Supplementary Training Modules on Good Manufacturing Practice

Validation

WHO Technical Report Series, No. 937, 2006. Annex 4.

World Health Organization

Validation

- Part 1. General overview on qualification and validation
- Part 2. Qualification of HVAC and water systems
- **Part 3. Cleaning validation**
- Part 4. Analytical method validation
- Part 5. Computerized system validation
- Part 6. Qualification of systems and equipment
- Part 7. Non sterile product process validation

Cleaning Validation

Part 3

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Validation

Objectives

To discuss principles and approaches to cleaning validation including:

- Protocols and reports
- Personnel and equipment
- Use of detergents
- Microbiology
- Sampling
- Analytical methods and
- Acceptable limits

Validation

Principle

- The objectives of GMP include prevention of possible contamination and cross-contamination
- Contamination by a variety of substances
  - *contaminants (e.g. microbes, previous products (both API and excipient residues), residues of cleaning agents, airborne materials (e.g. dust and particulate matter), lubricants and ancillary material, such as disinfectants*
- Also decomposition residues from product or detergents

1.1 – 1.2

Validation

Principle (2)

- Adequate cleaning procedures important
- Documented evidence needed - cleaning procedure will provide clean equipment, suitable for intended use.
- What is the objective of cleaning validation?
  - *product, detergent and microbial residues*
  - *prevent possible contamination and cross-contamination*

1.3 – 1.4

Validation

Principle (3)

- Where is cleaning validation required?
  - *Not necessarily for non-critical cleaning, e.g. between batches of the same product (or different lots of the same intermediate in a bulk process), or of floors, walls, the outside of vessels, and following some intermediate steps.*
  - *Considered important in multiproduct facilities - should be performed, e.g. for equipment, sanitization procedures and garment laundering.*

1.5 – 1.6

Validation

Scope

- Guidelines: General aspects of cleaning validation
- Excluding specialized cleaning or inactivation
  - *e.g. for removal of viral or mycoplasmal contaminants in the biological manufacturing industry.*
- Normally cleaning validation needed for critical cleaning, e.g.
  - *between manufacturing of one product and another*
  - *contact surfaces (products, drug products and API).*

2.1 – 2.2

Validation

General

- Written SOPs for cleaning processes – validated
- Cleaning policy and cleaning validation procedure to cover:
  - *contact surfaces;*
  - *cleaning after product changeover;*
  - *between batches in campaigns;*
  - *bracketing products for cleaning validation; and*
  - *periodic evaluation and revalidation of the number of batches manufactured between cleaning validations.*

3.1 – 3.2

Validation

General (2)

- The company has to prove consistency
- What are the variables when a cleaning procedure is followed?
- How many consecutive applications of the cleaning procedure should be performed?
- Training of personnel

3.3, 5.1

Validation

Cleaning validation protocols

- Approved by QC or QA and to cover, e.g.
  - *disassembly of system;*
  - *pre-cleaning;*
  - *cleaning agent, concentration, solution volume, water quality;*
  - *time and temperature;*
  - *flow rate, pressure and rinsing;*
  - *complexity and design of the equipment;*
  - *training of operators; and*
  - *size of the system.*

4.1.1 – 4.1.2

Validation

Cleaning validation protocols (2)

- The cleaning validation protocol should include:
  - *objectives, responsible people;*
  - *description of the equipment including the make, model, serial number or other unique code;*
  - *time intervals; bioburden; cleaning procedures;*
  - *equipment used for routine monitoring (e.g. conductivity meters, pH meters and total organic carbon analysers);*
  - *number of cleaning cycles; sampling procedures (e.g. direct sampling, rinse sampling, in process monitoring and sampling locations) and the rationale for their use*

4.1.3

Validation

Cleaning validation protocols (3)

- The cleaning validation protocol should include (2):
  - *data on recovery studies (efficiency of the recovery of the sampling technique should be established);*
  - *analytical methods;*
  - *acceptance criteria (with rationale for setting the specific limits) including a margin for error and for sampling efficiency;*
  - *cleaning agent to be used;*
  - *revalidation requirements.*

4.1.3

Validation

Cleaning validation protocols (4)

