

Istanbul June 1, 2001

## Cleaning Validation

Istanbul, Turkey  
June 1, 2001

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Istanbul June 1, 2001

## Aventis Pharma

**allegra**  
fexofenadine HCl 60 mg

**Exubera™** Inhaled Insulin

**LOVENOX® CLEXANE®**  
enoxaparin sodium

**Actonel™**  
(risedronate sodium)

**Ketek®**  
TELITHROMYCIN

**TAXOTERE®**  
(docetaxel)

**LANTUS®**  
insulin glargine

## Table of Contents for Presentation:

- \* Introduction- Summary of Regulations
- \* Cleaning Validation Program Overview
- \* Methods Validation
- \* Acceptance Criteria
- \* Sampling Techniques
- \* Protocol Execution
- \* The Required SOP's
- \* Documentation Content and format

## Cleaning Validation - Why do you need a Program ?



The FDA requirement for equipment to be cleaned prior to usage was first published in the 1963 GMP Regulations (Part 133.4) and once again in the 1978 cGMP Regulations (Part 211.67).

**Equipment should be cleaned to prevent contamination that would alter the safety, identity, strength, quality, or purity of the drug product.**

The Rules Governing Medicinal Products in the European Community (Chapter 5, Production) also reinforces the importance of cleaning:

**Before any processing operation is started, steps should be taken to ensure that the work area and equipment are clean and free from any starting materials, products, product residues or documents not required for the current operation.**

## Cleaning Validation - Why do you need a Program ?



The FDA "Guide to Inspection of Validation of Cleaning Processes", published in July 1993 requires:

**There should be written procedures (SOPs) detailing the cleaning processes for various pieces of equipment.**

**There should be written general procedures on how cleaning processes will be validated.**

**The general validation procedures should address who is responsible for performing and approving the validation study, the acceptance criteria, and when revalidation will be required.**

## Cleaning Validation - Why do you need a Program ?



The FDA "Guide to Inspection of Validation of Cleaning Processes", published in July 1993 requires:

**There should be specific validation protocols written in advance for the studies to be performed on each manufacturing system or piece of equipment which should address such issues as sampling procedures, and analytical methods to be used including the sensitivity of those methods.**

**The validation studies should be conducted in accordance with the protocols and the results of the studies should be documented.**

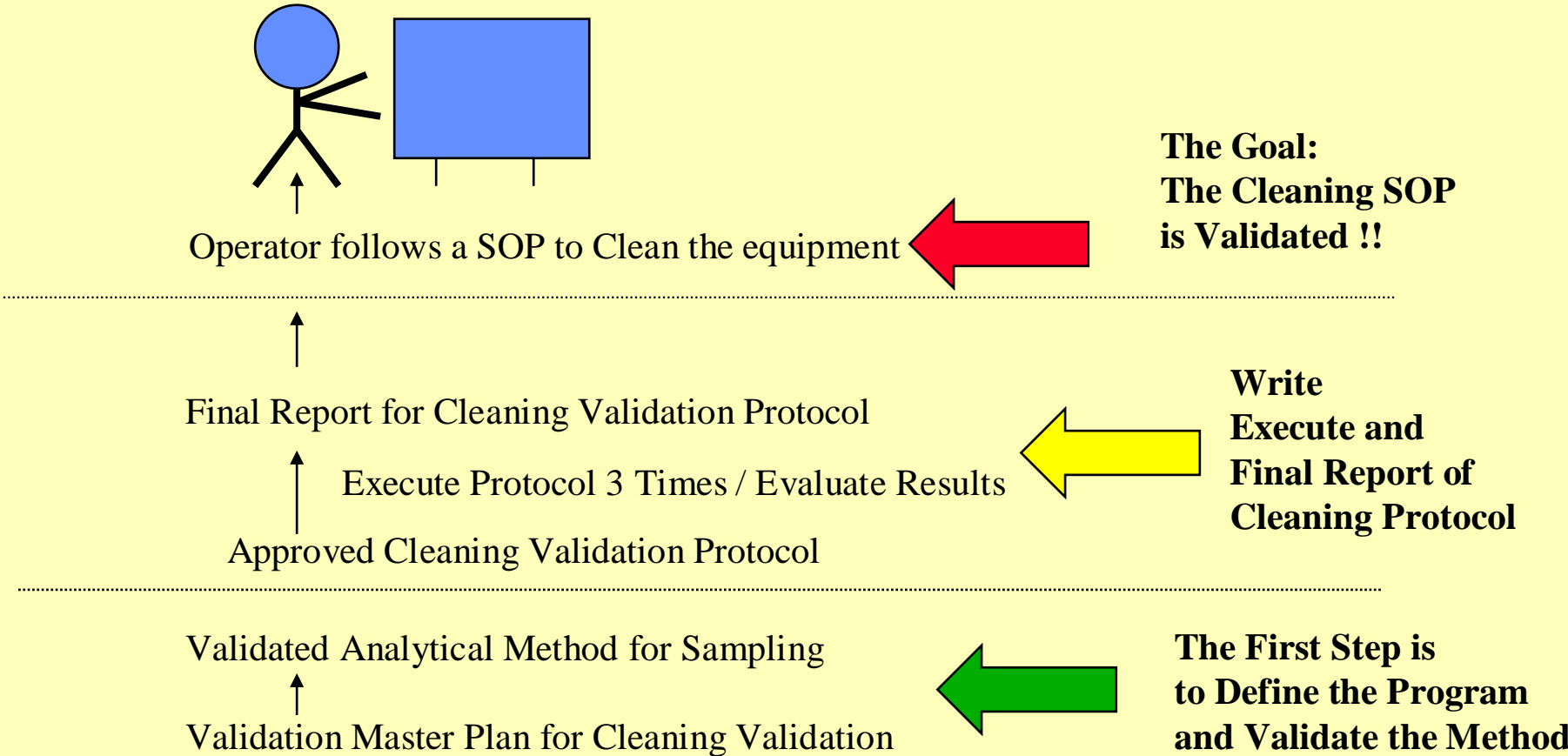
**There should be a final validation report which is approved by management and which states whether or not the cleaning process is valid. The data should support a conclusion that residues have been reduced to an acceptable level.**



