VALIDATION:

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Pharmaceutical process Validation : A tool for Pharmaceutical Compliance monitor

GMP (Adopted in 1975) In India

- Good manufacturing practices are the practices required in order to conform to guidelines recommended by agencies which control authorization and licensing for manufacture and sale of food, drug products, and active pharmaceutical products.

Verification and validation

"**Validation : is** the assurance in Contrast with *verification*.

Verification is : the evaluation in Contrast with *validation*.

VALIDATION

Proposed in 1970 1987

- Verification that something is correct
- or conforms to a certain standard.
- “ It is the process of ensuring that the data that are entered fall within the accepted limits. "

Validation is done by some assumptions

Assumptions

- By controlling critical steps of a process the uniformity of contents and other specifications become reproducible .
- By validation we can :-
- Know Truth
- Identify Error
- Ensure Reproducibility
- Avoid variation within batches

What Do We Validate?

- Plan
- Process
- Equipment
- Facility
- Personnel
- Packing
- Quality Control-Raw material
  Finished Product
- Transport
- Vendors

DEFNITION

"A validated manufacturing process is one that has been proved to do what it purports or is represented to do. The proof of validation is obtained through collection and evaluation of data, preferably, beginning from the process development phase and continuing through into the production phase. Validation necessarily includes process qualification (the qualification of materials, equipment, systems, building, personnel), but it also includes the control of the entire processes for repeated batches or runs."

FDA DEFINES

Validated process is One that does what it is purports to do. It is a product of evaluation of data obtained from process development ,during process to finished product.

It includes qualification of Process, Equipment System ,Building Personal ,Repeated batch runs, Quality control and also cleaning systems .

What Drug needs Validation ?

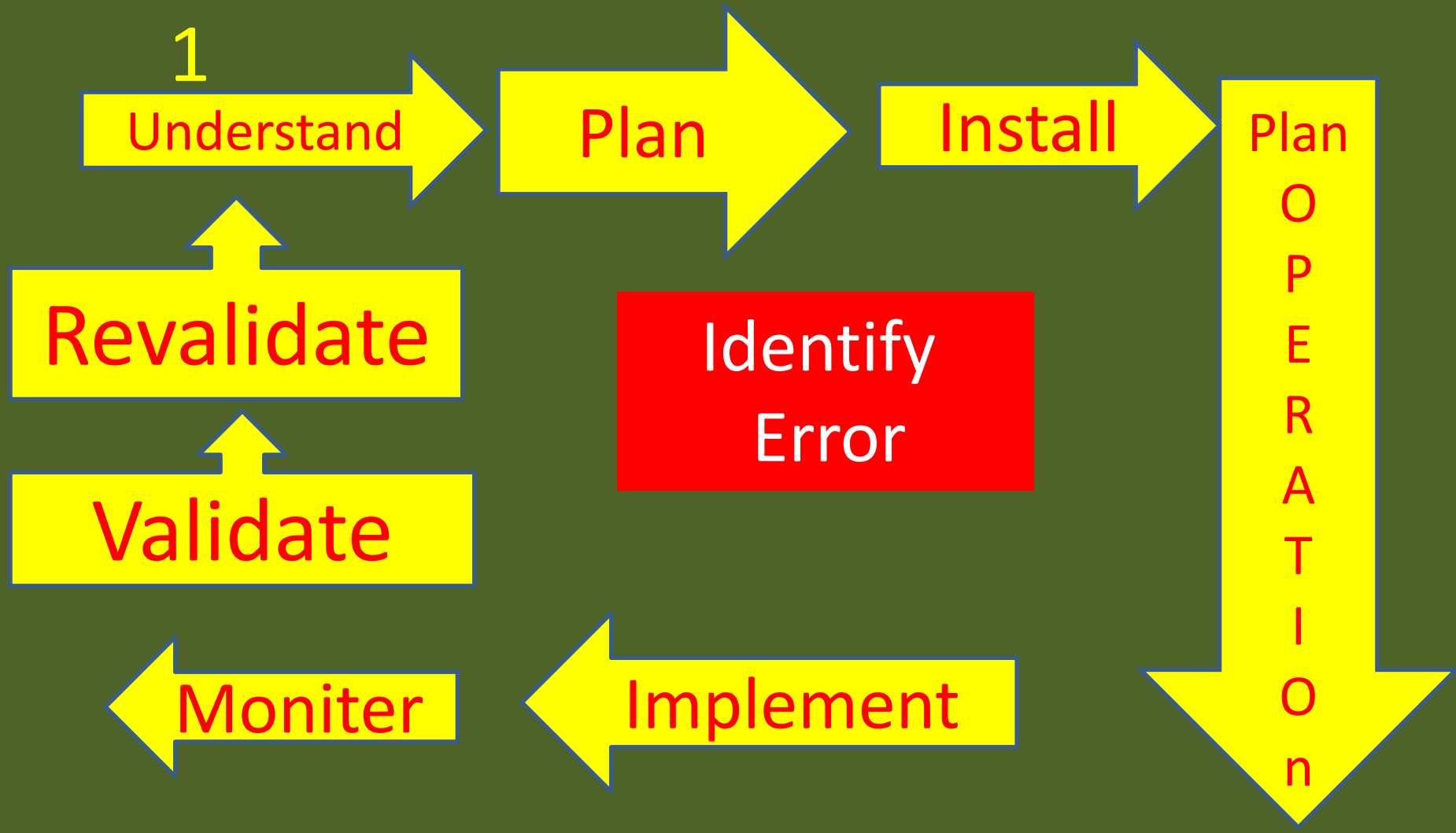
- Any Drug To Be Used For Humans Or Animals
- Including Medication Instruments.

Validation Is Team Effort
Team should Know…

- Why are we doing this?
- What has been done wrong?
- What have we done wrong?
- What is Validation?

Process validation is collection and evaluation of data, from the process design stage throughout production, which may provide evidence that a process is capable of consistently delivering quality products or otherwise.