- Cleaning agent used, scientifically justified and based on:
  - *the solubility of the materials to be removed;*
  - *the design and construction of the equipment and surface materials to be cleaned;*
  - *the safety of the cleaning agent;*
  - *the ease of removal and detection;*
  - *the product attributes;*
  - *the minimum temperature and volume of cleaning agent and rinse solution; and*
  - *the manufacturer's recommendations*

4.1.3

Validation

Cleaning validation protocols (5)

Bracketing:

- Very similar cleaning procedures for products and processes - no need for individual validation. “Worst case” may be acceptable and should be justified.
- Consider type of products and equipment; allowed only where products are similar in nature or property and processed on the same equipment; and identical cleaning procedures used.

4.1.4 – 4.1.6

Validation

Cleaning validation protocols (6)

Bracketing:

- Representative product - most difficult to clean.
- Equipment - only when it is similar or the same equipment in different sizes (e.g. 300 l, 500 l and 1000 l tanks).
  - *Alternative approach may be to validate the smallest and the largest sizes separately.*

4.1.7 – 4.1.8

Validation

Cleaning validation reports

- The relevant cleaning records – (***signed* by the operator, *checked* by production and *reviewed* by quality assurance) – and source data (original results)** should be kept.
- The results of the cleaning validation should be presented in cleaning validation reports stating the ***outcome and conclusion.***

4.2.1

Validation

Equipment

- Cleaning of contact surfaces to be validated, with consideration to “non-contact” parts. Critical areas should be identified.
- Dedicated equipment for:
  - *products which are difficult to clean,*
  - *equipment which is difficult to clean,*
  - *products with a high safety risk where it is not possible to achieve the required cleaning acceptance limits using a validated cleaning procedure.*

6.1– 6.2

Validation

Equipment (2)

- If one SOP for cleaning a piece of equipment, review:
  - *products being produced,*
  - *cleaning in a large campaign,*
  - *cleaning between batches of different products.*
- The design of equipment may influence the effectiveness of the cleaning process.
- Consider design, e.g. V-blenders, transfer pumps or filling lines.

6.3 – 6.4

Basic Principles of GMP

- Which are the critical areas for sampling?
- What would be considered an appropriate approach for cleaning validation for this piece of equipment?

Basic Principles of GMP

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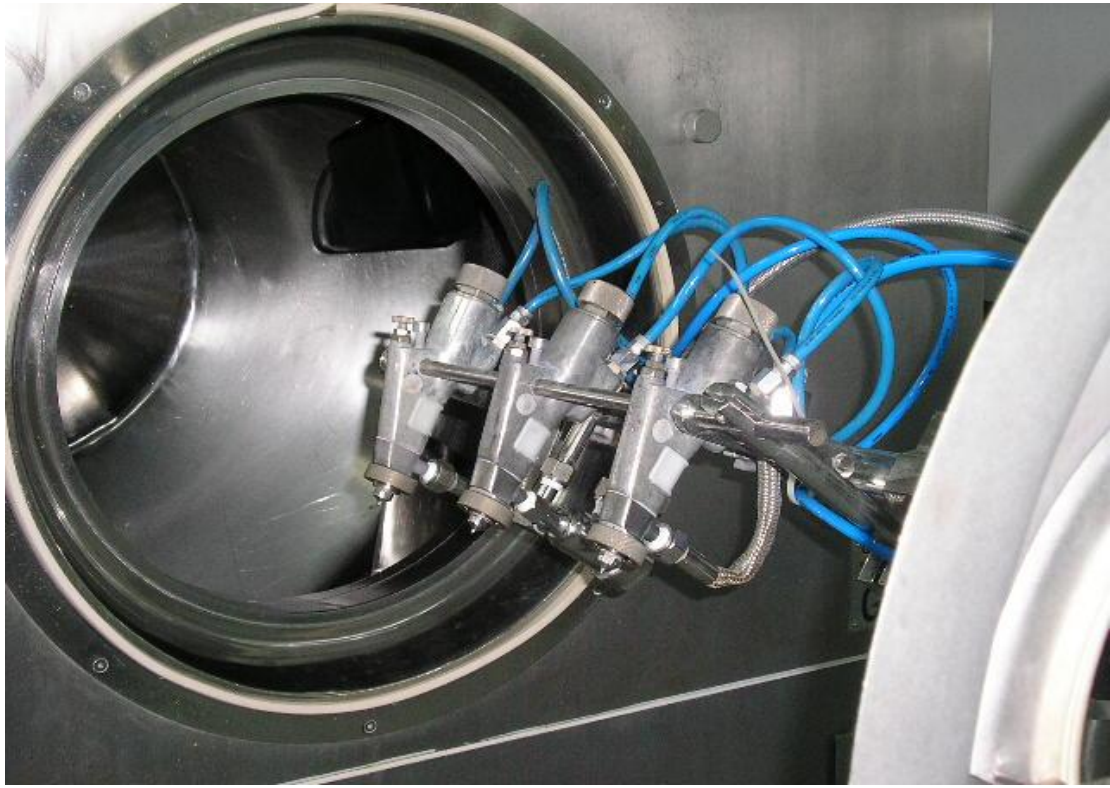


