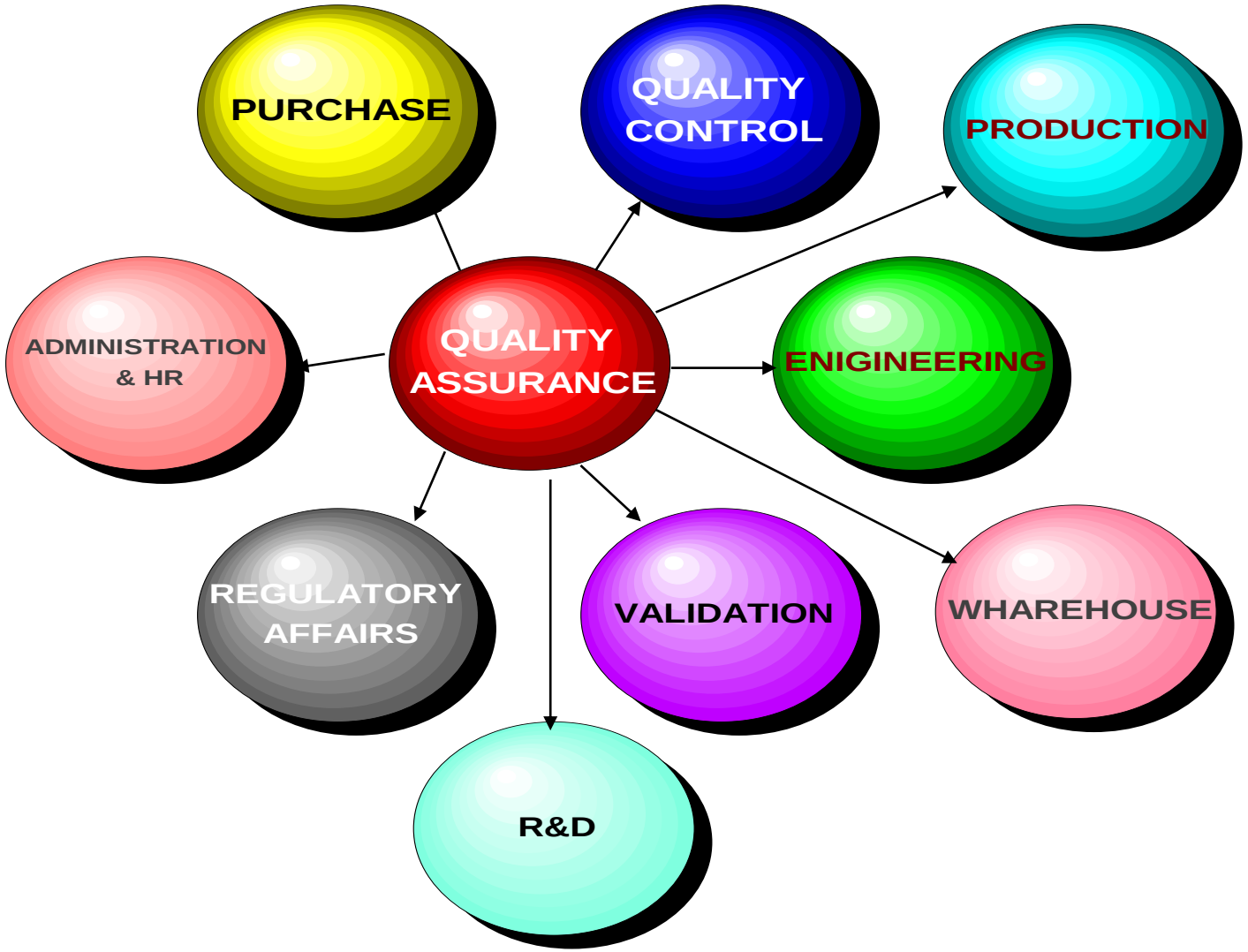
INTRODUCTION TO VALIDATION

Dr.K.Kathiresan.,M.Pharm.,Ph.D.,M.B.A.

