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Without measurement there is no control

Microbiological aspects of cleaning validation for sterile and not sterile process.
Process aligned with PAT and QbD guidelines and concepts

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Pharmaceutical processes

Non sterile production

- API
- Tablets
- Granules
- Syrups
- Topical (lotions, creams, ointments, etc.)

Critical Non sterile production

- Aerosol
- Nasal spray
- Powder inhalers

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Pharmaceutical processes

Sterile production

- Injections
- Ophthalmic preparations
- Irrigations solutions
- Hemodialysis solutions
- Topicals (for open wounds or critical applications)
- Radiopharmaceuticals
- Cell factories
- Compounding centers

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Sterile products

Non parenteral

- Eyes drops
- Topicals (creams, lotions, ointments, gauze)
- Irrigations solutions

Parenteral

- Ampoules
- Vials
- Bottles
- Syringes
- Bags

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Sterile products

Two categories of sterile products:

- those that can be sterilized in final container (terminally sterilized)
- those that cannot be terminally sterilized and must be aseptically prepared

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Aseptic Processes Steps

- Primary container washing
- Primary container depyrogenation/sterilization
- Compounding (product preparation and filtration)
- Filling and plugging
- Lyophilization
- Capping
- External washing (optional)
- Visual inspection
- Labeling
- Packaging

FDA Initiatives - Innovation

In the beginning in 2002, the FDA recognized the need for the pharma industry to be more innovative. Therefore, it launched:

- **A Critical Path Initiative**
- **Pharmaceutical Quality for the 21st Century – A Risk Based Approach**
- **Quality by Design (QbD)**
- **Process Analytical Technology (PAT)**

The Goal of all is to modernize and improve the quality of pharmaceutical manufacturing processes – encourage industry to implement risk-based, continuous, real time quality assurance

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Quality by Design (QbD)

Definitions:

Quality – "the suitability of either a drug substance or drug product for its intended use" – ICH Q8

Quality by design – uses process understanding to deliver product with the desired critical quality attributes.

Process understanding – in-depth knowledge of factors affecting a product's critical quality attributes (see PAT guidance).

Design Space – "the multidimensional combination and interaction of input variables and process parameters…. demonstrated to provide assurance of quality" – ICH Q8

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FDA's View on Quality by Design (QbD)

In a Quality-by-Design system:

- **The product is designed to meet patient requirements**
- **The process is designed to consistently meet product critical quality attributes**
- **The impact of starting materials and process parameters on product quality is understood**
- **Critical sources of process variability are identified and controlled**
- **The process is continually monitored and updated to assure consistent quality over time**

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What is Quality by Design (QbD)?

A systematic approach to development that begins with predefined objectives and emphasizes product and process understanding and process control, based on sound science and quality risk management.

(ICH Q8(R), step 2)

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What is Quality by Design (QbD)?

Quality by Design is:

- A systems for designing, analysis, and controlling manufacturing through timely measurements (i.e.during processing) of *critical quality parameters* (CQP) and performance attributes of raw and in-process materials and processes (CPP) with the goal of ensuring final product quality.

- It is important to note that the term analytical in QbD is viewed broadly to include chemical, physical, microbiological, mathematical, and risk analysis conducted in an integrated manner.

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Quality by Design (QbD) – A Systematic Approach to Pharmaceutical Development and Manufacturing

Aspects	Traditional	QbD
Pharmaceutical Development	**Empirical**; typically univariate experiments	**Systematic**; multivariate experiments
Manufacturing Process	**Fixed**	**Adjustable** within design space; opportunities for innovation **(PAT)**
Process Control	In-process testing for go/no-go; offline analysis	**PAT tools utilized** for feedback and feed forward controls
Product Specification	Primary means of control; based on batch data at time of submission	Part of the overall quality control strategy; based on desired product performance (safety and efficacy)
Control Strategy	Mainly by intermediate and end product testing	**Risk-based**; controls shifted upstream; ***reducing product variability;*** real-time release
Lifecycle Management	**Reactive to problems** & OOS; postapproval changes needed	**Continual improvement** facilitated

