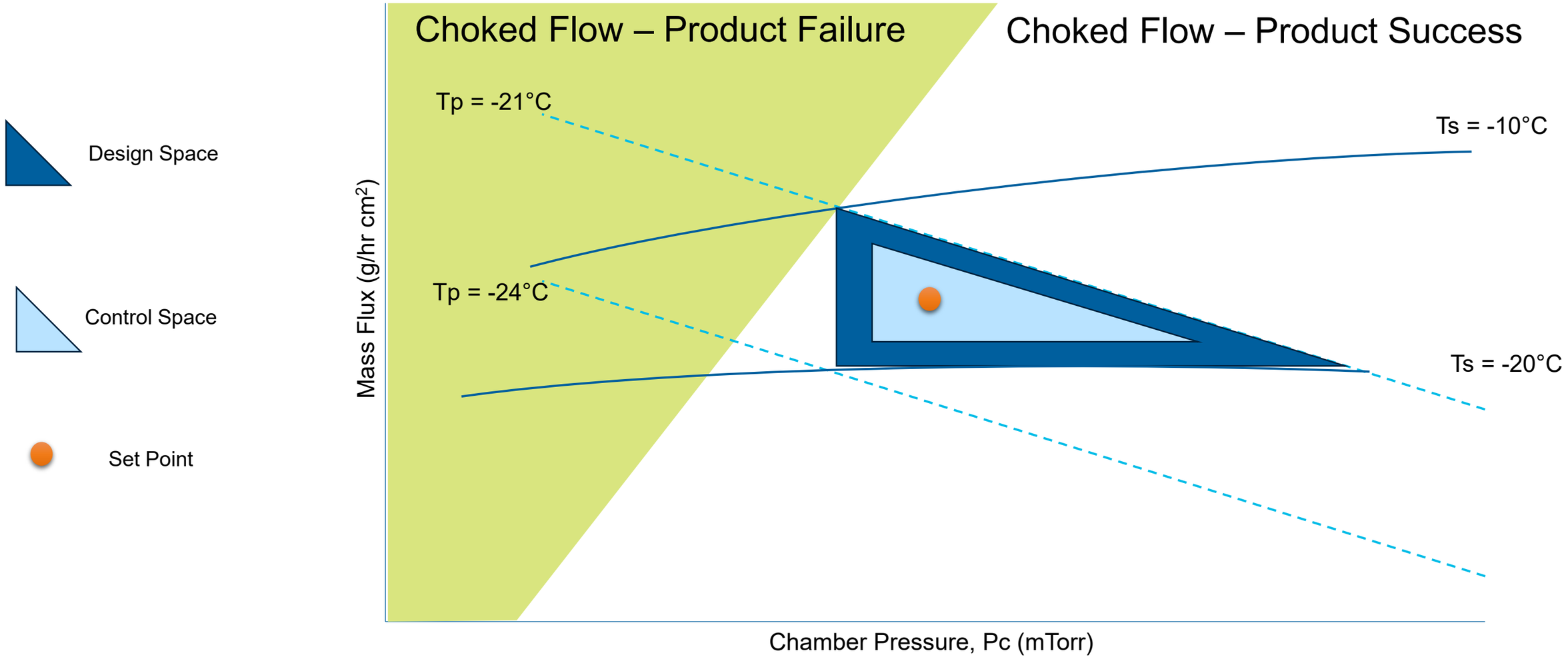
Enhanced Validation: By including PAT data in protocols:

- Ensure validation and optimization.
- Improve process efficiency and quality.

Predictive Analytics: Leverage historical PAT data for:

- Identifying trends and deviations.
- Making proactive, data-driven decisions.

Benefits of Process Analytical Technologies in the Context of Audits



Recreated from: https://www.americanpharmaceuticalreview.com/Featured-Articles/148761-Practical-Considerations-for-Freeze-Drying-Process-Design-Development-and-Scale-Up/

Industry 1.0 to 4.0

Industry 1.0 - Mechanization

- Starting point of modern manufacturing. Manual processing to non-electrical power-driven machinery.

Industry 2.0 - Electricity

- Electricity and electronic machines. Assembly lines with preset controls, allowing for basic process parameters.

Industry 3.0 - Automation

- Communicating technologies, continuous manufacturing, process analytical technologies

Industry 4.0 - Digitization

- Digital maturity, autonomous and independent manufacturing

POLL #2

What Industry does your organization operate in primarily?

