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Qualification / Validation

Quality Risk Assessment in the Pharmaceutical Industry - Challenges and Opportunities -

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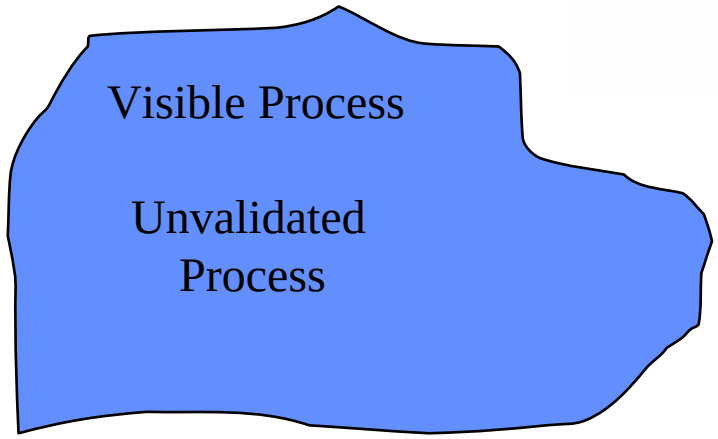
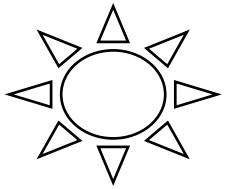
Novartis Switzerland

GMP Conference, 11.06.04, Istanbul

Qualification, Validation, Calibration

Validation/Qualification Iceberg





New System

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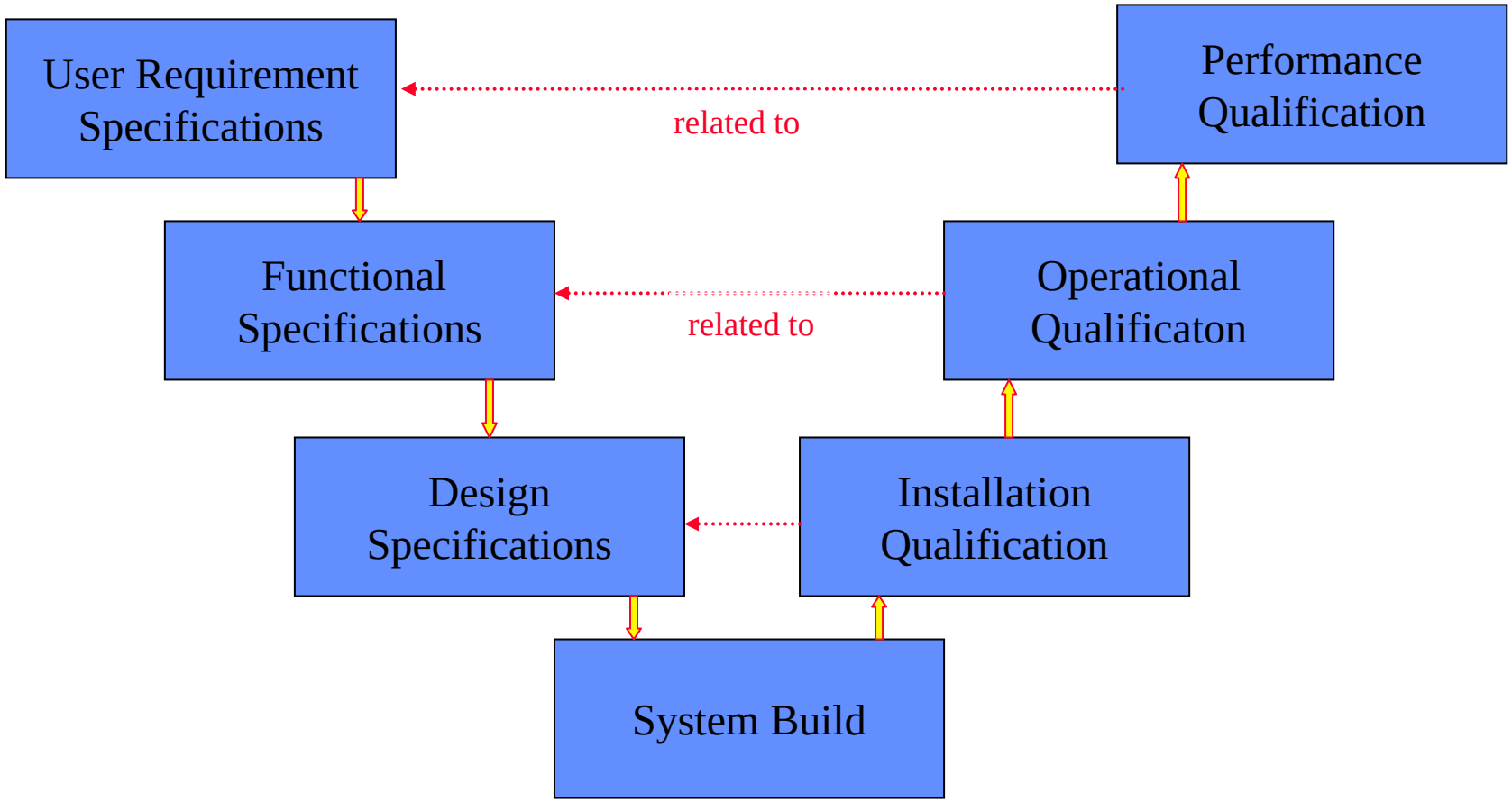
Validation / Qualification Approach