Validation

Detergents

- Released by quality control and meet food standards or regulations
- Composition known
- Easily removed with rinsing - demonstrated - with acceptable limits defined
- If persistent residues (e.g. cationic detergents) - avoided
- Consider also detergent breakdown

7.1 – 7.4

Validation

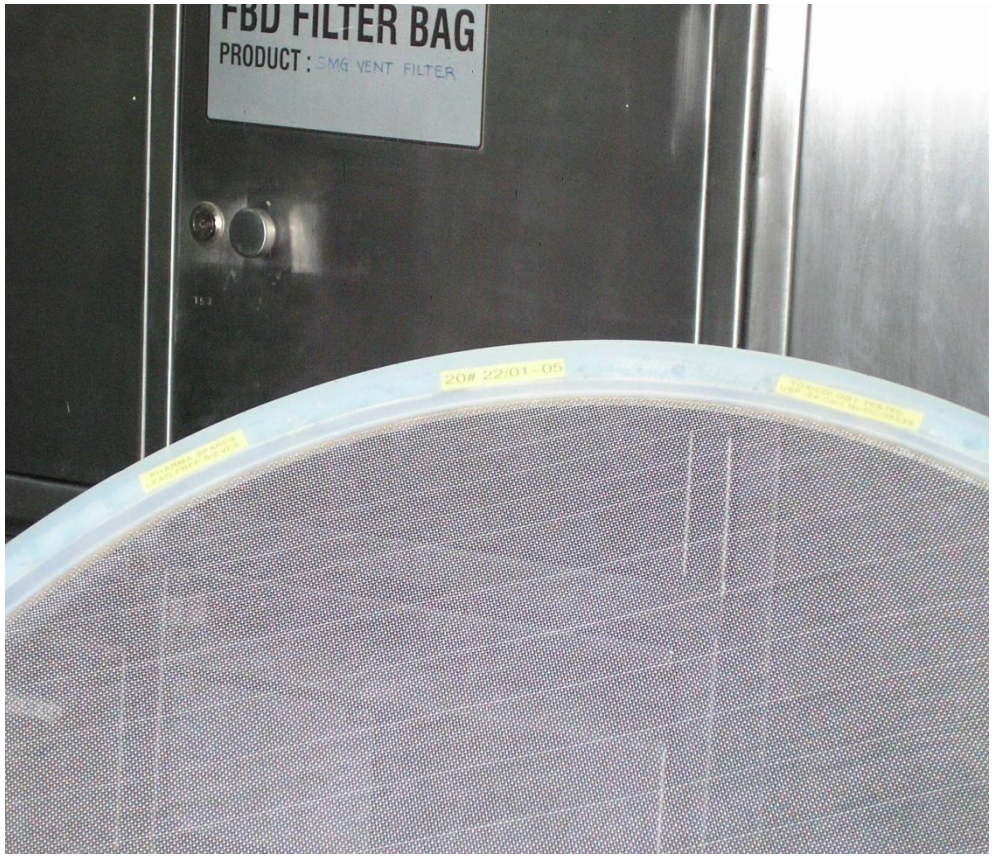
Microbiology

- Prevent microbial growth and remove contamination
- Documented evidence
  - *routine cleaning*
  - *storage of equipment*
- The period and conditions
  - *storage of unclean equipment before cleaning*
  - *between cleaning and equipment reuse*
- Equipment stored in a dry condition after cleaning (no stagnant water)
- Control of bioburden important