- ❑ Industry 1.0
- ❑ Industry 2.0
- ❑ Industry 3.0
- ❑ Industry 4.0

Industry 3.0 – Bulk Filling Line Process

Filler Sensors

- Time / Pressure
- In line weight checks
- Filling needle depth sensor

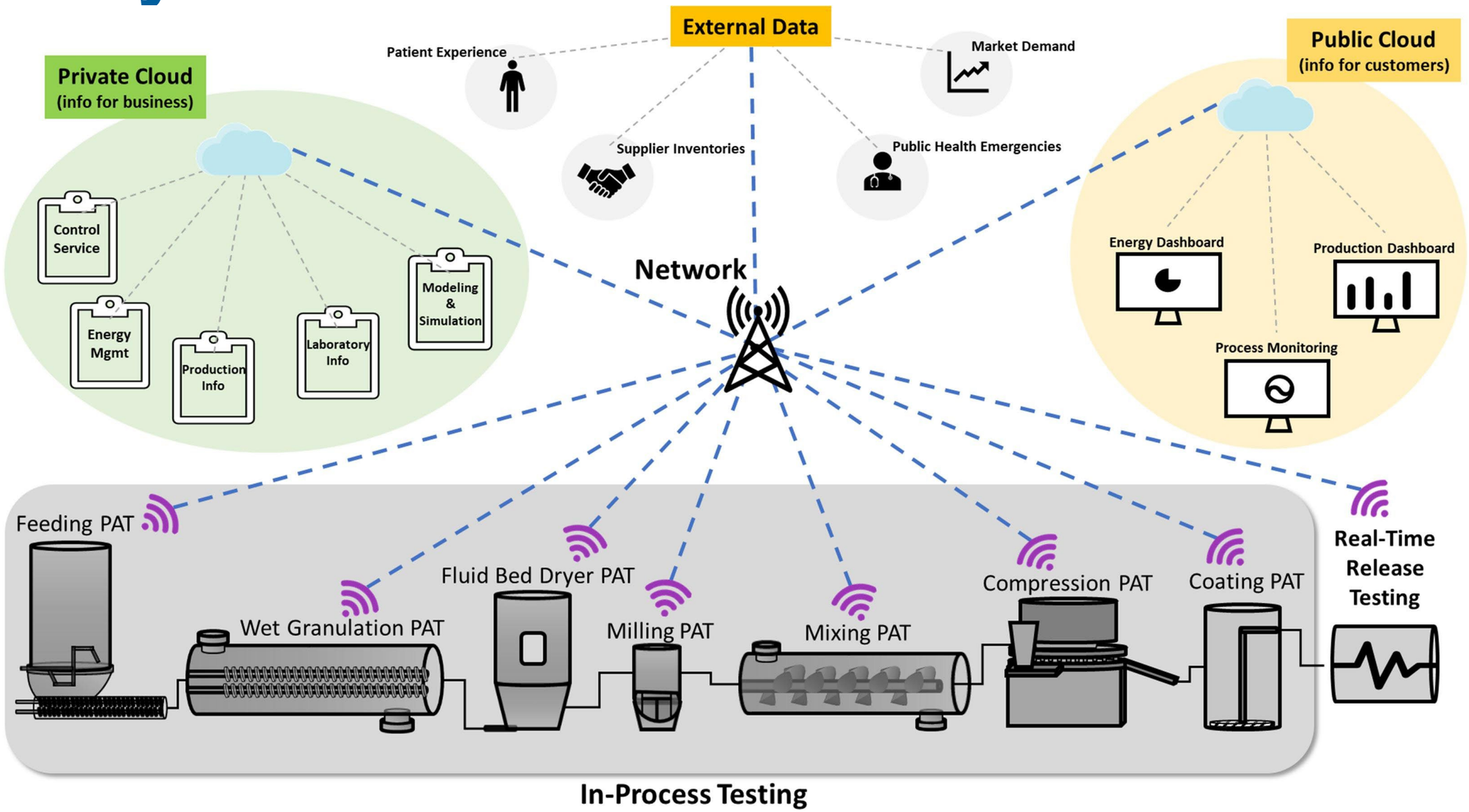
Finish Sensors

- Automated visual inspection
- Crimp verification
- Weight check

System Feedback

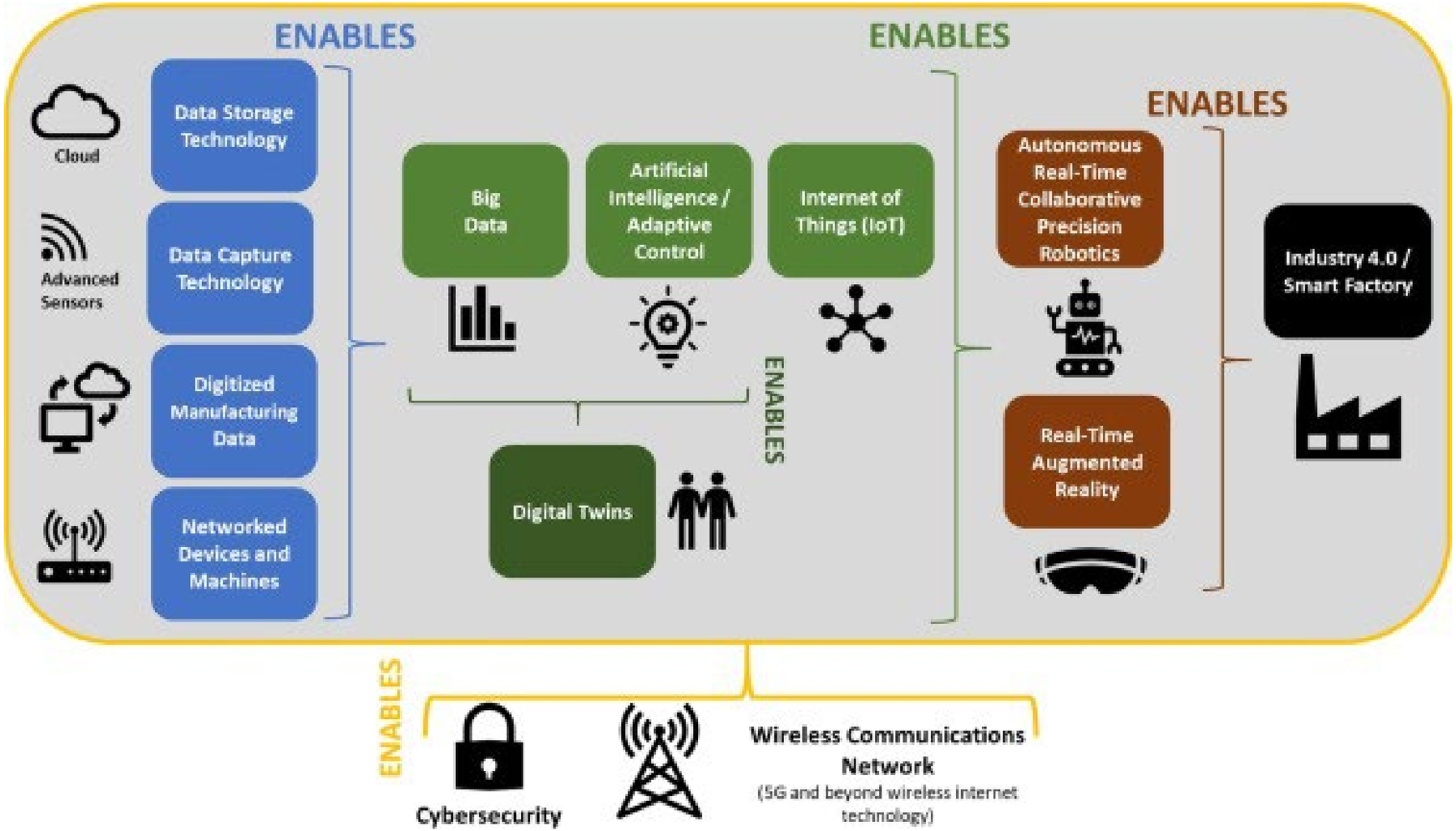
Adjustments made to speed, time, pressure as needed

Industry 4.0



Reference: https://www.sciencedirect.com/science/article/pii/S0378517321003598

Industry 4.0



Reference: https://www.sciencedirect.com/science/article/pii/S0378517321003598

Moving Towards Industry 4.0

Why make the transition now?

Not iterative (you don't need to go to 2.0, stop, wait, then go to 3.0)

- Similar to software, upgrade to the latest version

Changes take time. For larger organizations by the time, they see themselves at X.0, they'll already be a version behind.

Increase understanding of industry and regulation trends.

Key Takeaways from Today

If you're involved with audit/inspection teams, do what you can to be the most efficient courteous team in your organization.

Understand and embrace new methodologies, think about how you would implement them in your organization.

Have a mix of easy wins (digital validation) and long-term goals (IoT / AI usage) for consistent success.

Audience Discussion

Share your perspective on:

- ❑ What are your audit best practices
- ❑ Advice for those new to the industry
- ❑ Best / worst audit experiences
- ❑ Introducing new technologies