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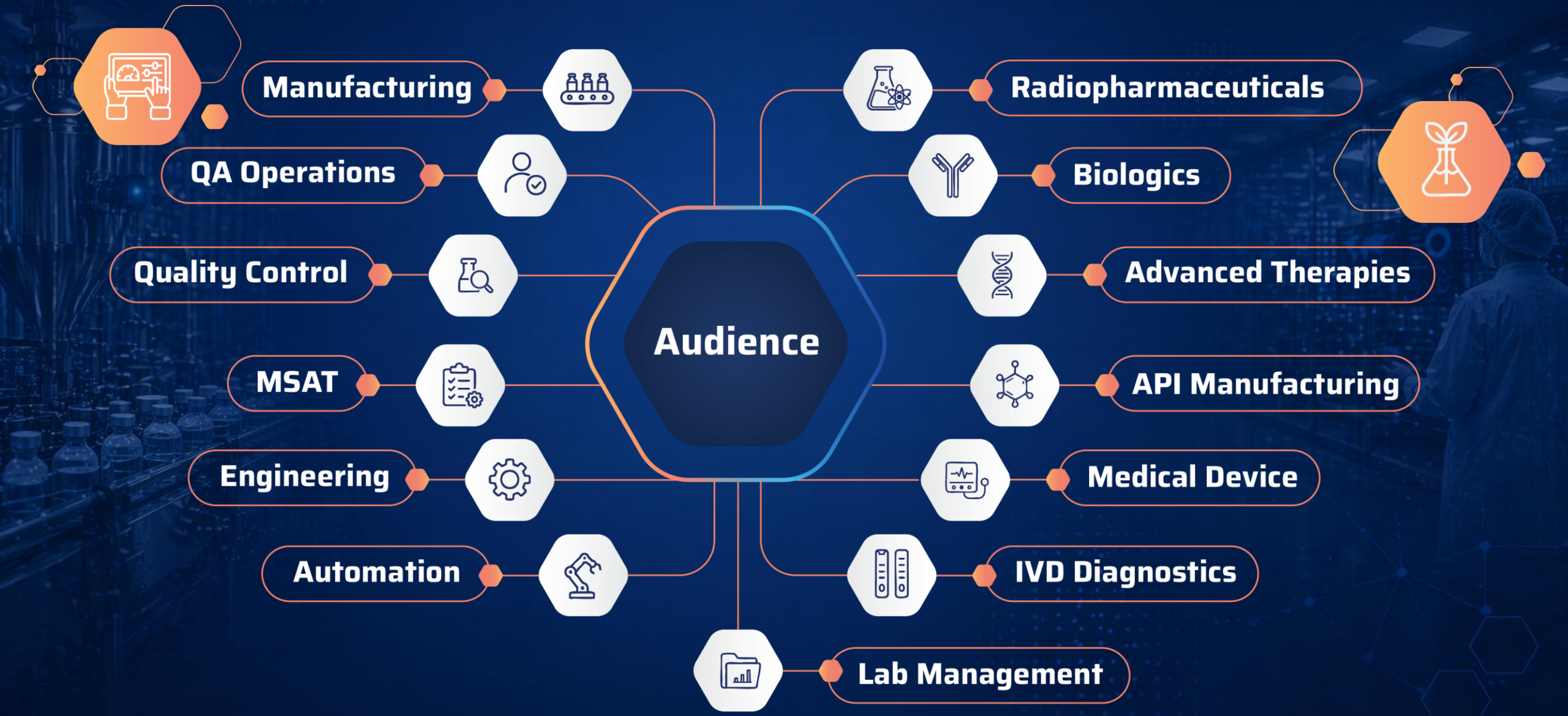
# Advance Smarter, Proactive Contamination Control

## Via Factory Floor Digitization

# Agenda

1. Introduction & Audience
2. Objectives
3. Contamination Overview
4. Digital Maturity Roadmap
5. Digitization's Key Business Drivers
6. CCS Key Design Aspects
7. Enterprise Integration
8. Planning Implementation & Usage
9. Role of Process Validation
10. Key Takeaways

# Who Should Consider This?



# Objectives


## Discover

how to strengthen manufacturing operations with data-driven decisions that take advantage of real-time data management and analysis


## Get strategic

insights into how digital production floor enables effective contamination control

## How to use

automated controls to reduce human-caused errors, prevent mix-ups in labeling, material tracking, sampling errors, and process execution

# What is Contamination?

## EU GMP Annex 1 & 11 Context

**Contamination** is the undesired introduction of foreign agents or substances (impurities) into a pharmaceutical product, process, or environment.