8.1 – 8.5

Basic Principles of GMP

- What is important about cleaning validation for components/ parts of equipment?
- Consider also the different materials, e.g. stainless steel contact surfaces, silicon seals and others



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Validation

Sampling (General)

- Clean as soon as possible after use
  - *especially topical products, suspensions and bulk drug or*
  - *where the drying of residues will directly affect the efficiency of a cleaning procedure*
- Two methods of sampling:
  - *direct surface sampling and*
  - *rinse samples*
- Combination of the two - most desirable

9.1.1 – 9.1.2

Validation

Sampling (General) (2)

- Re-sampling:
  - *not to be done before or during cleaning*
- Constant re-testing and re-sampling:
  - *can show that the cleaning process is not validated*
  - *may indicate presence of unacceptable residue and contaminants resulting from an ineffective cleaning process*

9.1.3

Validation

Direct surface sampling (direct method)

- Most commonly used method
- Use “swabs” (inert material) - type of sampling material should not interfere with the test
- Factors to be considered include:
  - *supplier of the swab,*
  - *area swabbed, number of swabs used, whether they are wet or dry swabs,*
  - *swab handling and swabbing technique*

9.2.1

Validation

Direct surface sampling (direct method) (2)

- Other factors include:
  - *location from which the sample is taken (including worst case locations, identified in the protocol)*
  - *composition of the equipment (e.g. glass or steel)*
- Critical areas (hardest to clean)
  - *e.g. in semi-automatic/fully automatic clean-in-place systems*
- Use appropriate sampling medium and solvent

9.2.2 – 9.2.4

Validation

Rinse samples (indirect method)

- Allows sampling of:
  - *a large surface*
  - *areas that are inaccessible or that cannot be routinely disassembled*
- Provides an "overall picture"
- Useful for checking for residues of cleaning agents
- In combination with other sampling methods such as surface sampling