## **FDA & EP Expectations :**

- \* Written procedures (SOPs) detailing the cleaning processes used for various pieces of equipment.
- \* Written general procedures on how cleaning processes will be validated.
- \* General validation procedures to address who is responsible for performing and approving the validation study, the acceptance criteria, when revalidation will be required and a final report approved by management.

**OVER VIEW OF A CLEANING VALIDATION PROGRAM**

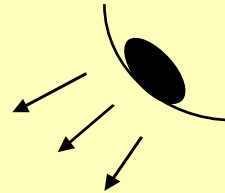




## BASIC PHILOSOPHY OF CLEANING VALIDATION

Cleaning must be performed according to a documented cleaning procedure. Evaluation of the effectiveness of the cleaning procedure must be performed by evaluating:

Qualitatively (visual)



Quantitatively (microbial bioburden as appropriate, residual drug, and cleaning agent levels)

## **BASIC PHILOSOPHY OF CLEANING VALIDATION**

A protocol to document the cleaning validation process must be written and executed a replicate number of times.

Once a cleaning procedure is validated, it comes under change control.

Equipment should be cleaned according to the validated cleaning procedure, or further cleaning validation is required.

## METHODOLOGY

The primary concerns are the active drug substances and the cleaning agents. Excipients are not considered critical contaminants.

The two categories of targeted substances remaining on product contact surfaces are:

Chemical : 1) Actives 2) Excipients and 3) Cleaning Agents

Microbial

## ***Method Validation - General Concepts***

The criteria stated in CFR 211.194(a) were originally intended for validation of methods used for testing pharmaceutical products. Typical analytical parameters that should be considered in the validation of all analytical methods are :

- |                |                          |
|----------------|--------------------------|
| 1) Accuracy    | 4) Linearity             |
| 2) Precision   | 5) Limit of Quantitation |
| 3) Specificity | 6) Range                 |

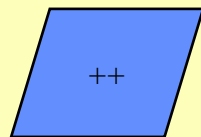
## ***Cleaning Method Specificity***

A key parameter for cleaning validation methodology is obtaining maximum recovery from the selected solvent (or diluent) and swab combination. This process may entail several factors, for example:

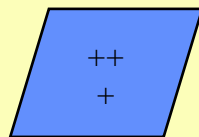
- Selection of Cleaning solvent
- Selection of Diluent
- Selection of Swab material
- Selection of Extraction solvent

## Chemical Recovery from Spiked Swabs:

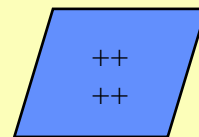
The recovery obtained from spiked swabs should be determined by spiking the swabs minimally at four concentrations across the range of approximately 50% - 125% of the targeted concentration.