- Microbial
- Particulate
- Chemical/Pyrogen
- Radioactive

**Data contamination** refers to the introduction of inaccuracies, alterations, incompleteness, or unauthorized changes into GMP-relevant data (e.g., batch release, quality control, or regulatory submissions)

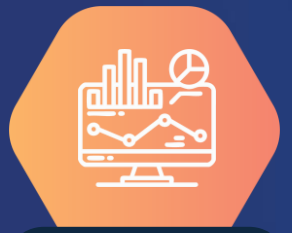
- Inaccuracies
- Alterations
- Incompleteness
- Unauthorized Changes

# What is Contamination?

**Types of Contamination:**

Product

Cleanroom



Data

- Sources of Contamination:
  - **Mix-ups** –Contamination or misidentification of materials, components, labeling, in-process materials, or finished products caused by human or system errors (e.g., wrong materials, incorrect labeling, poor segregation, or inadequate line clearance, inadequate procedures, insufficient training, or poor facility/material flow design).
  - **Residual / Retention** – Carryover of material on product contact surfaces after cleaning, sanitization, or disinfection from one product to another or batch to batch.
  - **Mechanical Transfer** – Transfer by mechanical means of contaminants, including from non-product contacting parts or transfer systems, via gowns, cart wheels, work benches, spills, leaks, etc.
  - **Airborne Transfer** – Transfer of contaminants, ingredients, powders, or other materials via airborne suspension (e.g., aerosols, dust, or suspended particulates) that can disperse through air currents, HVAC systems, or room airflow and deposit onto product contact surfaces, equipment, or other products.

# Contamination Control Strategy Key Design Aspects

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## Facility

- Design
- Personnel Flow
- Material Flow
- Waste Management
- Barriers
- Construction & Finishes
- HVAC Controls & Monitoring
- Utilities Controls & Monitoring
- Air Filtration
- Cleaning & Disinfection
- Maintenance

## Equipment

- Containment
- Cleanability & Sanitization
- System & Assembly Integrity
- Maintenance

## Process

- Design
- Pre Use Set up / Post Use
- Unit Operations
- Cleaning & Sanitization
- Sterilization
- Maintenance
- Sampling
- Utility Connections

## Automation

- Design ALCOA+
- Data Transmission
- Data Collection
- Data Storage
- Data View
- Data Maintenance
- Data Recovery
- Sequencing
- Process Execution/Steps
- Tuning
- Alarms
- Permissives

**Types of Contamination**

Sources of Contamination

| Product | Cleanroom | Data Contamination |
|---|---|---|
| Mix-Up | Mix-Up | Mix-Up |
| Residual | Residual | |
| Mechanical Transfer | Mechanical Transfer | |
| Airborne Transfer | Airborne Transfer | |

# Contamination Control and Prevention
# = People + Technology + Process

- Contamination Does Not Only Pertain to Microbiology or Product Carryover
- Smarter Contamination Controls Rely on Automation, Analytical and Engineering Solutions