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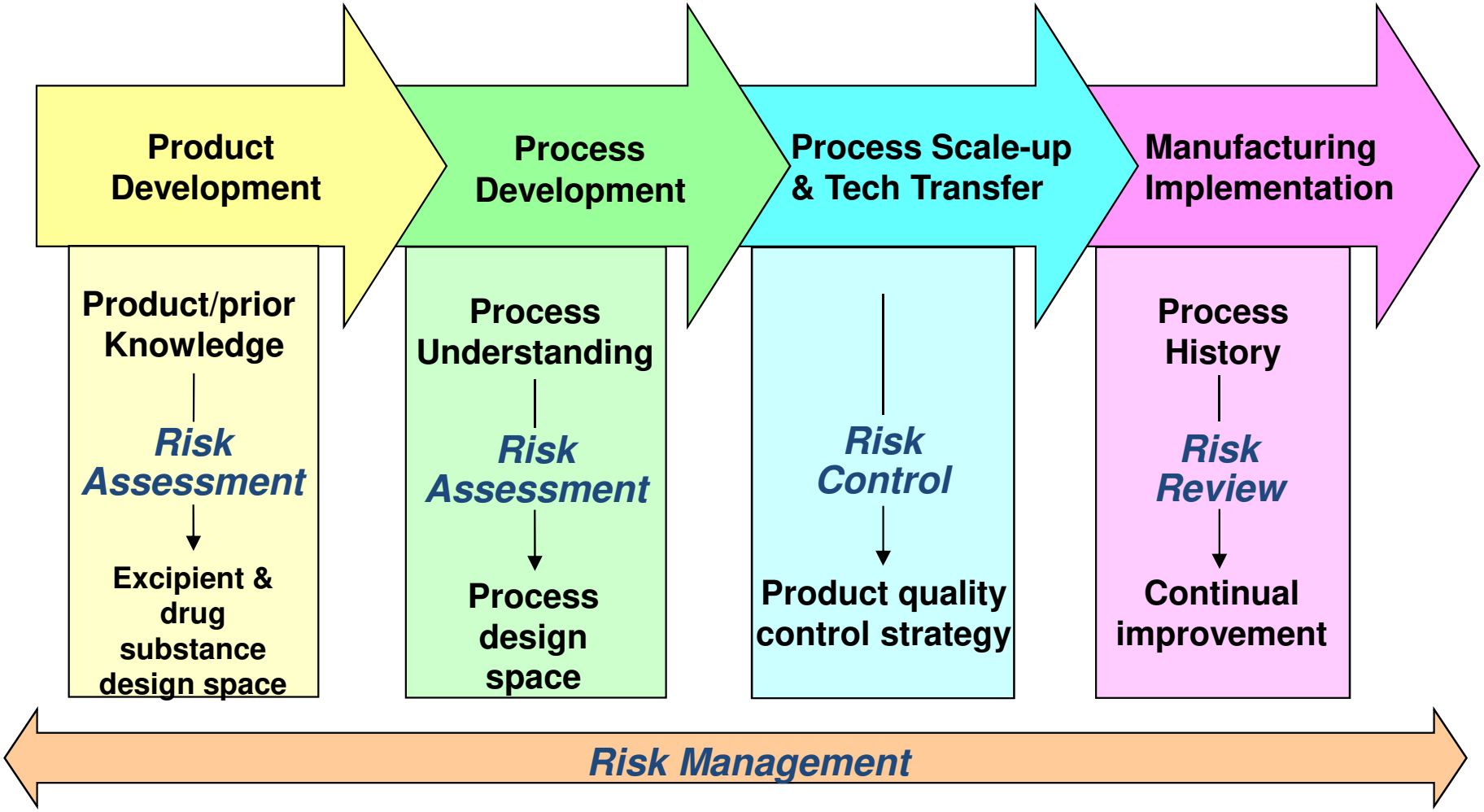
Role of Quality Risk Management in Development & Manufacturing



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Quality by Design Implementation

"Quality by Design" implementation

- ICH Q9, ICH Q10 and the new FDA guideline for Process Validation

➢ PROCESS DESIGN

- Identification of **CQA** (Material & Components, Intermediates Critical Quality Attribute), **QCPP** (Quality Critical Process Parameters) through Process Understanding and Risk Analysis Tools