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Quality Risk Assessment in the Pharmaceutical Industry

Risk Assessment has become a key concept in the decision making process of today's pharmaceutical industry. Its impact affects many disciplines including:

- **Engineering**
- Manufacturing
- Project Management
- **Quality**
- Safety
- Environmental

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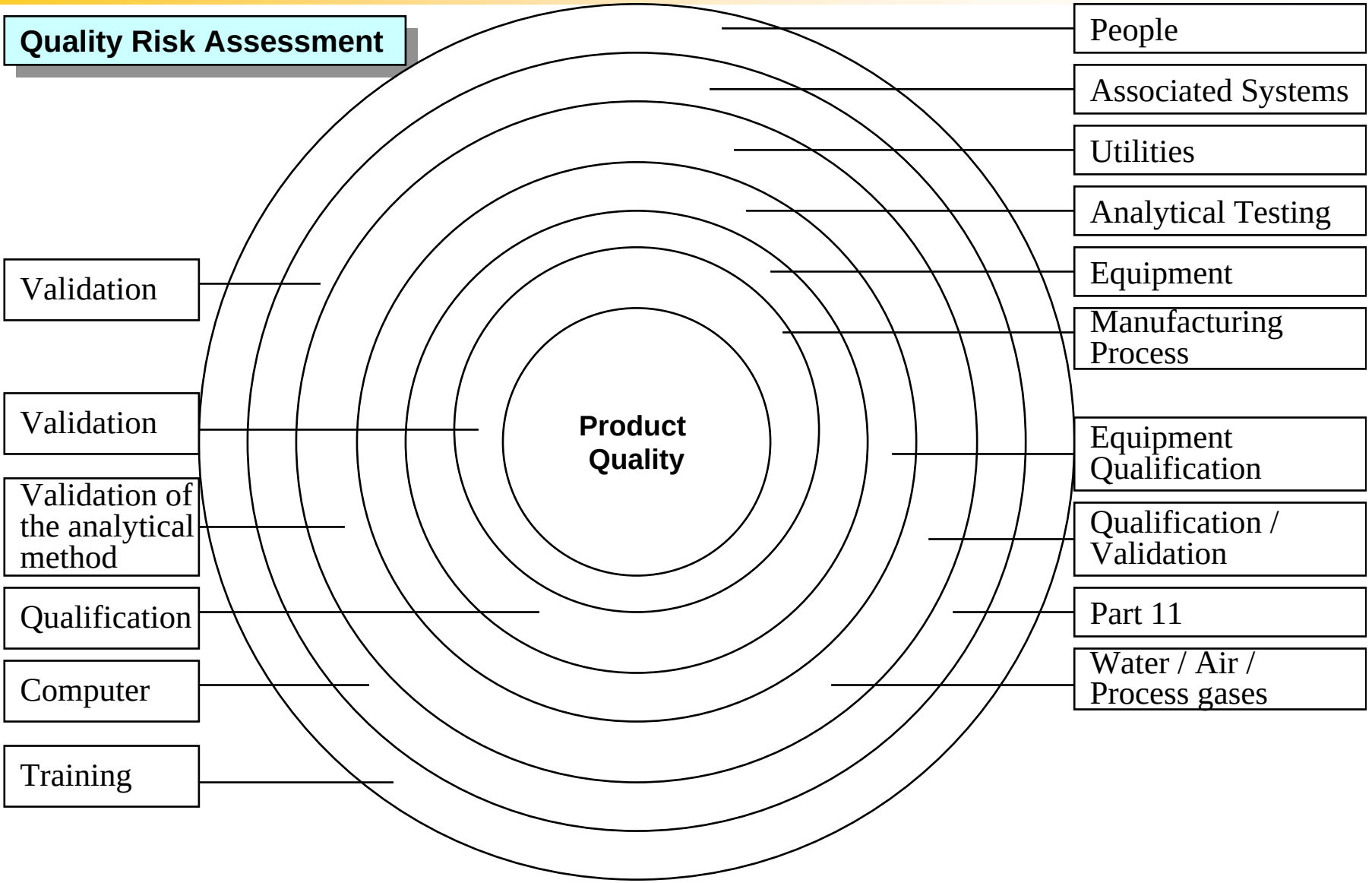
Quality Risk Assessment