9.3.1

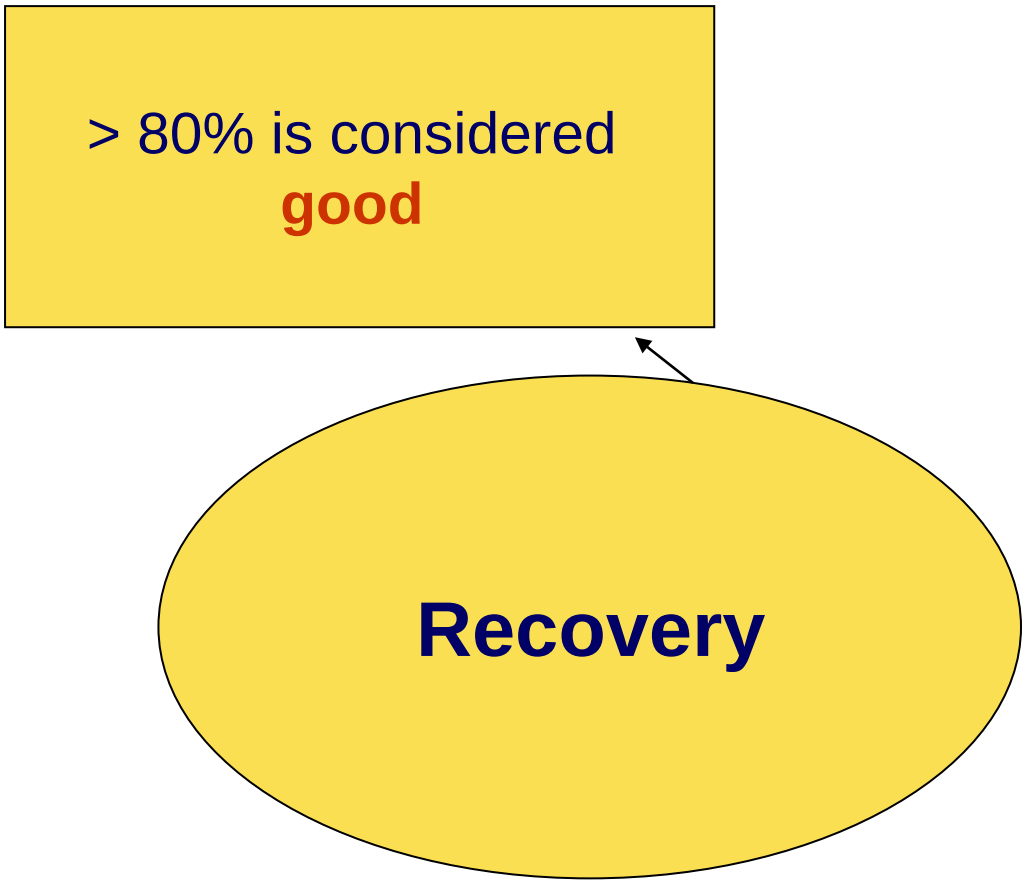
Validation

Rinse samples (indirect method) (2)

- The manufacturer has to provide evidence that samples are accurately recovered
- What is considered acceptable in terms of recovery?

9.3.2

Validation



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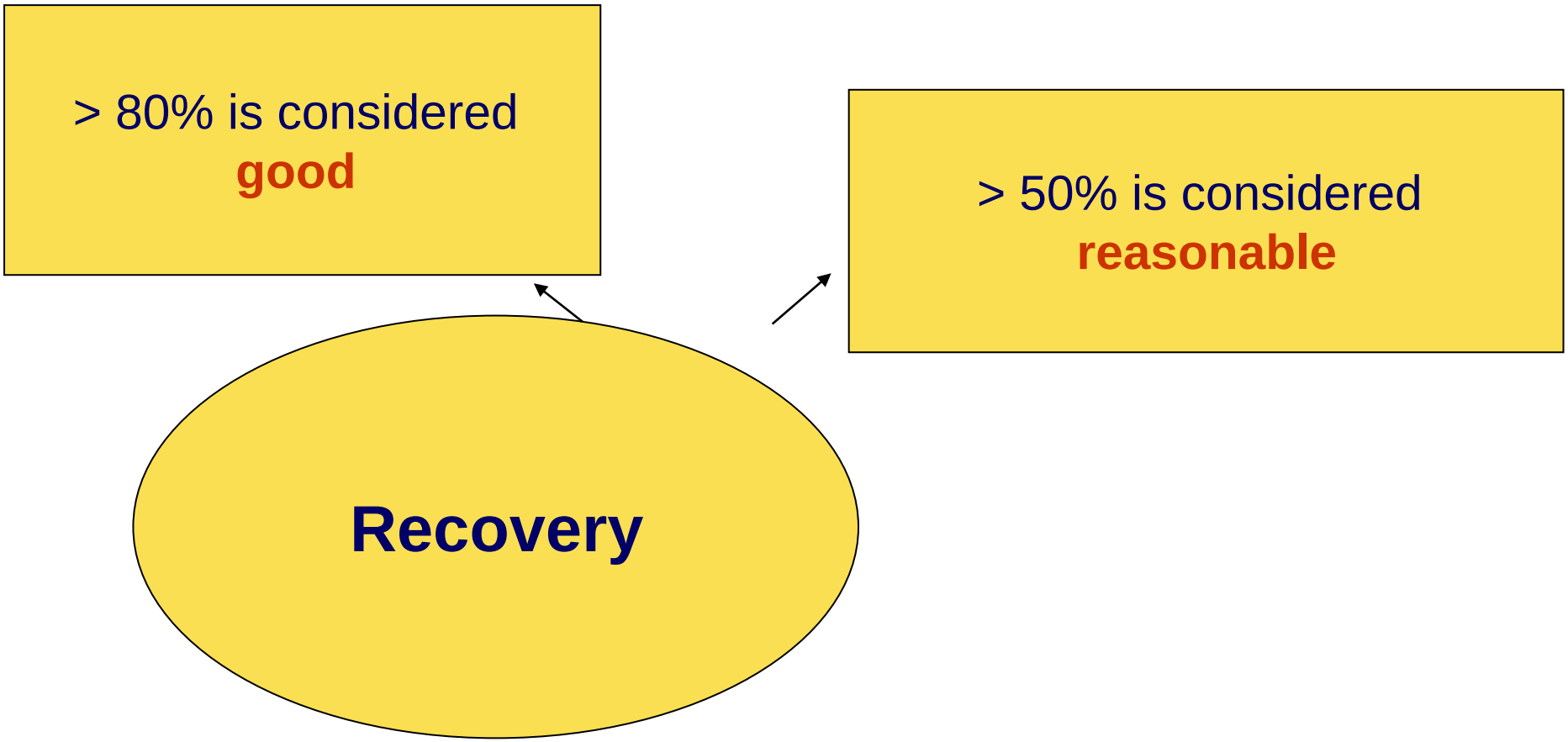
Validation