Associate Professor

Department of Pharmacy

Annamalai University


PURCHASE
QUALITY CONTROL
PRODUCTION
ADMINISTRATION & HR
QUALITY ASSURANCE
ENIGINEERING
REGULATORY AFFAIRS
VALIDATION
WHAREHOUSE
R&D

WHY VALIDATION?

The pharmaceutical industry uses expensive materials, sophisticated facilities & equipment's and highly qualified personal.

The efficient use of these resources is necessary for the continued success of the industry. The cost of product failures, rejects, reworks, recalls, complaints are the significant part of the total production cost.

Detailed study and control of the manufacturing process – validation is necessary if failure cost is to be reduced and productivity improved.

V ery

A rduous

L engthy

I nvolved

D etailed

A ttempt to

T est

E verything

Def.

"Establishing Documented Evidence, which provides a high degree of assurance that a specific process will consistently produce a product meeting its pre-determined specification and quality attributes".

USFDA

There are different approaches for validating a pharmaceutical industry

- Prospective validation
- Retrospective validation
- Concurrent validation
- Revalidation

Prospective Validation

- pre-planned protocol.
- This approach to validation is normally undertaken whenever a new formula, process or facility must be validated before routine pharmaceutical formulation commences

Retrospective validation

- what it purports to do on review and analysis of historical information (Process control)

Concurrent validation

- process monitoring of critical processing steps and product testing

Revalidation

- This is carried out when there is any change or replacement in formulation, equipment plant or site location, batch size and in the case of sequential batches

Various types of validations :

- Equipment/Instrument validation :
  - **DQ**
  - **IQ**
  - **OQ**
  - **PQ**
- Area Qualification
- Analytical Method validation
- Cleaning validation
- Process Validation

IQ - Verification that the equipment/system is installed in a proper manner and that all of the devices are placed in an environment suitable for their intended operations.

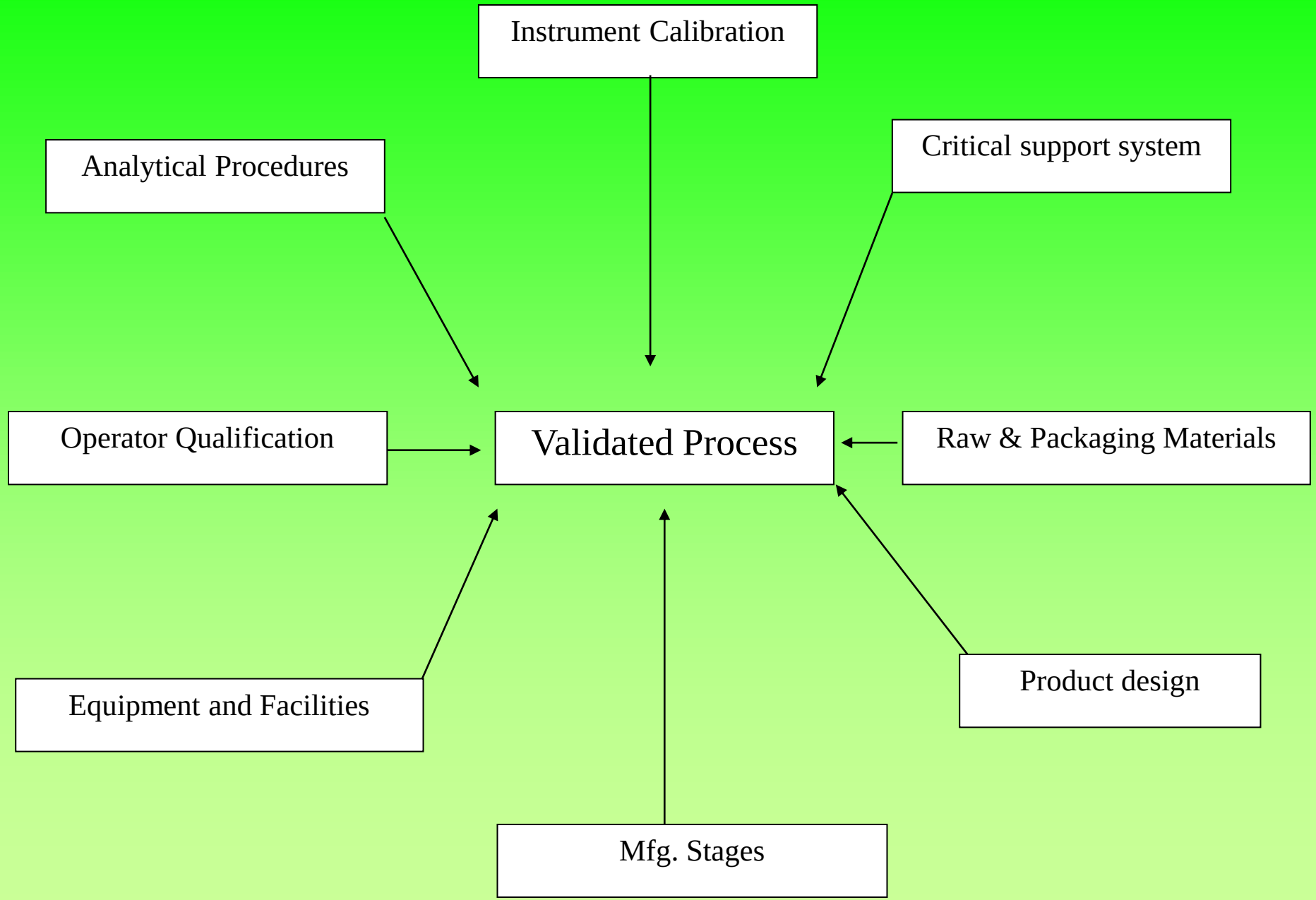
OQ - Verification that the equipment performs as expected throughout the intended range of use.