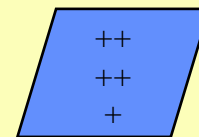
50%



75%



100%



125%

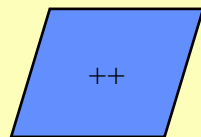
## **Chemical Recovery from Spiked Swabs:**

The recovery from the spiked swab is determined separately from the spiked plate in order to give an indication of the efficiency of the solvent versus swabbing process.

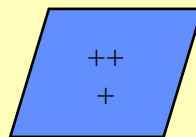
A guideline for recovery from a spiked swab should be 90% or greater to insure an acceptable recovery from the spiked plate.

## Recovery from Spiked Plates / "Coupons"

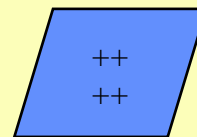
The recovery obtained from spiked plates should be determined similarly to the spiked swabs. At least four concentrations across the range of approximately 50% - 125% of the targeted concentration should be used.



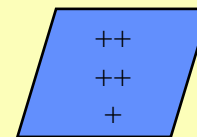
50 %



75%



100%



125%



## Recovery from Spiked Plates / "Coupons"

A guideline for recovery from a spiked plate should be greater than 75% to insure that an accurate representation of the surface cleanliness is obtained.

**Micro Recovery from Spiked Swabs  
and Plates / "Coupons"**

For microbial recovery, sufficient microorganisms should be seeded to allow recovery and may vary depending on both the microorganism and method used.

Generally, recoveries using direct contact plates is greater than for swabbing or rinse methods.

## ***Cleaning Method Stability Issues***

### **Surface "Aging":**

For chemical analysis, the length of time after cleaning of process equipment in which swabbing must occur should be determined.

### **Swab "Aging":**

The length of time in which the swabs must be extracted should be determined.

## ***Reporting Results***

### **Quantity Per Defined Area:**

All results which are obtained should be calculated relative to a defined swab area. This allows further calculation relative to the entire process train of equipment.

For microbial bioburden testing, results should be reported as CFU (colony forming units) per defined area or test. For contact plates and swabs, results expressed as CFU / 25 cm<sup>2</sup>, or for rinse samples CFU / mL, are typical.

## ACCEPTANCE CRITERIA

The FDA does not set specific acceptance specifications for residue levels due to the great variety of equipment, processes, and products in the pharmaceutical industry.

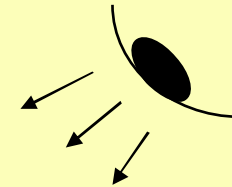
The FDA Cleaning Guideline states:

”The firm’s rationale for the residue limits established should be logical based on the manufacturer’s knowledge of the materials involved and be practical, achievable, and verifiable.”

## ***Active Drug Substances & Cleaning Agent Criteria***

The acceptance criteria for Active Drug Substances and Cleaning Agents consist of two major components:

1) Qualitative, that being visually clean.



2) Quantitative analysis.

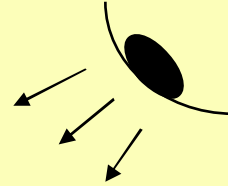
## ***Active Drug Substances & Cleaning Agent Criteria***

The requirements for these two components:

- 1) Qualitative, that being visually clean.
- 2) Quantitative analysis.

Must be met on a minimum of three separate, consecutive executions of a cleaning validation protocol for the cleaning process to be considered validated.

## Visually Clean



Visual inspection after cleaning must be performed and documented. The requirement for this component applies to all product contact surfaces of any equipment that has been cleaned and dried.

The requirement is that the surfaces of the equipment must be inspected, to the extent possible, to verify that they are clean and free of any visible residue or film.