Procedure


1
Understand
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Revalidate
Identify
Error
Validate
Moniter
Implement

Types Of Validation

- 1 Prospective validation – Predefined Setting of Criteria, Test at least three lots
- 2 Retrospective validation - Old
- 3 Concurrent Validation – Simultaneous
- 4 Revalidation

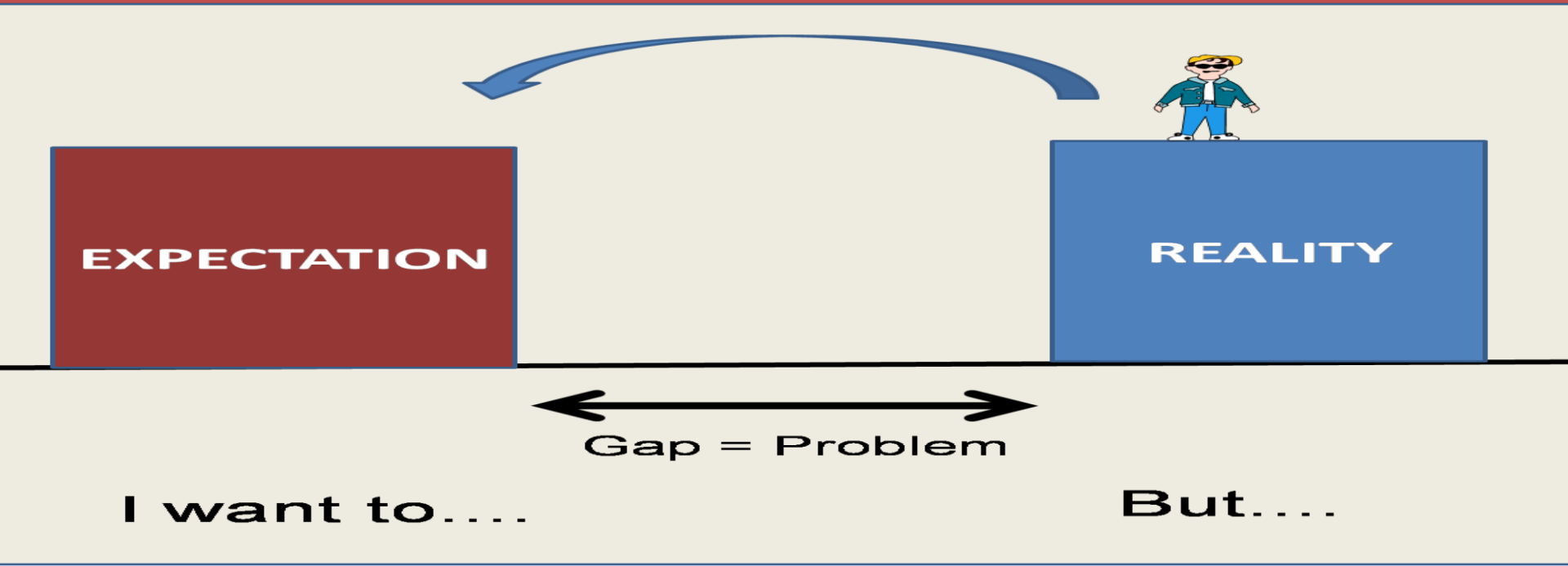
1) Prospective validation

Prior to process implementation

Based on preplanned protocols.

For a new formula (or within a new facility)

Before routine pharmaceutical production commences



2) Retrospective validation

is used for facilities, in use that have not undergone validation process

by using historical data to provide the necessary evidence .

Therefore,

this type of validation is only acceptable for well-established processes.

3) Concurrent validation

Concurrent validation is , based on information generated during actual imputation of the process.

This shows that the manufacturing process is in a state of control.

4)Revalidation

- Repeating the original validation effort or any part of it,
- It includes investigative review of existing performance data.
- This is essential to maintain the validated status of the plant.
- Possible reason for this may be :
  Any change in the Plant ,Premise ,Product or Process .

Stages of Validation

- Stage 1 : Process Design,
- Stage 2: Process Qualification,
- Stage 3 :Continued Process Verification

Process Validation Includes

Equipment validation
Facilities validation
HVAC system validation
Cleaning validation
Process validation
Analytical method validation
Computer system validation
Packaging validation
Cold chain validation

Similarly, the activity of qualifying systems and equipment is divided into a number of subsections including the following:

Design qualification (DQ)

Component qualification (CQ)

Installation qualification (IQ)

Operational qualification (OQ)

Performance qualification (PQ)

Sources of Errors

- Environment
- Raw Material
- Machine
- Humans
- Procedures
- Process
- Formulations
- Impurities

Emphasis

- Impurity Profile
- Solvent Recovery
- Polymorphism
- Cleaning
- Process
- Stability
- Packaging
- Official Standards

Quality Assurance Factors

- 1 . SOP Guidelines
- 2. Technical and development Reports
- 3. Master batch Records (Manufacturing Procedures)
- 4. Cleaning Procedures
- 5. PPF-Process flow diagram
- 6. Raw Material Test Procedures
- 7. Analytical Methods for Finished Products
- 8. Personnel Training

(cont.-)

- 9.Equipment maintenance Program
- 10.Instrument maintenance and calibration Program.
- Packaging and Labelling Practice
- ANY RAW MATERIAL SUBSTITUTION PROGRAM ?