➢ PROCESS QUALIFICATION

- Development and validation of RMM (sampling tools + rapid/advance measuring systems) for identified CQA and QCPP
- Real Time Release of the Drug Product must be on the basis of microbial control results obtained in CQA and QCPP

➢ PROCESS VERIFICATION in continuous

- Process Verification must be defined in the RTR strategy through periodical trend evaluation

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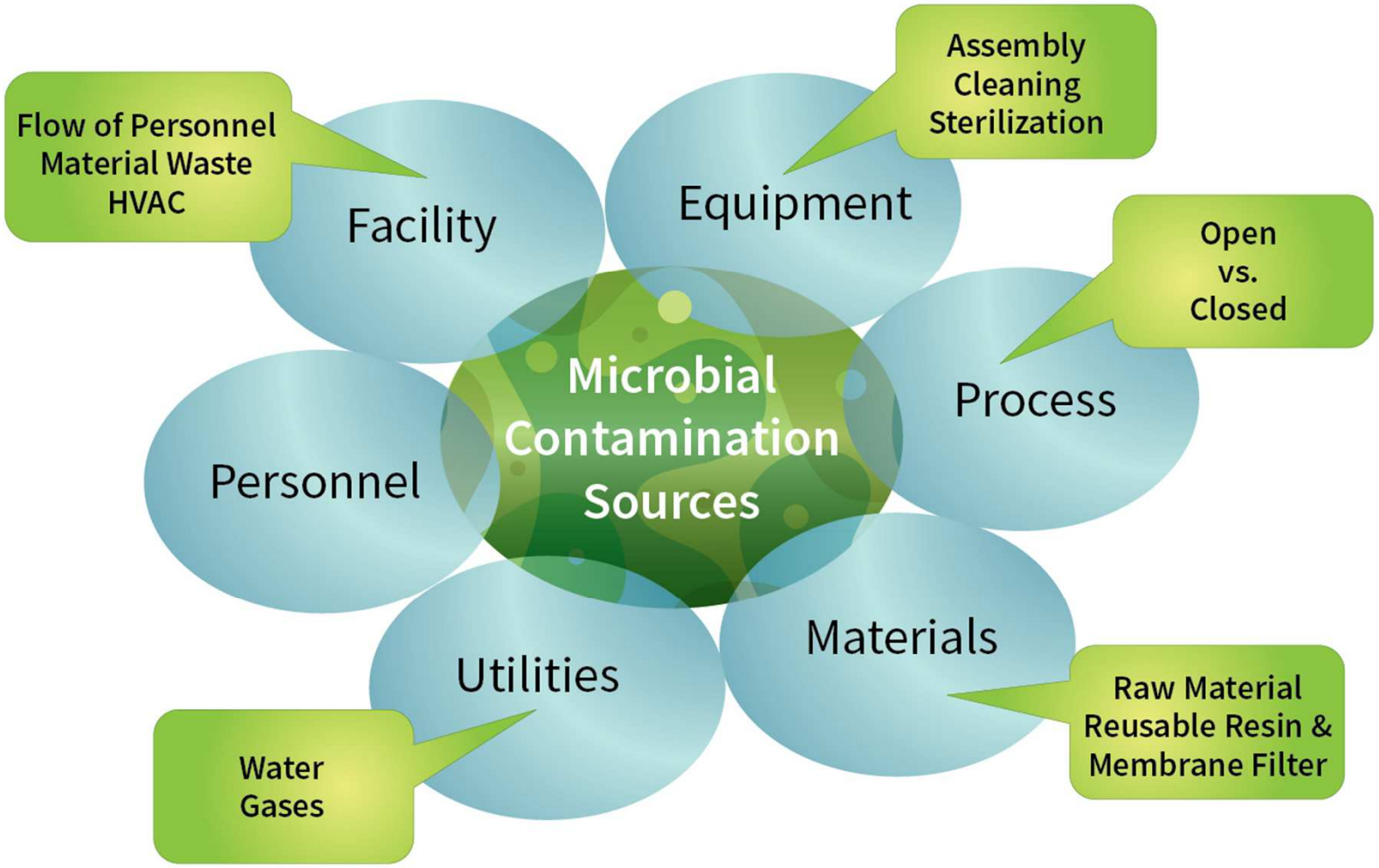
Pharma Process Contamination