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Risk Assessment:

Each step in a process is assessed on its influence on product quality.

- Critical steps have to be validated/qualified
- Uncritical steps → no activities are required

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Equipment Qualification

- User Requirement Specifications (URS)
- Design Qualification
  - Conceptual Design
  - Basic Design
  - Detail Design
- Installation Qualification

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Equipment Qualification

- Operational Qualification
- Performance Qualification
- Calibration and Maintenance Programs
- Retrospective Qualification

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Equipment Qualification

Design Qualification

"Defining the quality parameters required of the equipment and manufacturer"

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Equipment Qualification

Installation Qualification

"Assurance that the intended equipment is received as designed and specified."

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Equipment Qualification

Operational Qualification

"Confirmation that the equipment functions as specified and operates correctly."

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Equipment Qualification

Performance Qualification

“Confirmation that the equipment consistently continues to perform as required”.

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Validation

To prove that a process works is, in a nutshell, what we mean by the verb to validate.

E. Frey, FDA

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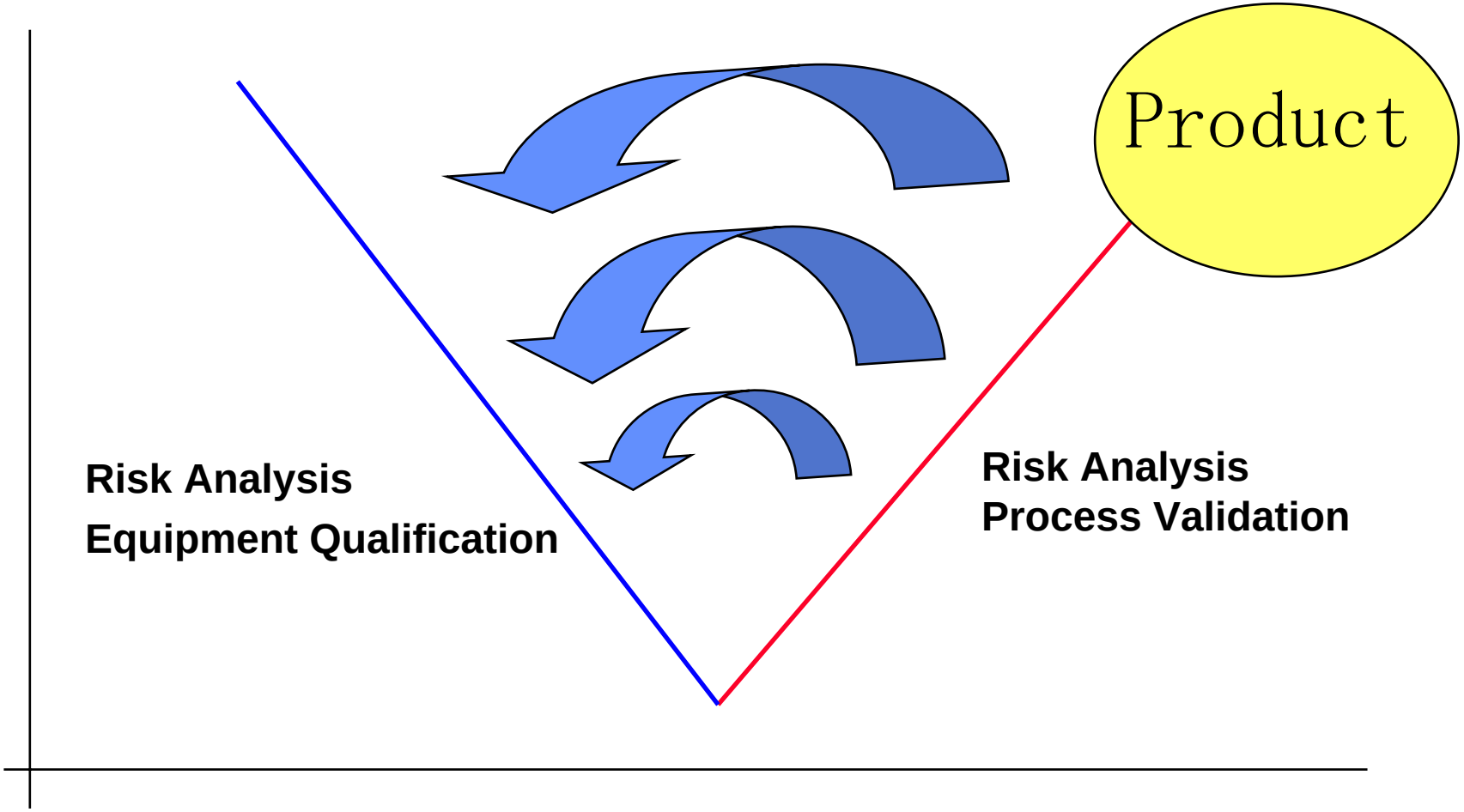
Validation