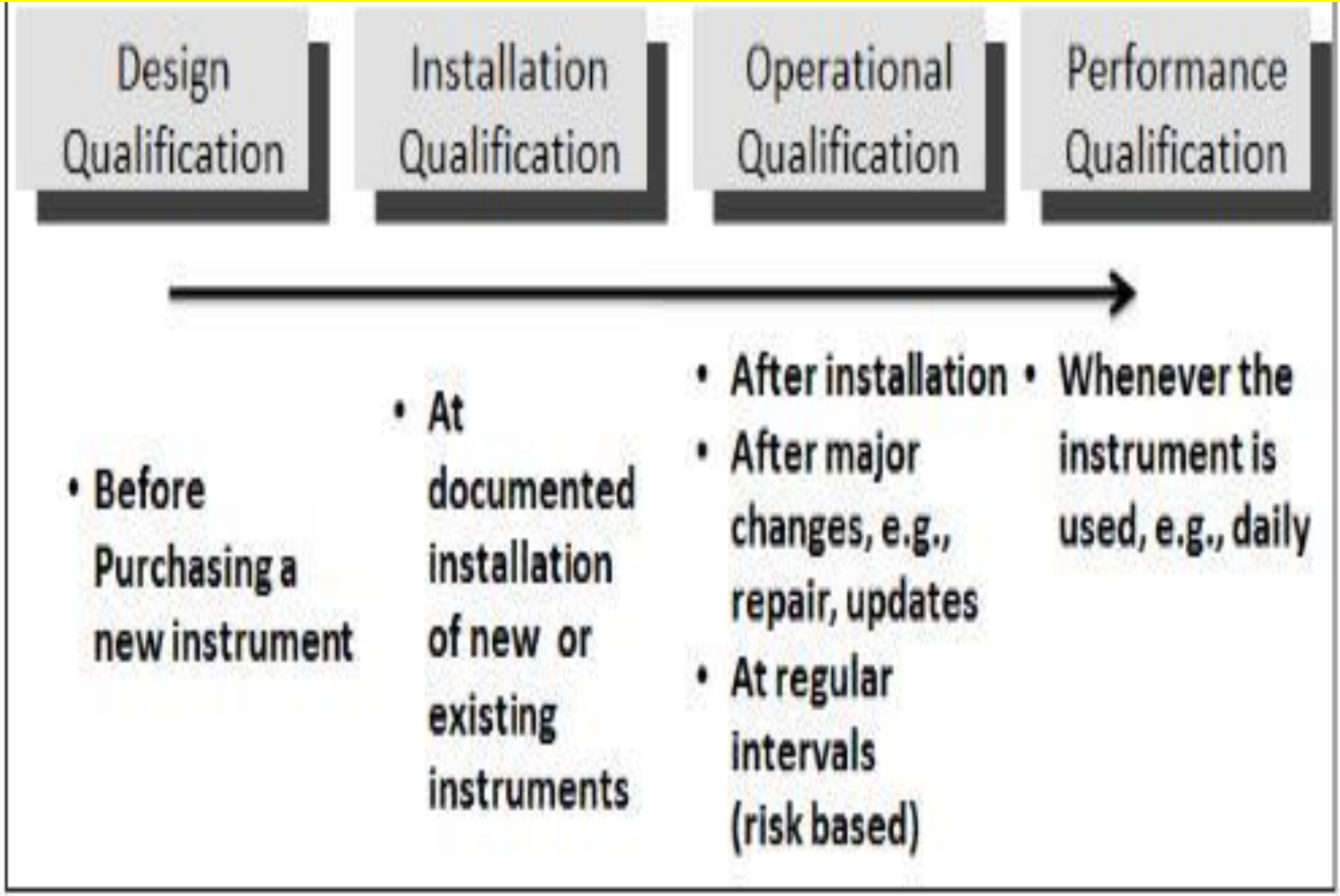
Controls

- Equipment
- Personnel Training and Qualification
- Component Control
- Manufacturing Control
- Lab Control analytical Tests
- Packaging Control
- Labelling control
- Records
- Physical Facility
- Master Batch Records

Others

- Cross Contamination
- New Equipment
- Complaints Disposal
- Internal Rejection Records
- Reworking Batches
- Packaging And Labelling

INSTRUMENTS



Dosage Forms Validation

The basic principles are:

- equipment be correctly installed in accordance with an installation plan
- requirements for calibration, maintenance and cleaning be covered in approved SOP's
- tests be conducted to assure that equipment is operating correctly, under normal and "worst case" conditions
- operator training requirements pertaining to new equipment be conducted and documented.

SOME EXAMPLES

Sterile Products

- 1 Environment
- Sterilizer...Oven , Tunnel, Filter (pore Size)
- Area Radiation
- Air Circulation, Pressure
- Workers
- Endo toxins

Sterile Products validation

- Determine Microbial limits on Statistical Basis

  Of Viable as well as Nonviable organisms

Sterilize Equipment daily

Monitor for Microbial contamination all personnel of each shift

Monitor particulate matter

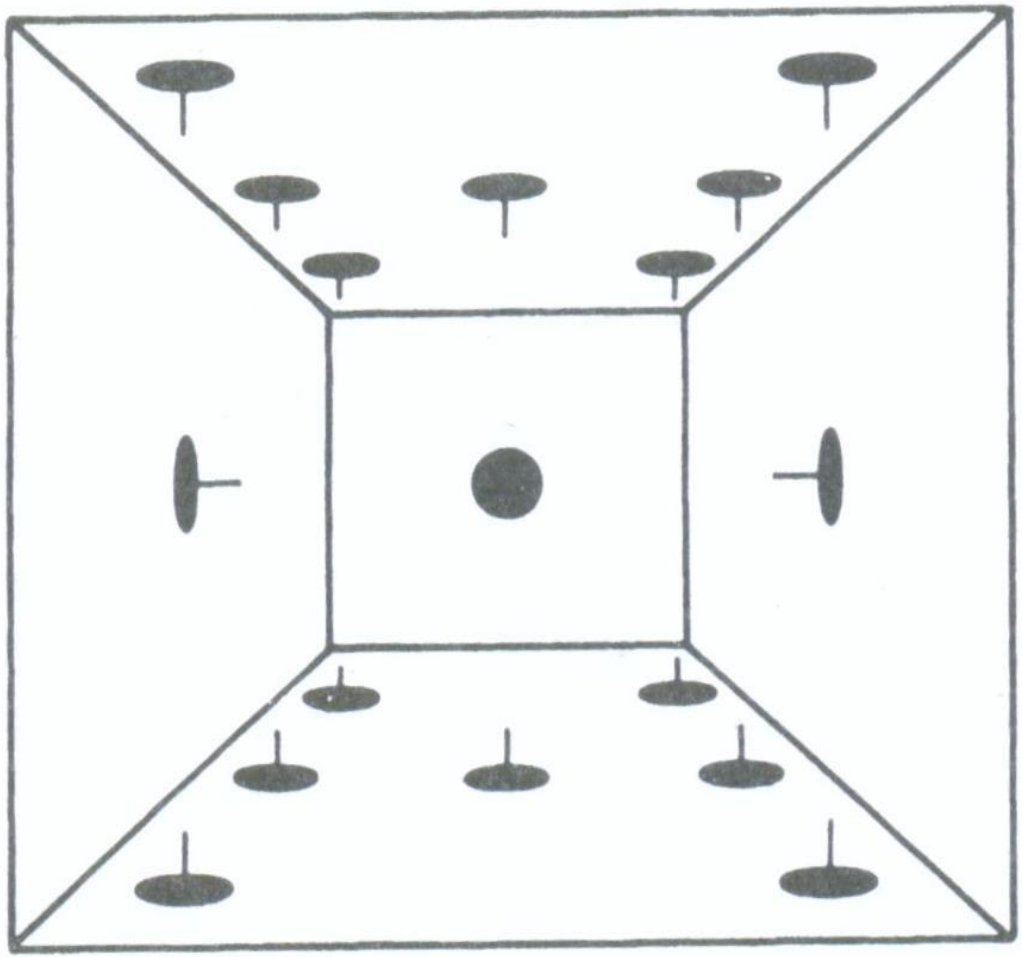
Location of area sampling to be representative