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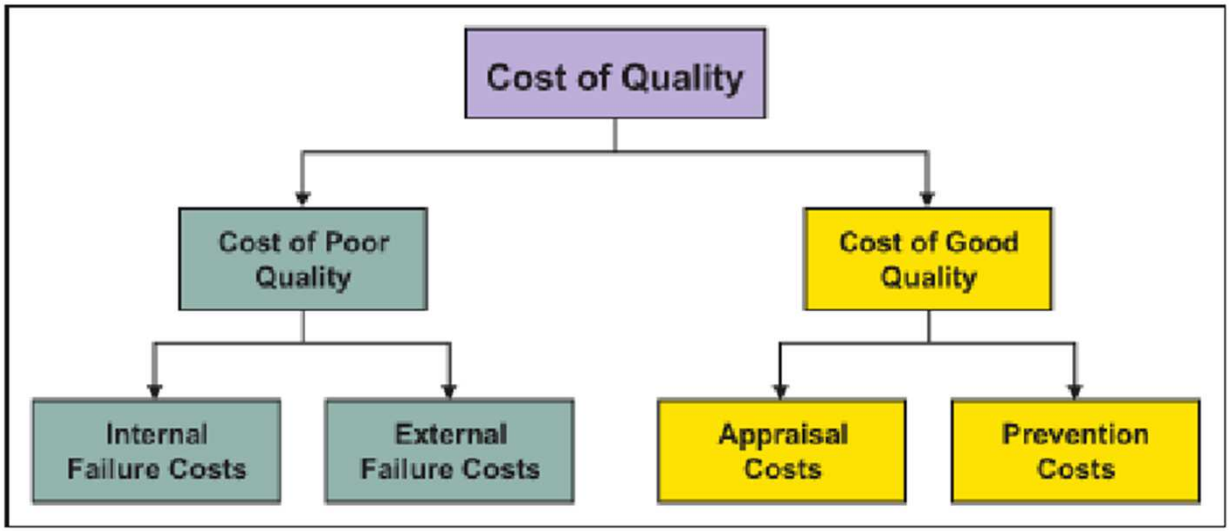
The Cost of Quality

- The Cost of Quality is the sum of four cumulative types of costs:
  - Appraisal, Detection, Internal Failure, External Failure
- The Cost of Poor Quality is the cost associated with producing defects, which includes internal failure costs and external failure costs.



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Concluding Comments

- FDA quality initiatives will lead to a fundamental paradigm shift in pharmaceutical manufacturing:
  - Quality control strategies based on product knowledge and process understanding
  - Industry held accountable for ensuring product quality
    - Management of some CMC changes based on clearly defined and agreed upon risk-based criteria without additional regulatory filing
  - A more scientific and risk-based approach regulatory oversight

Microbiological aspects of cleaning validation for pharma process

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Cleaning: Key Issues

- Chemical Cleaning of the environment vs. cleaning of process (product contact) materials.
- Microbiological Cleaning
- Designing for Cleanability and Contamination Control
- Validation Acceptance Criteria

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Cleaning an isolator compared to cleaning a clean room - I

- There are no real differences between an isolator and a clean room regarding cleaning of product contact surfaces.
- The basic principles used in calculating cleaning acceptance criteria are no different for isolator-based processing than for a clean room.

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Cleaning an isolator compared to cleaning a clean room- II

- Cleaning of non-product contact surfaces in an isolator are also generally similar to clean room aseptic operations.
- In both cases the environment is being cleaning to a required level of cleanliness to meet a defined safety objective.
- Generally, for most products visually clean is a suitable acceptance criterion for environmental cleaning.
- For products with special attributes in terms of toxicity, teratogenicity, carcinogenicity or simply pharmacological activity defined levels of cleanliness may be required.