- Process Validation
- Cleaning Validation
- Computer system Validation
- Validation of Analytical Methods
- Part 11 Compliance

- Risk based approach is key !!!
- Focus on Product, not only on technology

Link between Validation/ Qualification



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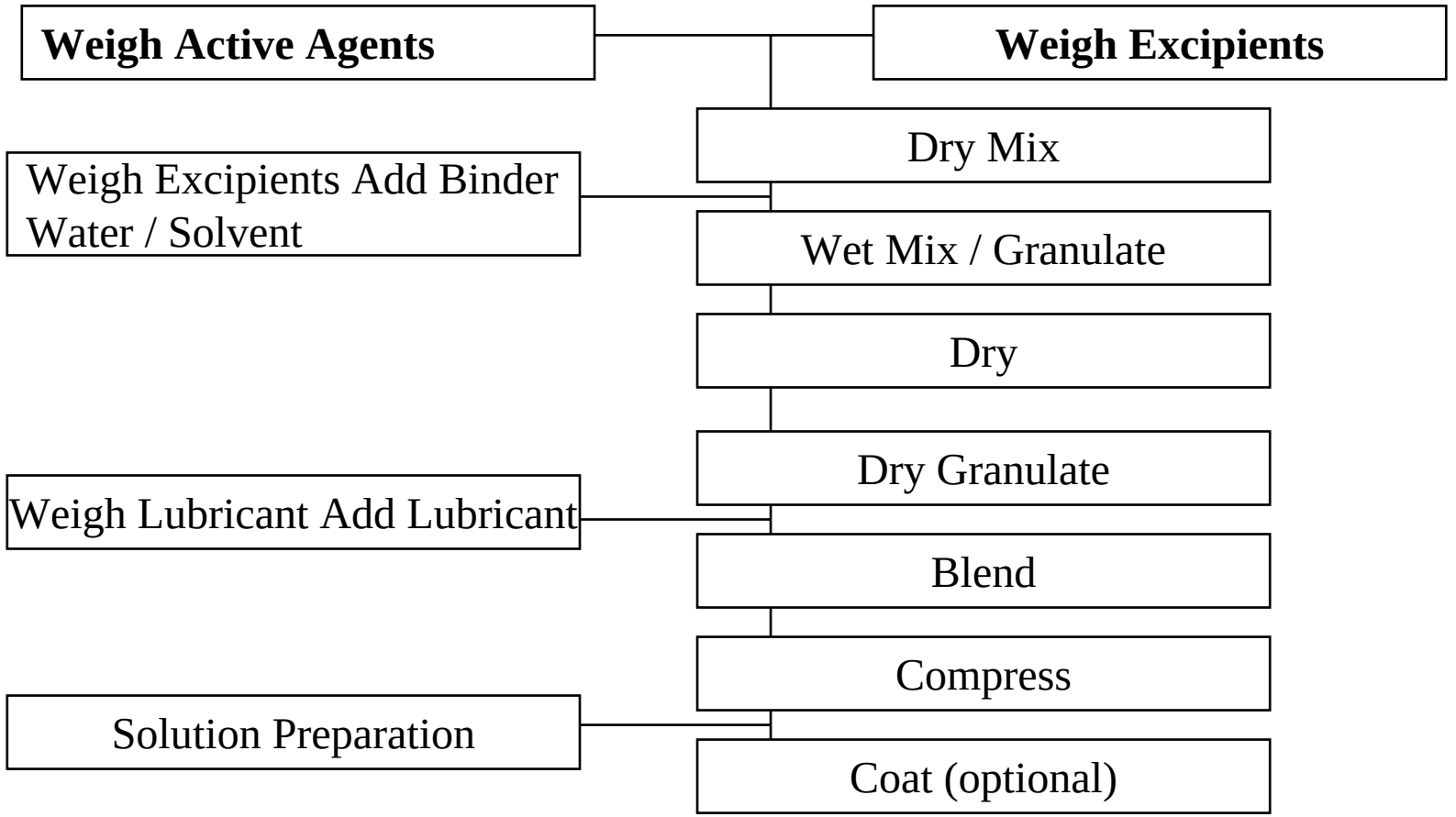
Quality Risk Analysis