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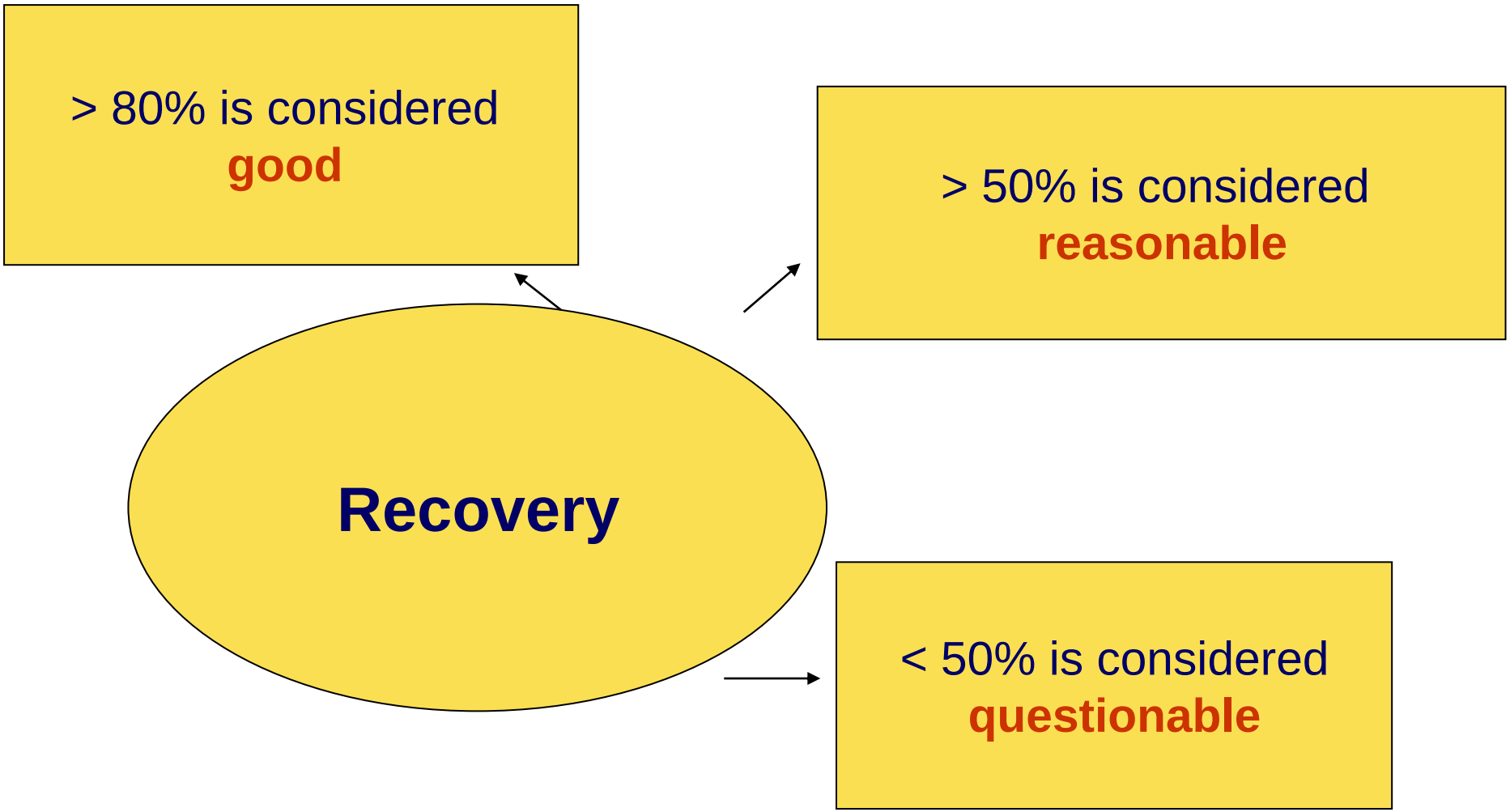
Validation