## **Analytically Clean for Active**

The requirement for this component applies to all product contact surfaces of any equipment that has been cleaned and dried. The requirement is composed of two elements:

- 1) The average active drug residual test results of all samples per each major piece of equipment must be:
  - Standard therapeutic dosage drug actives  
Not more than 100 micrograms per 100 cm<sup>2</sup>
  - Low therapeutic dosage drug actives  
Not more than 10 micrograms per 100 cm<sup>2</sup>

## **Analytically Clean for Active**

- 2) The individual active drug residual test result must be:
- Standard therapeutic dosage drug actives  
Not more than 200 micrograms per 100 cm<sup>2</sup>
  - Low therapeutic dosage drug actives  
Not more than 20 micrograms per 100 cm<sup>2</sup>

## Analytically Clean for Cleaning Agent

The follow two requirements apply to all product contact surfaces that have been cleaned and dried.

- 1) The average cleaner residual test results of all samples per each major piece of equipment must be:
  - Standard LD 50 cleaning agents  
Not more than 200 micrograms per 100 cm<sup>2</sup>
  - Low LD 50 cleaning agents  
Not more than 100 micrograms per 100 cm<sup>2</sup>

## Analytically Clean for Cleaning Agent

2) The individual cleaner residual test result must be:

- Standard LD 50 cleaning agents  
Not more than 400 micrograms per 100 cm<sup>2</sup>
- Low LD 50 cleaning agents  
Not more than 200 micrograms per 100 cm<sup>2</sup>

## ***Sampling Techniques***

Swabbing and rinse sampling are the two primary means of sampling which are used for cleaning validation sampling.

Swabbing techniques involve the use of a swabbing material, often saturated with a solvent, to physically sample the surfaces.

Rinse sampling involves passing a known volume of solution over a large area and analyzing the recovered solution.

## ***Sampling Techniques***

The use of swabs to remove/collect residual samples has become a widely accepted procedure. It is the "preferred" technique by most regulatory agencies as compared to "rinse" samples.

The swabbing technique allows direct surface analysis of "hard to clean" or "hot spot" areas.

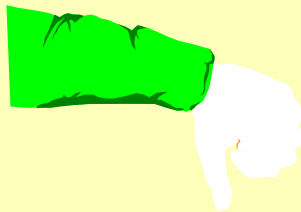
## **Sampling Responsibility:**

The personnel performing the sampling operation ,  
in particular swab sampling, need to be "qualified".

There should be documented training and data to  
demonstrate the ability of the samplers to follow the  
sampling instructions.

## Swabbing Technique Uniformity:

The swabbing method needs to be very efficient, reproducible, and documented.



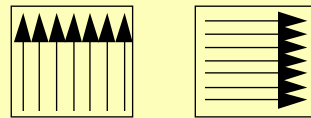
A "random rub" method is usually not reproducible.



## Swabbing Technique Uniformity:

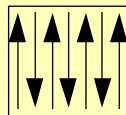
The "Squeegee Method" has been demonstrated to meet this criteria. This method entails passing the swab over a defined area in two different directions, first from top to bottom and then from side to side. The swab dimensions should be assumed to be 10cm x 10cm, unless otherwise specified.

Swab Method



First  
Second  
"Squeegee Method"

or



## Microbiological Sampling

To evaluate microbial bioburden:

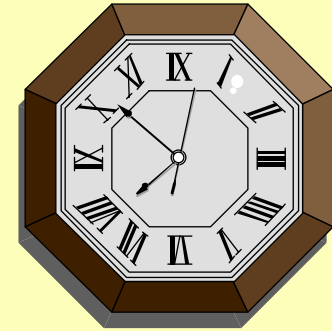
Direct contact plates

(RODAC: Replicate Organism Detection and Counting)

provide quantitative analysis and are suitable for flat surfaces. Swabbing is suitable for irregular surfaces, and although it may be regarded to be more qualitative than quantitative, it has been accepted as a satisfactory method due to its adaptability to a variety of surfaces.

***Sampling Timing:***

**When to Sample After Cleaning ?**



In general, after a surface has been cleaned, ensure that it is at least visually clean (i.e. residue free) and dry before sampling the sites.

**DO NOT** swab any surface area until it has passed the appropriate qualitative (or visual) inspection acceptance criteria.

## **Time Between End-of-Manufacturing to Beginning-of-Cleaning**

The duration of hold time between the End-of-Manufacturing and the Beginning-of-Cleaning should be discussed and evaluated during the cleaning validation (this is because the cleanability varies for different products). The data generated will benefit the development of the SOP for routine production condition.