Flow Chart for a Solid Dosage Form Process



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Quality Risk Analysis
Key Parameters

Process Stage	Parameter	Worst Case Values
Raw materials	Particle size	Min-Max values
Active agent	Surface area	
Wet mixing	Binder temperature	Target +/- x° C
	Binder volume	Min-Max used in Pilot Scale
	Mixing time	Normal time +/- x minutes
Drying	Granule moisture	Upper-lower in process spec
Blending	Granule particle size	Upper-lower in process spec
Compression	Compressor speed	Normal production range (e.g. 100000/hr-150000/hr)
	Pre-compression pressure	Min-Max
Coating	Inlet air temperature	Target + / - x
	Spray rate	target rate + / - x

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Quality Risk Analysis
Critical Process Parameter

Parameters:	Colette gral mixer Agitator - Speed 2 Chopper - off Mixing time - 5 minutes
Sampling Regimen:	After mixing take 12 samples from the mixing bowl using a sample thief. Samples to be taken 4 top, 4 middle, 4 bottom. Sample to be 300 mg approx.
Testing:	Analyse each sample for active agent content
Acceptance	All individual values to be within + 7 - 10 % of the group Crite mean RSD to be less than 6 %. The mean to be within + 7 - 5 % of the theoretical value

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Solid dosage form

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Tool box
Risk Assessment

- FMEA (= Failure Mode and Effect Analysis)
- HACCP (= Hazard Analysis Critical Control Points)
- FTA (= Failure Tree Analysis)
- System Kepner-Tregoe
  - Analysis of the situation
  - Analysis of the problem
  - Analysis of the decisions
  - Analysis of potential problems

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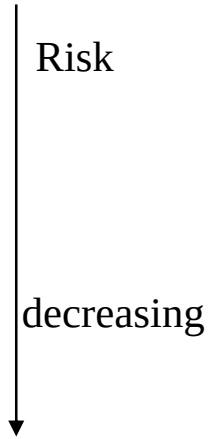
Tool box
Risk Assessment

- FMEA (Failure Mode and Effect Analysis)

→ Define the “Risk Priority number” (- RPN)