PQ - Verification that the system is repeatable and consistently producing a quality product.

DQ - Document verification of the design f equipment and manufacturing facilities.

Elements of Validation:

The validation of a process requires the qualification of each of the important elements of the process. The relative importance of an element may vary from process to process. Some of the elements commonly considered in a process validation study are presented below


Instrument Calibration
Analytical Procedures
Critical support system
Operator Qualification
Validated Process
Raw & Packaging Materials
Equipment and Facilities
Product design
Mfg. Stages

Thank U

Analytical Method Validation

by using HPLC

Dr.K.Kathiresan,M.Pharm., Ph.D.,M.B.A.,

Associate Professor

Department of Pharmacy

Annamalai University

For method validation the FDA designated the specifications and is listed in USP and can be referred to as the "Eight steps of method validation“.

These terms are referred to as "Analytical performance parameters", or sometimes as "analytical figures of merit“

International Conference on Harmonization (ICH) divides the "validation characteristic" somewhat differently, as outlined in the table.

SL. No.	USP PARAMETERS	ICH PARAMETERS
1	Accuracy	Accuracy
2	Precision	Precision
3	Limit of Detection	Limit of Detection
4	Limit of Quantitation	Limit of Quantitation
5	Specificity	Specificity
6	Linearity & Range	Linearity
7	Ruggedness	Range
8	Robustness	Robustness
9	-	System Suitability

The difference in the USP and ICH terminology is for the most part 1, however, with one notable exception that is ICH treats systems suitability as a part of method validation, where as the USP treats in it in a separate chapter (<621>).

Discussions of definition of analytical performance parameter are given below

Accuracy

It is a measure of exactness of an analytical method, or the closeness of agreement between the value that is accepted as either a conventional, true value or an accepted reference value and the value found.

Recovery percentage

About 25 mg of drug WRS, was weighed accurately, into a 50 ml volumetric flask, was dissolved in mobile phase and diluted to volume with the mobile phase (Stock solution).

1.0 ml of stock solution was transferred to 4 different 50 ml volumetric flasks and 0.0, 0.2, 0.4, and 0.6 ml of stock solution was added and the volume was made up with the mobile phase and mixed.

Separately each solution was injected and the percentage recovery of drug was calculated by recorded chromatogram.

Precision

It is the measure of the degree of repeatability of an analytical method under normal operation and is normally expressed as the percent relative standard deviation for a statistically significant number of samples.

According to the ICH, precision should be performed at 3 different levels: repeatability, intermediate precision and reproducibility.

Repeatability is the results of the method operating over a short time interval under the same condition (inter-assay precision).