Validate Aseptic area

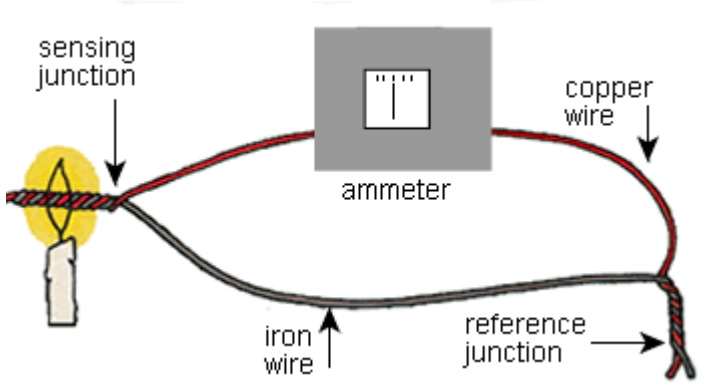
Consider Kinetic Expression For Microbial Destruction

- D Value =Time required to reduce by one decimal ie. 90 % ie. From 1000 to 100
- D Value=Log of microbial Population / Time
- Z value= Probability of Non Sterility
- Z Value =T2 – T1 / Log d1 – Log D2
- F Value= Equivalent Time

Heat Distribution And Circulation



Suggested location of Thermocouples



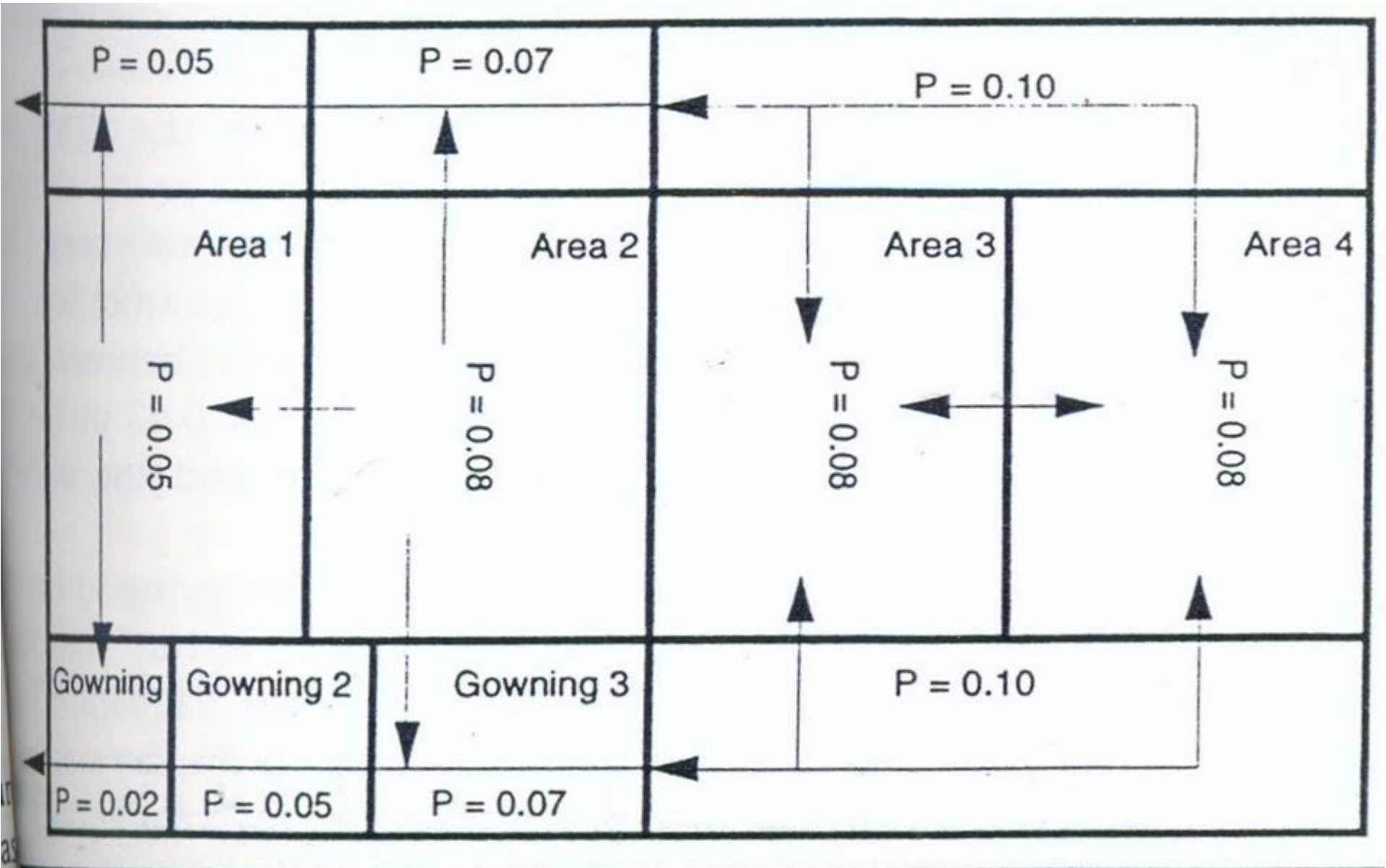
Validating Dry-Heat Sterilizers

Batch (oven)	Tunnel sterilizer
Intake air system	Positive pressure to entrance
Exhaust air system	Even distribution of heat
Internal air circulation	Belt speed recorder
Exhaust HEPA filter	HEPA-filtered cooling air
Static pressure gauge	Exhaust HEPA filter
Heater current	Heater current
	Particulate control

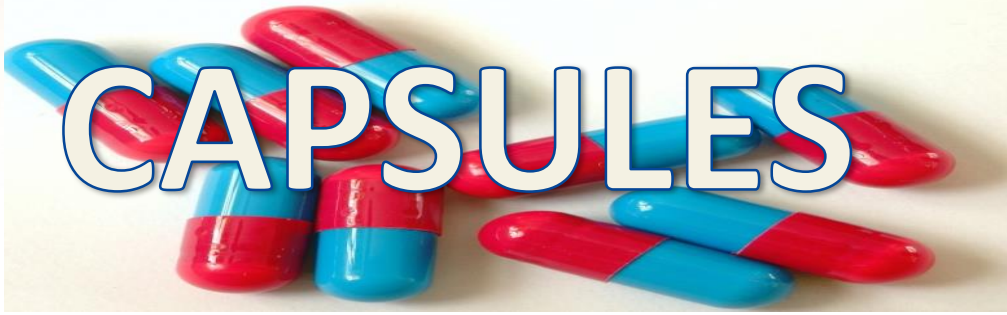
Equipment Needed

1. Temperature recorders and thermocouples
2. Constant-temperature baths
3. Amp meters
4. Monometers
5. Dioctylphthalate generators
6. Particle counters
7. Velometers
8. Tachometers

AIR FLOW PATTERN



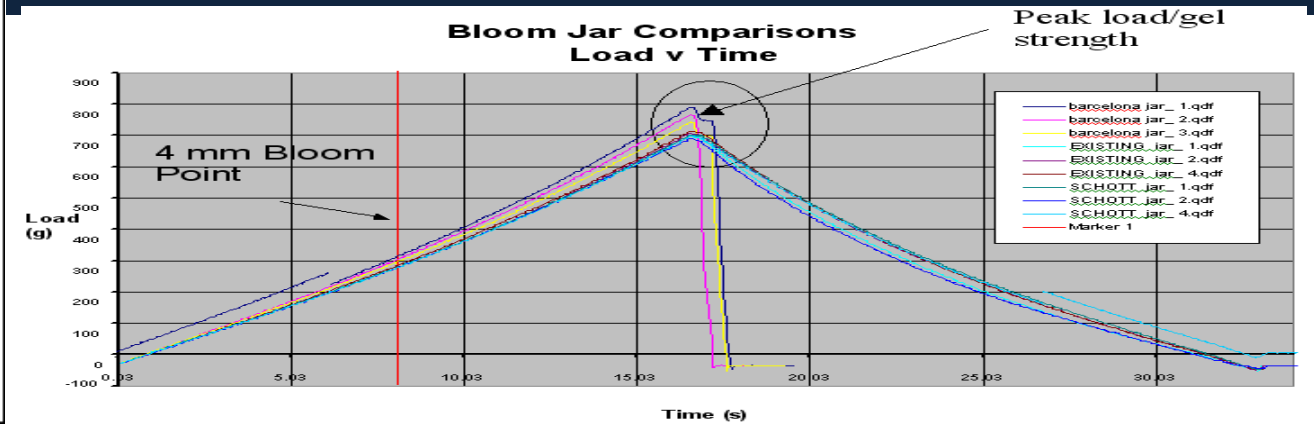
GELS AND CAPSULES



- Gelatin+Water+Plasticizer+colour—Uniform mix -> Form 2 Ribons ->Pour in Die ->Seal after filling.
- Blend Time} ;-High exposure to high temp. Deteriorates Gelatin
- Mix Time -----Do ------