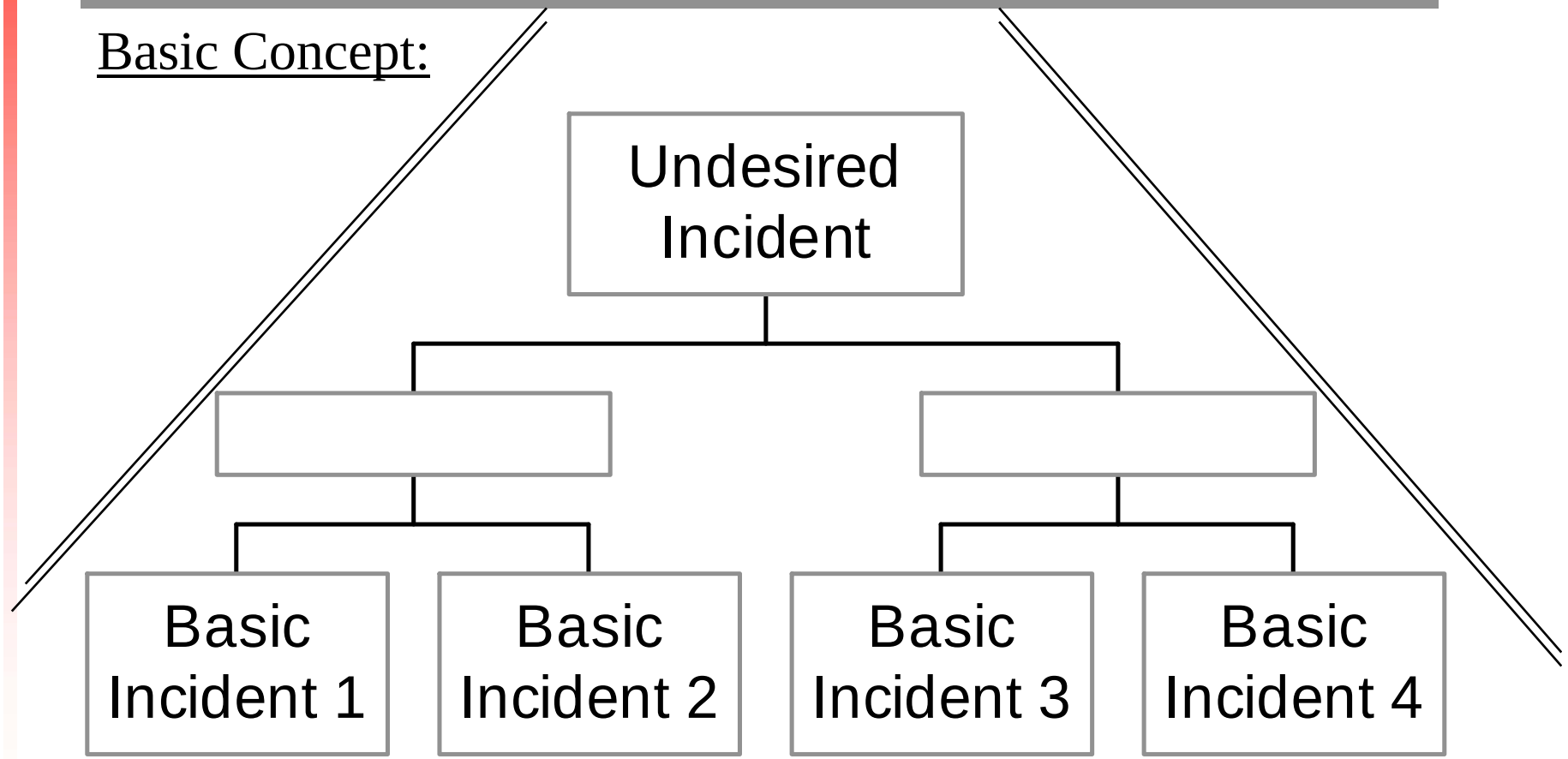
Example: Steam sterilisation Process

- **Steampressure / Temperature in the autoclave**
- **Sterilisation Time**
- **Measures to avoid air in the autoclave**
- **Treatment of the product before and after the process**



FTA (Failure Tree Analysis)

Basic Concept:



Risk Assessment

Key Success Factor:

Training and Skills of people

- Scientific skills
- Broad - Experience in pharmaceutical Industry
- Leadership, Responsibilities

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Change / Deviation

“Change” usually refers to a planned alteration which is documented and considered before implementation. Normally, changes are either permanent or have a fixed period of validity.

“Deviation” represents a change which may occur for a variety of reasons during operations, or may be observed to have happened after the operation.

Normally, deviations are not permanent and represent single events

“Planned Deviations” ??

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Documentation

- Validation Master Plan
- Qualification Master Plan
- GMP Risk Analysis
- Validation Protocol
- Test protocol (including specification)
- Validation Report
- Summary of Deviations / Issues

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Change Management

Who made the change

Why was the change necessary

When was the change implemented

What international consequences arise:

- Risk / benefit assessments
- Cost / benefit assessments
- Regulatory impact

Who gave approvals

Changes are necessary - Uncontrolled changes are dangerous

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Computer Simulations in Conventional Clean Rooms (Sterile Manuf.)