## ***Sampling Documentation: Data Sheet***

Documentation of the sampling tasks during cleaning validation is necessary.

- Sampled Date/Time.
- Sampled By.
- Sampling Procedure/Methodology.
- Sample Site(s).
- Time/Date Sample Delivered to Test Lab
- Special Sample Storage Instructions.
- Comments (to record any deviations).



## ***Sample Sites : How to chose sites and where ?***

### **Manufacturer Recommendation**

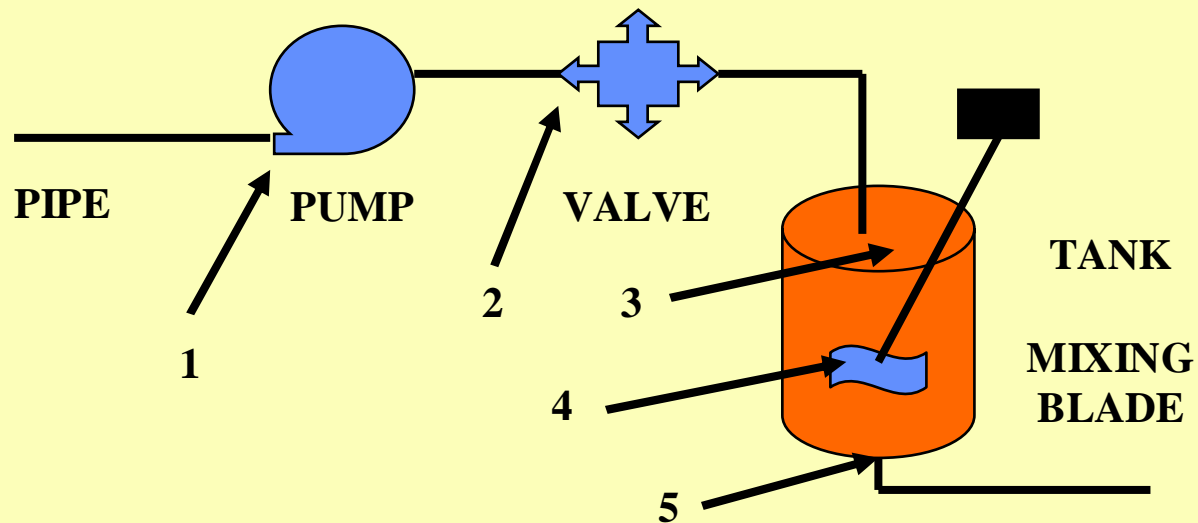
One approach is to consult with the manufacturer for suggested swab sites.

### **Past/Present Experiences**

Identify the sites with the most product build-up, sites which are difficult to access when the equipment is not disassembled, sites which may have significant product flow.

## Diagram of Sample Sites

Prepare a diagram and/or use still photos to identify the sampling site(s). This will significantly help the individuals doing the sampling.



## Microbiological Considerations

Factors to consider when choosing sampling sites include:

- 1) High product contact locations where microbial contamination would most likely affect product quality
- 2) Sites most likely to support microbial growth and represent the most inaccessible or difficult areas to decontaminate (worst case)
- 3) Examples *of areas to sample* include valves, transfer lines, pumps, and gaskets.



## ***Sample Quantity:***



### **Number of Sample Sites ?**

The number of sample sites to be selected should be based on (i) equipment product contact surfaces, and (ii) adequate coverage to provide a high degree of confidence that the validated cleaning procedure ensures the overall equipment has been properly cleaned per the cleaning SOP.

***Sample Quantity:***

**Number of Sample Sites for Active**

For chemical analysis, a minimum of five (5) sampling sites are required per major piece of equipment (i.e. tank, tablet press, granulator). If five testing sites cannot be obtained due to a limited surface area from a specific piece of equipment, document the rationale and obtain QA approval for the site(s) to be tested.

## Number of Sample Sites for Micro

From a microbiological standpoint, the number of samples should be sufficient to represent the equipment and assess cleanliness, giving consideration to the sample sites selected as noted above.

The production area classification and the formulation ingredients that would support growth should also be taken into consideration. *For example*, a class 100 facility will require more samples than a class 100,000 facility.