# Digital Maturity Roadmap*

*Based on ”Digital Plant Maturity Model (DPMM) 3.0 Addendum to the DPMM v1 white paper”, BioPhorum Operations Group Ltd., October 2023

| Areas | L1<br>Pre-Digital Plant (Manual) | L2<br>Digitally Siloed (Visible) |
|---|---|---|
| Digitally Connected Shop Floor | Manual, paper-based plant with a low level of localized automation | Standalone networks |
| Manufacturing Technologies & Automation | “Isolated” production data available | “Islands of Automation” |
| Process Development | Manual, paper-based data transcribed to PFDs | Manual, paper-based data transcribed to PFDs |
| Process Data & Analytics | Paper-based data transcribed from floor operation to excel based spreadsheets | Limited usage data historian for analytics |
| Enterprise Integration | Site-specific systems | Limited company-wide enterprise integration, no integration of machine to enterprise |
| Quality Control & Laboratory Technologies | QC testing performed manually | Electronic workflows, adoption of LIMS, no integration |
| Quality Management | Manual, paper based QMS, adoption of eQMS with limited functionality | Adoption of eQMS with expandable functionality, no integration nor analytics |

# Digital Maturity Roadmap*

*Based on ”Digital Plant Maturity Model (DPMM) 3.0 Addendum to the DPMM v1 white paper”, BioPhorum Operations Group Ltd., October 2023

| Areas | L3<br>Connected Plant (Optimized) | L4<br>Predictive Plant (Preventive / Intelligent) |
|---|---|---|
| Digitally Connected Shop Floor | PC-based equipment secure enterprise connectivity with monitored data security and compliance. | Integration of the plant-to-value-chain.<br>Predictive alerts instead of threshold alarms.<br>Data is aggregated in cloud with standardized data modeling. |
| Manufacturing Technologies & Automation | MES/EBR with QA review by exception.<br>Continuous feedback loops for process controls. | AI-enabled predictive planning and scheduling (i.e., line clearance, cleaning, labor force, products).<br>Enterprise Recipe Management (ERM).<br>Smart maintenance by utilizing real-time data monitoring |
| Process Development | Digital transfer from development to manufacturing. | Integration of product development and manufacturing – PLM. |
| Process Data & Analytics | Islands of real-time process analytics. | Predictive analytics (“what can happen and when”). |
| Enterprise Integration | End-to-end integration across the enterprise, ERP, LIMS/LES, MES, QMS, and automation layer. | Plant-to-supply chain visibility with limited external collaboration (suppliers / CMOs). |
| Quality Control & Laboratory Technologies | Integrated lab and production data with traceability. | On-line / at-line testing enabling risk-based real-time release. |
| Quality Management | Real time training, smart “nanny” controls on production execution. | Digital simulations and virtual environments used to qualify, re-qualify, and continuously assess personnel. |

# Digitization's Key Business Drivers
in Managing Contamination

## Digitally Integrated Shop Floor

### Manufacturing Technologies & Automation

Integrate automation and robotics to minimize manual interventions and process variability

### Enterprise Integration

Enable real-time data sharing across all modalities: development, engineering, quality, operations, and supply chain


### Data Analytics

Implement advanced trend analysis and predictive modeling to proactively identify and mitigate adverse patterns before they materialize into operational issues

### Quality Management

Digitize field quality control and environmental monitoring

Implement simulated training environments

Enable real-time tracking and analysis of equipment issues, process deviations, and product failures

# Smarter Contamination Controls Across End-To-End Value Chain:

Development » Manufacturing » Distribution » Patient

Design Domains

Examples SMARTER Contamination Controls

## Robotics

Automated material, equipment handling & transfer

## Data Acquisition & Analytics

Integrated machine-to-enterprise analytics for contamination risk prediction:

- Root cause analysis
- OEE performance
- Production optimizations
- Operations management
- Asset performance
- Alarm management
- Anomaly detection
- Environmental monitoring and trending

## Business Management

- Materials management and delivery by eKanban
- Dynamic delivery optimization for time sensitive materials and products

## Manufacturing Execution

- Electronic batch and recipe-driven processes
- Release by Exception
- Advanced equipment status tracking
- Production planning optimized by advanced analytics
- Track & Trace
- Digitally controlled and verified cleaning & disinfection
- Real-Time Location Systems (RTLS)
- On-line & At-line testing
- Closed & single-use platforms