> 80% is considered
good
> 50% is considered
reasonable
Recovery
< 50% is considered
questionable

Validation

Batch placebo method

- A placebo batch is manufactured and checks are done for carry-over of the previous product
  - *Expensive and laborious process*
  - *Little assurance that the contaminants are dislodged*
  - *Particles not necessarily uniformly dispersed*
  - *Method used in conjunction with rinse and/or surface sampling method(s)*
  - *Samples taken throughout the process of manufacture*
  - *Sensitivity of the assay may be greatly reduced by dilution of the contaminant*

9.4

Validation

Analytical methods

- Validated analytical methods – able to detect residuals or contaminants:
  - *specific for the substance(s) being assayed*
  - *at an appropriate level of cleanliness (sensitivity)*

- Sensitive and specific - may include:
  - *chromatographic methods (e.g. high pressure liquid chromotography (HPLC), gas chromotography (GC), and high pressure thin-layer chromatography (HPTLC)). Others include (alone or in combination), e.g. total organic carbon (TOC), pH, conductivity, ultraviolet (UV) spectroscopy, and ELISA*

10.1, 10.2, 10.5

Validation

Analytical methods (2)

- Validation of the analytical method should include, e.g.
  - *precision, linearity and selectivity (the latter if specific analytes are targeted);*
  - *limit of detection (LOD);*
  - *limit of quantitation (LOQ);*
  - *recovery, by spiking with the analyte; and*
  - *reproducibility*
- Detection limit (sufficiently sensitive) to detect the established acceptable level of residue / contaminants

10.3 – 10.4

Validation

Establishing acceptable limits

- Limits: Practical, achievable and verifiable
- Rationale: Logical, based on knowledge of materials
- Each situation assessed individually
- Principal reactant **and** other chemical variations
- Screening (thin-layer chromatography) in addition to chemical analyses where necessary

11.1 – 11.3

Validation

Establishing acceptable limits (2)

There should be no residue from:

- Previous product
- Reaction by-products and degradants
- Cleaning process itself (e.g. detergents or solvents)

Remember: Uniform distribution of contaminants is not guaranteed

11.4

Validation

Establishing acceptable limits (3)

- The limit-setting approach can:
  - *be product-specific*
  - *group products into families and choose a worst case product*
  - *group products into groups according to risk, e.g. very soluble products, products with similar potency, highly toxic, or difficult to detect products*
  - *use different safety factors for different dosage forms based on physiological response (this method is essential for potent materials)*

11.5

Validation

Establishing acceptable limits (4)

- Limits may be expressed as:
  - *a concentration in a subsequent product (ppm),*
  - *limit per surface area (mcg/cm²), or*
  - *in rinse water as ppm.*
- Limits for carry-over of product residues should meet defined criteria.
- What are the three most commonly used criteria?

11.6 – 11.8

Validation

Establishing acceptable limits (5)

- The three most commonly used criteria are:
  - ***Visually clean*** *No residue visible on equipment after cleaning. Spiking studies to determine the concentration at which most active ingredients are visible. (May not be suitable for high potency, low-dosage drugs.)*
  - ***No more than 10 ppm*** *of one product will appear in another product (basis for heavy metals in starting materials).*
  - ***No more than 0.1%*** *of the normal therapeutic dose of one product will appear in the maximum daily dose of a subsequent product.*

11.9

Validation

Establishing acceptable limits (6)

- The most stringent of three options should be used
- Certain *allergenic ingredients* and *highly potent material* should be *undetectable by the best available analytical methods*
  - *e.g. penicillins and cephalosporins*
  - *e.g. anovulent steroids, potent steroids and cytotoxics*
- Dedicated manufacturing facilities needed

11.10 – 11.11

Validation

- Group session