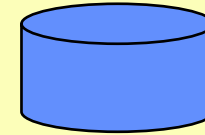
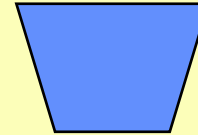
## **Sample Area/Volume**

The amount of unit sample area or rinse sample volume is dependent of the validated analytical method and sometimes other processing variables.

For example, if the analytical method refers to swab surface area of 10 cmx 10 cm, then it should be consistent for the cleaning validation.

***Sample Storage & Identification:***

**Type of Container**



The sample should be stored in a proper type of container so as prevent contamination or alteration during storage.

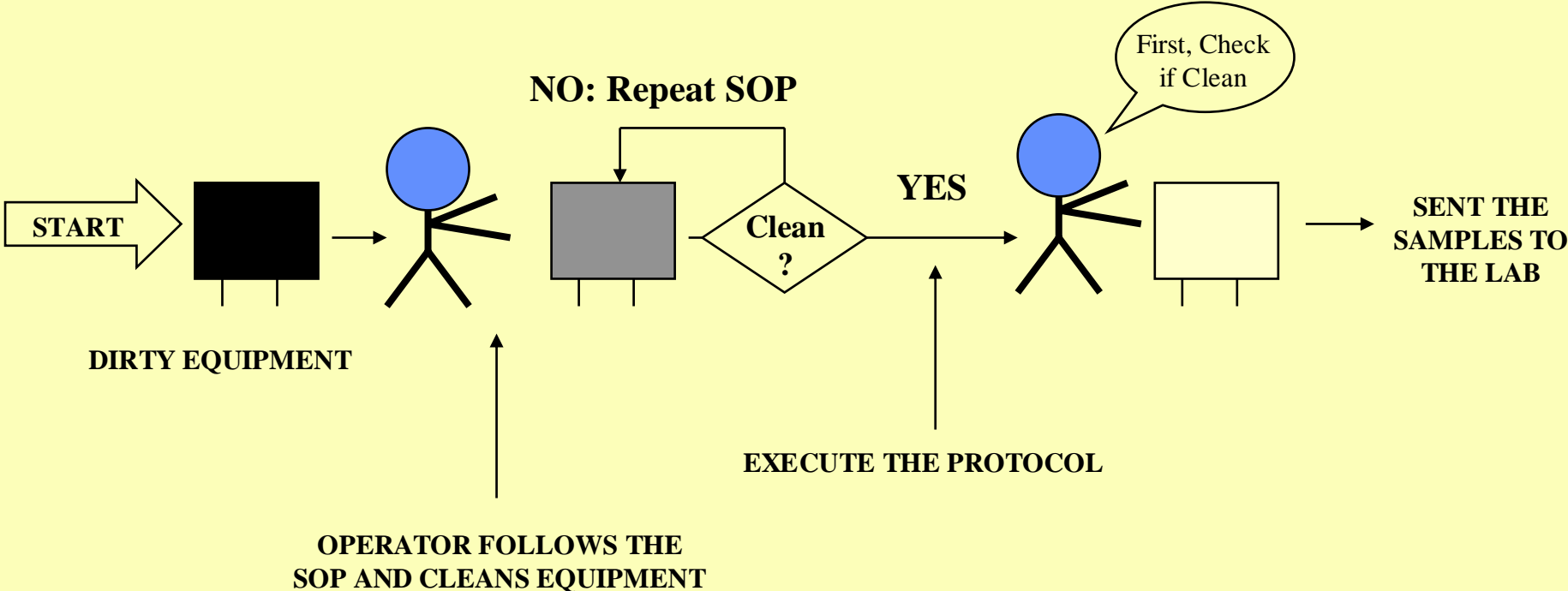
Microbiological samples should be protected from contamination and desiccation.

## Labeling of Samples

All storage containers should be properly labeled:

- Last batch/Lot number.
- Equipment asset number.
- Last product name.
- Sample number and description.
- Date and time sample was collected.
- Sampler signature/date.
- Expiration date and time of sample.
- Comment section.