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Possible Non-Product Contact Cleaning Validation Criteria

- Visually clean- suitable for many products, particularly those with no special employee or environmental exposure concerns
- Clean to safe level for personnel contact without additional safety measures- such as protective clothing or equipment.
- Establish limits and validate in a manner analogous to product contact parts- necessary only when extreme cleanliness requirements exist.

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Isolator Microbiological Cleaning

- Disinfection as we know it in clean rooms is not required for isolators - decontamination will eliminate bioburden.
- Surfaces should be visually clean and dry at the end of changeover activities.
- Cleaning with particle free wipes and mild cleaning solutions is adequate. Solvents or other disinfectants not routinely required.
- Deeper cleaning is generally required after initial isolator installation and assembly.

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Bioburden Control

- Bioburden Control in isolators is straightforward-isolators are inherently difficult environments for microbial colonization.
- Provided the isolator is clean and dry proliferation of microorganisms will not occur.
- Spills of media in validation or media residues from monitoring should be removed quickly and effectively.

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Design for Ease of Cleaning

- Smooth polished surfaces impervious to cleaning process
- Sloped floor-typically ~a 1:20 slope-with drains at all low points
- Avoid or at least minimize flat ledges and surfaces
- Minimal use of absorbent materials
- Maximum use of disposable items
- Protected location for filters
- Easy access and inspection of all locations to be cleaned
- Maintenance & adjustments made externally
- Cleaning between double glazing panels should be considered.

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Cleaning Systems

- Automatic C-I-P has been successfully implemented, but must consider protection of filters, and sensitive electronics.
- Manual spray-wands are frequently used in lieu of full automatic C-I-P.
- Clean water is the most common cleaning agent, other agents are necessary only of material to be cleaned is not water soluble.

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Relative Importance of Cleaning

- Containment only - prepare, use, CLEAN
- Aseptic & Containment – prepare, DECONTAMINATE, use, CLEAN
- Aseptic only – prepare, DECONTAMINATE, use, clean. Depending upon the application, the criticality of the cleaning process shifts relative to the use of the system.
- Decontamination can be considered a very well controlled type of microbiological cleaning.

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Validation- Some Critical Points to Consider

- Use product knowledge to develop pragmatic acceptance criteria. Exposure level data, both short and long term can be used in risk analysis and criteria setting.
- Focus on the cleaning process- suitability of analytical method as well as process criteria such as flow rates etc. must be evaluated.
- Reliability and reproducibility of the process must be evaluated.
- Consider both eventful and uneventful operation. Emergency planning is a must in critical containment applications

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Use good science and engineering- Be Practical!

- Avoid the tendency to over complicate in design, cleaning process and validation- design or validation targets that can't be met you will ensure failure.
- Avoid the tendency to think that every activity we undertake in isolators must be perfect- perfection is not attainable! Develop scientifically sound specifications and design and validate to them.
- Always develop a rationale for procedures and validation approaches
- Ensure that your rationale is reviewed by all relevant disciplines within your organization.

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Cleaning validation

PURPOSE

- To provide guidance on performing cleaning validation exercises
- To provide rationales, procedures and acceptance criteria in the definition of a cleaning validation protocols
- To ensure that all cleaning procedure are formally validated
- To provide assurance that any contaminant can be removed to the level defined in the acceptance criteria
- To ensure a satisfactory removal of cleaning agents from contact surfaces

SAMPLING METHOD

- Sampling operation must be defined in procedures
- The following 3 sampling methods are generally used to measure the effectiveness of cleaning procedures:
  - Direct surface swabbing (“swab”)
  - Rinse solution analysis (“rinse”)
  - Preparation of a subsequent batch (“placebo”)

[If placebo testing is used it should be carried out alongside either swab or rinse testing].

ANALYTICAL METHODS

- The analytical method must be validated.
- The analytical method must be sensitive and the limit of quantization must be determined.
- The efficiency of the recovery of the sampling method must be assessed.
- The swab storage conditions and stability must be assessed

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Final Thoughts:

1. **Begin with the end in mind**
2. **You be the expert**
3. **It's O.K. to take some chances in process development**
4. **Monitor and improve**

"When you're done improving, you're done."

-Bo Schembechler
Former University of Michigan
Head Football Coach

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Questions?

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