- Die rotation Speed - Contact Time-No Seal
- Gelatin Ribbon Thickness-Capsule wall may leak
- Humidity in Product - Deteriorate contents

Bloom Test For Gelatin

Create a 6.67% solution in Bloom bottle, Stirr. Leave for 3 hours .Place in a 65°C bath for 20 minutes. Cool . Put the PROBE . Measure the Force with instrument .



Solid Doses Forms

- Validate all Raw Materials/ Excipients
- (Quality of Finished products depends upon quality of raw Materials).
- Test Ageing, Physical, Chemical, Microbial Stability and Interactions with containers.

- (cont.)
- Assess in process :- Moisture contents ,Particle Size ,Blend Uniformity, Weight Uniformity ,(granules).
- In Process variations Stability of drug Substance with Additives. Test Partical Size Distribution, Surface area ,True and Bulk Density, Flow Rate , Hygroscopisity , Compressibility Drug Uniformity .
- Mixing Time and milling Uniformity.
- Disintegration, Dissolution, Stability DURING and AFTER DRYLNG
- Air flow Rate during DRYING

- (cont.)
- Coating Stability ,Taste Masking , Drug Release
- Safety in Handling , Aesthetics
- EQUIPMENT :-
- Blender and Granulator:-Mixing Time and Speed, Solvent addition Rate.
- Dryer :- Time, Temperature, Air Flow,
- Tablet Machine :-Compression force, Volume,
- Punch Shape and Size, Ejection Force .