# Smarter Contamination Controls Across End-To-End Value Chain:

Development » Manufacturing » Distribution » Patient

Design Domains

Examples SMARTER Contamination Controls

## Process Controls

- Equipment Automation with advanced industrial IoT
- Predictive Maintenance

## Quality Systems

- Release by Exception
- Training Verification in MES/EBR
- Mixed Reality-based training
- Supplier and materials quality tracking
- Smart workforce upskilling

## Laboratory Technologies

Sample management & analysis with Modern Microbial Methods (MMMs)

# Enterprise Integration for more effective CCS

Most contamination problems happen because humans make mistakes or processes are not tightly controlled. **The fix is connecting all the systems, to track, verify, and automate.**

Contamination Source

**Mix up - Human Error**

**Cause of Contamination**

Wrong, expired or OOS materials due to poor inventory tracking

**Automation Controls / Detection**

**ERP (Enterprise Resource Planning) → materials management**

Contamination Source

**Mix up - Human Error**

**Cause of Contamination**

Operators' lack of access to procedures and no training verification before completing the manufacturing process step

**Automation Controls / Detection**

**EDMS (Document Management) → training, SOPs, work instructions**

Contamination Source

**Mix up / Mechanical transfer - Manual Operations**

**Cause of Contamination**

Incorrect process settings (e.g., alarms, parameters, valve sequencing)