- To be in compliance with all microbiological and particulate requirements, the **design of the sterile facilities** plays the most important role.
- Computer simulation studies of air flows should be used to analyse the most critical areas.
- Detailed analysis was made with regard to conflicting areas of class 10`000 and critical class 100 areas in order to prevent any possible contamination of the product.
- Detailed qualification of the balance is a prerequisite for a successful implementation of these design concepts.

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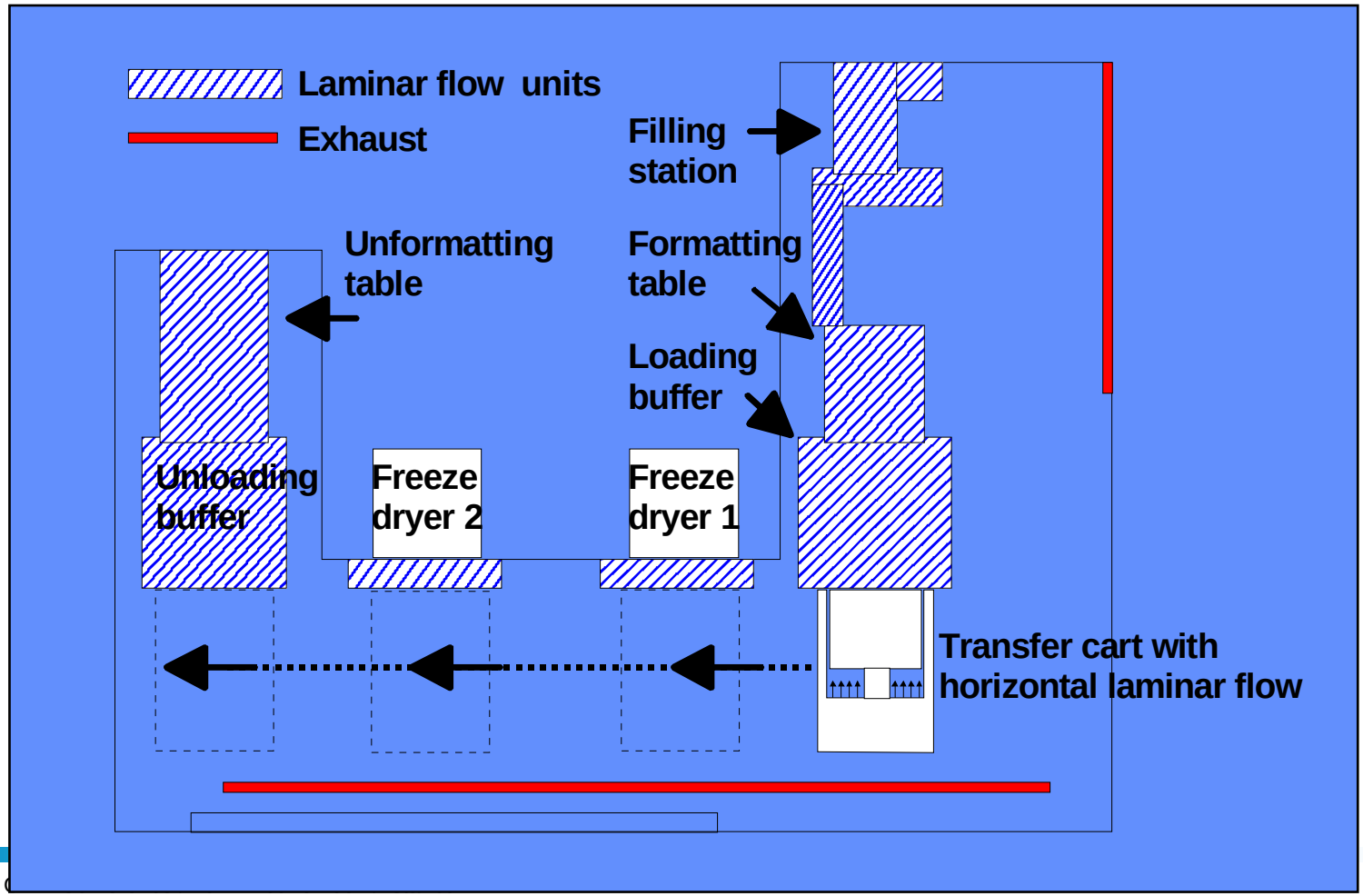
Initial Air Handling Design

Picture shows air inlets (units) and air exhaust systems



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Improved Air Handling Design

Picture shows new and modified air inlets (LF units) and air exhaust systems