. Coating :- Spray Gun Capability

VALIDATION OF ANALYSIS



- 1) Specificity
- 2) Precision
- 3) No Day to Day or time Variation
- 4) No Operator Variation
- 5) No Instrument Variation
- 6) No Lab Variation
- 7) Limit of Detection And Quantification

Validation Of Packaging

- Purpose of Packing
- Protection From Physical Damage , and Contamination During Storage ,Transport, Display and Use.
- Presentation
- Identification
- Instruction

Types:

Glass

Borosil

Flint

Soda

Metal

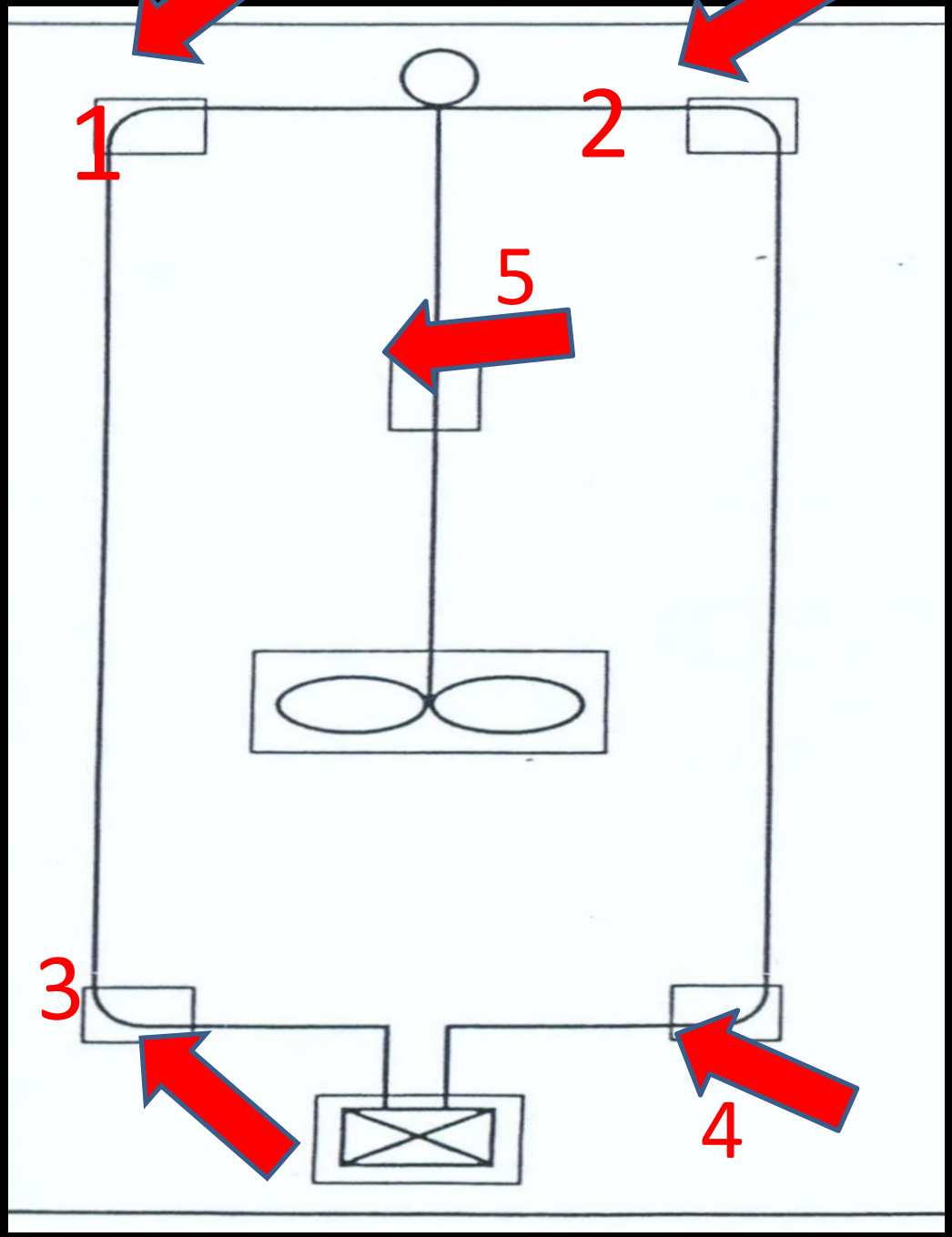
Paper Board

Plastic

- (cont.)

Normally 3 layers

- CHECK :-
- Pressure and Vacuum Behavior
- Dye Penetration,
- Vapor and Particle leak,
- Visual,
- Light Transmission,
- Aging,
- Vehicle,
- Vibration,
- Sterility,
- Bar Code Retention