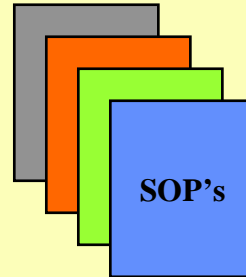
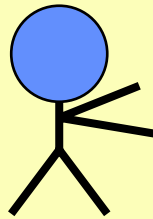
**EXECUTION OF CLEANING VALIDATION PROTOCOL**



———— EXECUTE DURING THE TRIAL BATCH ———>

==== EXECUTE FOR 3 VALIDATION BATCHES =====>

***Training***



Training documentation is required for all associates involved in the cleaning process. The training documentation should include content of the training, who did the training, when it was performed. The following people need training:

**Manufacturing associate training**

**Sampling associate**

**Analyst**



## ***Summary of Standard Operating Procedures***

The following items need to be addressed by SOP(s):

**Equipment Cleaning**

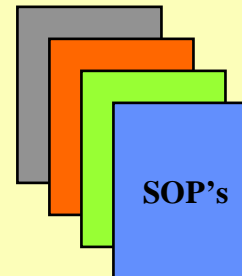
**Visual Cleaning Validation**

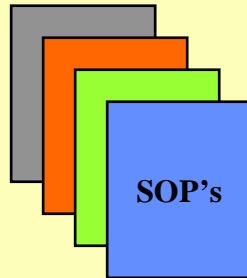
**QA Reviews & Approves the Documentation**

**Change Control**

**Methodology**

**Training**

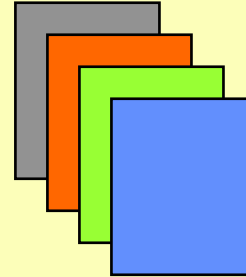




## Content for Cleaning SOP's

- 1) Concentration and amount of cleaning agent(s) to be used.
- 2) Soak time, Rinse time and volume.
- 3) Compatibility of cleaning agent with product.
- 4) Temperature of the cleaning agent and the equipment.
- 5) Any mechanical force or pressure to be used.
- 6) Identify and control the length of time between the end of processing of the product and the beginning of cleaning.
- 7) Drying procedures.

## DOCUMENTATION SECTION



Documentation of cleaning validation is an essential part of any cleaning validation program. Documentation must meet the requirements for records in the cGMPs.

Specific reference to cleaning records in the cGMPs are:

**Sanitation - 211.56 (b)**

**Equipment Cleaning and Maintenance - 211.67 (b)**

**Equipment Cleaning and Use Log - 211.182**

## **Sanitation - 211.56 (b)**

There shall be written procedures assigning responsibility for sanitation and describing in sufficient detail the cleaning schedules, methods, equipment, and materials to be used in cleaning the buildings and facilities; such written procedures shall be followed.

## **Equipment Cleaning and Maintenance - 211.67 (b)**

Written procedures shall be established and followed for cleaning and maintenance of equipment, including utensils, used in the manufacture, processing, packing, or holding of a drug product. These procedures shall include:

- (1) Assignment of responsibility for cleaning
- (2) Maintenance and cleaning schedules
- (3) A description of the methods, equipment, and materials used in cleaning and maintenance operations
- (4) Records shall be kept of maintenance, cleaning, sanitizing, and inspection.

***Content for the Cleaning Validation Protocols:***

**Product Identity**

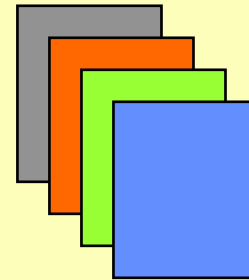
**Acceptance Criteria**

**Sample Sites and Rationale**

**Cleaning Agents and Concentration**

**Cleaning Method**

**Approvals**



## ***Cleaning Validation Final Reports***

At the conclusion of the cleaning validation, a validation report should be issued to document the result of the studies and include the following sections:

**Conclusions**

**Results**

**Sampling record**

**Test Method**

**Deviations**

**Protocol**



## ***Cleaning Validation Final Reports***

### **Conclusions**

Should support a conclusion that the residues (bioburden) have been reduced to an acceptable level and that the studies are valid.

### **Results**

The results can either be in the form of raw data or a summary of data.



**SITE TOPKAPI - CLEANING VALIDATION**

- Team : Representatives from QC, QA, Production
- Prioritizing: Pentoxyfilline -->Prednicarbate -->Glimepiride --> .....
- Criteria: Solubility, toxicity,maximum equipment, galenic Representation
- Follow up :Production checks cleaning practices

Istanbul June 1, 2001

THANK YOU FOR YOUR TIME

GOOD LUCK !!!

ANY QUESTIONS ??????