**Automation Controls / Detection**

**Process Controls → control of the sequence of operations**

Contamination Source

**Mix up - Manual Material Handling**

**Cause of Contamination**

Incorrect material labeling

**Automation Controls / Detection**

**Barcodes / Labels → labeling and identification of materials**

Contamination Source

**Mix up - Human Error / Process Variability**

**Cause of Contamination**

Manual data entry and analysis of KPIs (performance indicators) and CPPs

**Automation Controls / Detection**

**Analytics → monitoring and insights**

Contamination Source

**Mix up - Human Error / Sample Mishandling**

**Cause of Contamination**

Sample mishandling, incorrect test results, or false negatives

**Automation Controls / Detection**

**LIMS – Laboratory Information Management System → sample management**

Contamination Source

**Mix up - Human Error**

**Cause of Contamination**

Calibration status expired on the processing equipment used for production

**Automation Controls / Detection**

**CMMS (Maintenance System) → calibration and preventive maintenance**

Contamination Source

**Mix up - Human Error**

**Cause of Contamination**

Missing or incorrect entries in the equipment cleaning status

**Automation Controls / Detection**

**eLogbooks → equipment status**

Contamination Source

**Mix up - Human Error**

**Cause of Contamination**

Oversight or incorrect documentation of process step execution

**Automation Controls / Detection**

**MES/EBR (Manufacturing Excellence Software) – electronic batch records**

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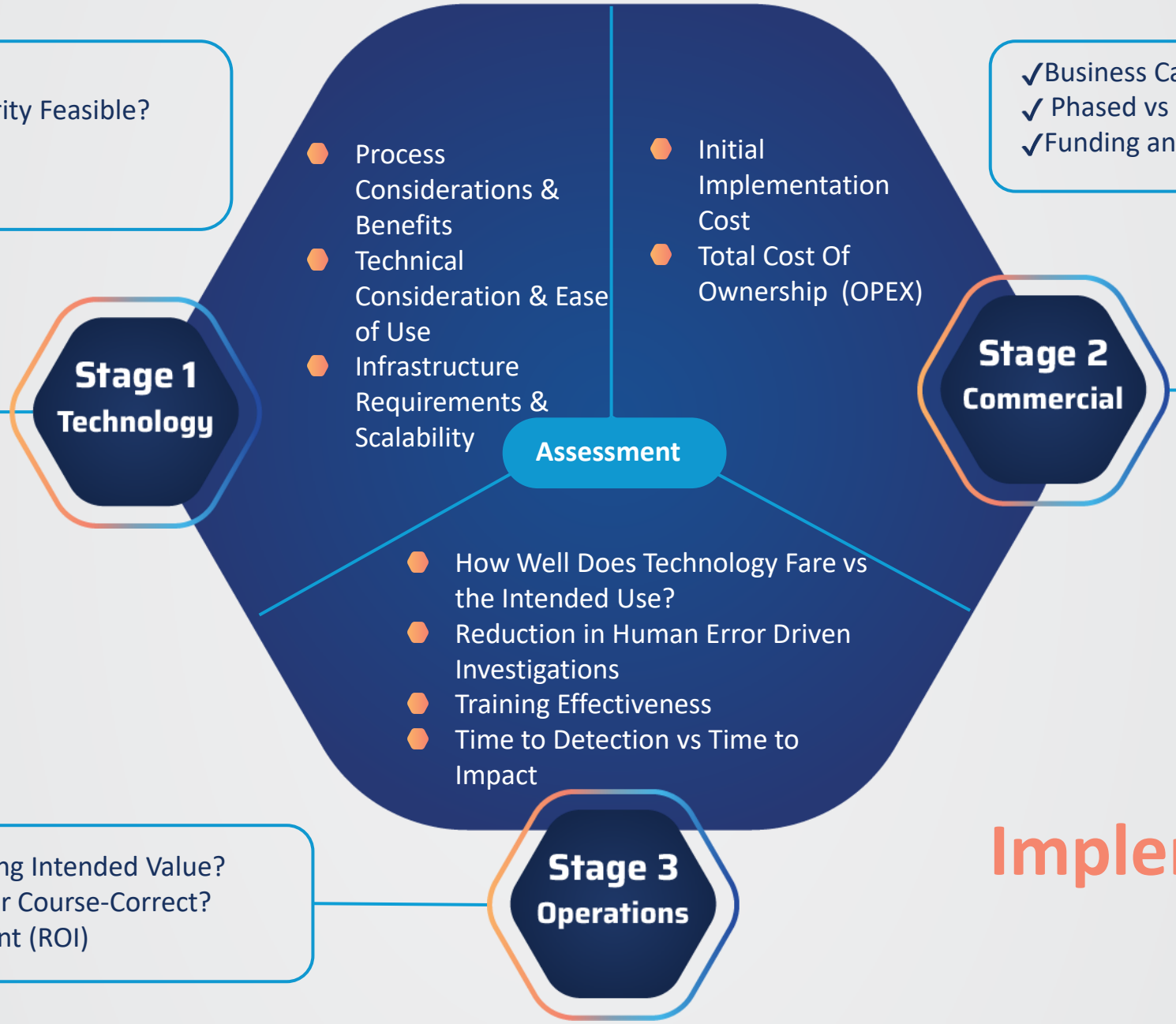
## Decision Outputs

✓ Fit-for-purpose?
✓ Validation and Data Integrity Feasible?
✓ Proceed
X Stop




✓Business Case Approved?
✓ Phased vs Enterprise Rollout?
✓Funding and Roadmap Defined

✓ Technology Delivering Intended Value?
✓ Expand, Optimize, or Course-Correct?
✓ Return on Investment (ROI)

# Planning, Implementation, Usage

Smarter Controls

# Role of Process Validation

## in an Effective Contamination Control Strategy

1

### Process Design

- CCS Design Review / Risk Assessment
- Facility
- Equipment/Automation
- Process

2

### Process Qualification

- Process Development Studies
- Verification and Validation of controls identified in CCS RA
- Data Integrity Verification
- Performance Qualification

3

### Continuouss Process Verification

- CCS Review via Periodic Validation Review
- EM Data Trends
- Preventive/ Demand Maintenance
- Change Controls
- CAPAs / Exceptions
- Facility Walkdowns
- Gamba walks

Process Validation serves as the confirmation mechanism that the CCS works as intended


# Key Takeaways

- Proactive contamination control REDUCES downtime and risk to adulterated product, and aids in maintaining audit compliance, while digital production REMOVES reliance on manual controls
- Built-in smarter controls ENABLE proactive, human-in-the-loop contamination management
- Modern digital production floor NEEDS easily deployable, scalable solutions that unlock operational excellence and ensure robust compliance in contamination control and data integrity