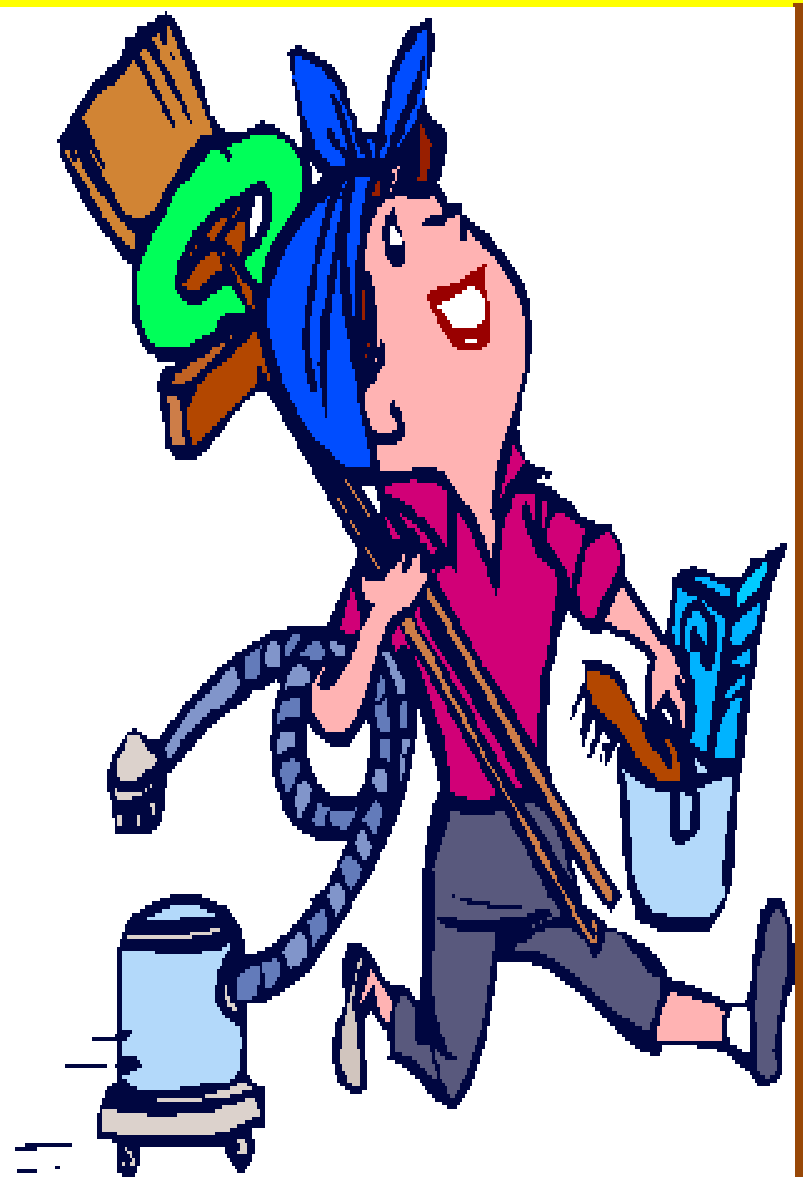
Checking Cleaning Points

Cleaning : Aim Is To Determine Presence of Residue

- HPLC to detect residual particals
- ELISA for biological products
- **ELISA**
- The enzyme-linked immuno sorbent assay (ELISA) is a test that uses antibodies and color change to identify a substance.
- TOC-Total Organic Carbon. This is superior to HPLC

Total organic carbon is the amount of carbon bound in an organic compound and is often used as a non-specific indicator of water quality or cleanliness of pharmaceutical manufacturing equipment. .

Cleaning: Equipment, Utensil, Premise



- 1.Written Procedure
- Assignment of Responsibility
- Maintain Schedule
- Disassembling and reassembling Schedule
- Protection from Contamination
- Inspection before use
- Removal of previous batch

Validation Of Cleaning

Organic solvent

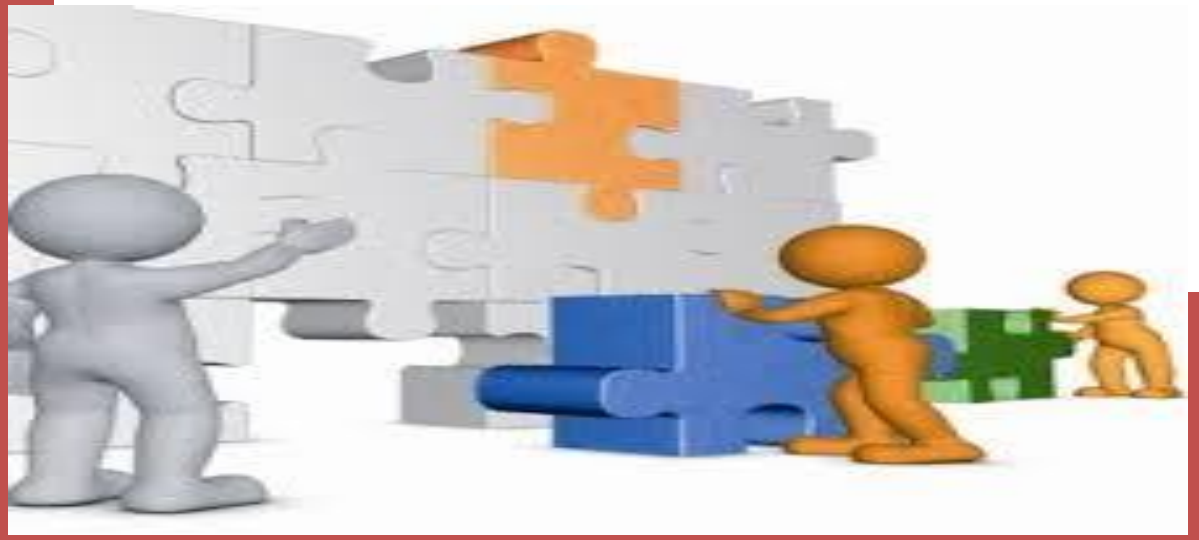
Pressurised water

Visualised Pipe with Optic fiber

Video Camera in Equipment

Determine Total Organic Carbon

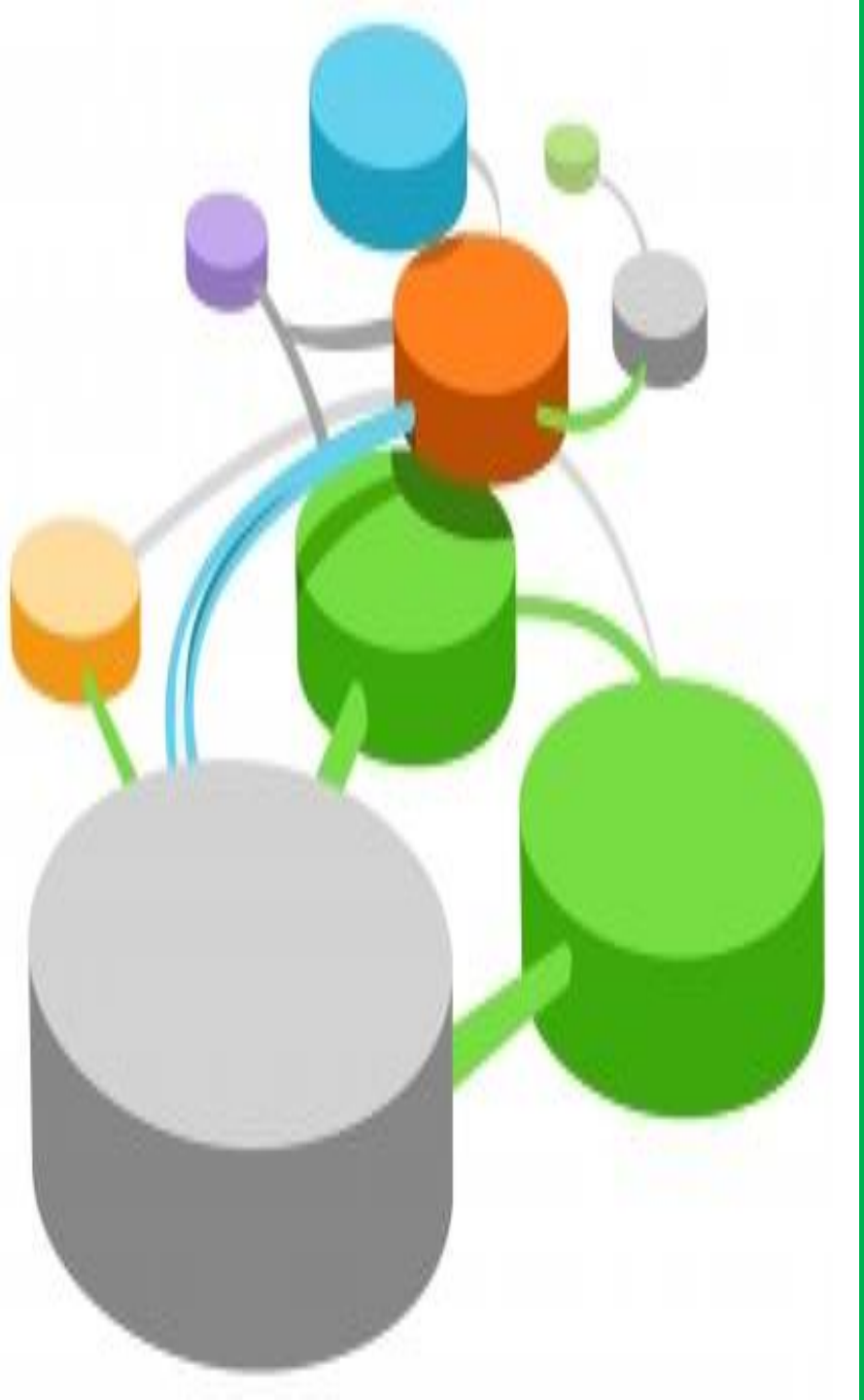
Facility



- Rooms Classified
- Airflow pattern
- Pressure Pattern and Pressure Difference
- Personnel flow pattern
- Material flow pattern

Plan and Do

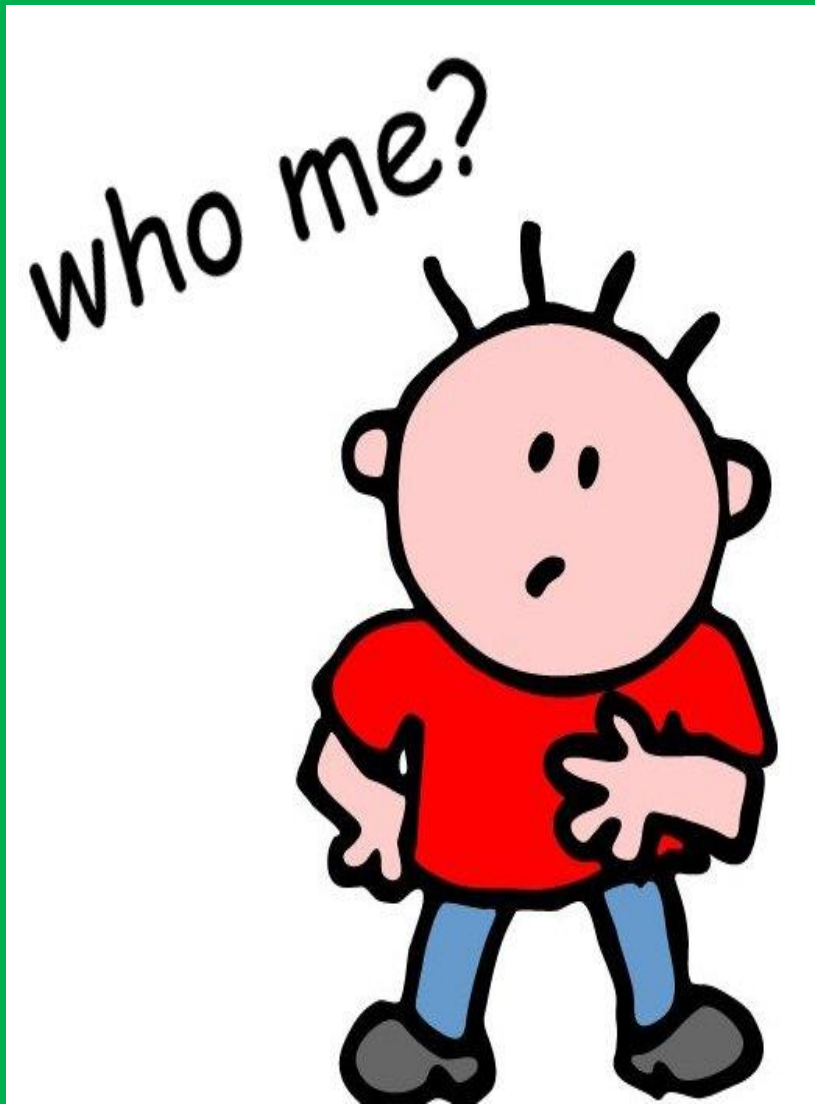
- Write what you DID
- If it is not written it is NOT DONE
- Computerised validation may be used PROVIDED
- The programme itself is validated



- .Methods would Depend upon
- Product
- Process
- Equipment
- Aims and Objectives
- Modify your Validation Methods accordingly.

You May Be

- Required to Validate,
- Or
- Subjected to validation.
- Get ready for : BOTH



Thank

You