Intermediate precision is the result from within lab variations due to random events such as different day's analysts, equipment, etc

Reproducibility refers to the results of collaborative studies of the laboratories

Procedure

About 25 mg of drug WRS, was accurately Weighed, into a 50 ml volumetric flask, dissolved and diluted to volume with the mobile phase. 1.0 ml of this solution was diluted to 50 ml with the mobile phase and mixed (10 ppm).

Separately equal volume (about 20 µl) of above solution was injected six times and recorded the chromatogram.

Specificity

Specificity is the ability to measure accurately and specifically the analyte of interest in the presence of other components that may be expected to be present in the sample matrix.

It is a measure of the degree of interference from such things as other active ingredients, excipients, impurities, and degradation products, ensuring that a peak response is due to a single component into two separate categories: identification, and assay / impurity tests.

Procedure

System suitability solution:

About 25 mg of drug (Terbutaline Sulphate) WRS and 7 mg of 3,5- dihydroxy-w-t-butyl amino acetophenone hydrochloride was weighed into a 50 ml volumetric flask, dissolved and diluted to volume with the mobile phase.

LOD

The limit of detection (LOD) is defined, as the lowest concentration of an analyte in a sample that can be detected, not quantitated.

It is a limit test that specifies whether an analyte is above or below a certain value.

It is expressed as a concentration at specified signals - to - noise (S/N) ratio, usually two - or three - to - one.

The ICH has recognized the signal to - noise (S/N) ratio convention, but also lists two other options to determine LOD: Visual non-instrumental methods and a means of calculating the LOD.

Procedure

About 25 mg of drug WRS, was accurately weighed, into a 50 ml volumetric flask, dissolved and diluted to volume with the mobile phase. 1.0 ml of this solution was diluted to 50 ml with the mobile phase and mixed. 1.0 ml of this solution was diluted to 100 ml with the mobile phase and mixed (0.1 ppm).

Equal volume (about 20 μL) of above solution and mobile phase (Blank) was separately injected and recorded the chromatogram.

LOQ

The limit of quantitation (LOQ) is defined as the lowest concentration of an analyte in a sample that can be determined with acceptable precision and accuracy under the stated operations of the method.

The ICH has recognized the 10 - to - 1 signal - to - noise ratio as typical, and also, like LOD, lists the same two additional options that can be used to determined LOQ, visual non - instrumental methods and a means of calculating the LOQ.

PROCEDURE

About 25 mg of drug WRS, was accurately Weighed, into a 50 ml volumetric flask, dissolved and diluted to volume with the mobile phase. 1.0 ml of this solution was diluted to 50 ml with the mobile phase and mixed. 5.0 ml of this solution was diluted to 100 ml with the mobile phase and mixed (0.5 ppm).

Equal volume (about 20 µL) of above solution and mobile phase (Blank) was separately injected and recorded the chromatogram

Linearity & Range

Linearity is the ability of the method to elicit test results that are directly proportional to analyte concentration with in a given range.

Linearity is generally reported as the variance of the slopes of the regression line.

Range is the interval between the upper and the lower levels of analyte that have been demonstrated to be determined with precision, accuracy and linearity using the method as written

Procedure

About 25 mg of Drug WRS, was accurately weighed, into a 50 ml volumetric flask, dissolved and diluted to volume with the mobile phase (Stock solution).

0.4, 0.6, 0.8, 1.0, 1.2 and 1.4 ml of above stock solution was transferred to separate six 50 ml of volumetric flasks and diluted with mobile phase to volume and mixed, so the resulting solutions contained 4, 6, 8, 10, 12 and 14 ppm of Drug respectively.

Equal volume (about 20 μL) of each solution was injected separately and recorded the chromatogram.

Ruggedness

This is a degree of reproducibility of the results obtained under a variety of conditions, expressed as % Relative Standard Deviation (RSD).

This condition includes different laboratories, analyst, instruments, reagents, days etc.

ICH did not address ruggedness specifically instead, it covered the topic of ruggedness as part of precision

Procedure

Different analysts carried out the performance of the method, on different days and on different instruments.

Robustness

It is a capacity of a method to remain unaffected by small deliberate variations in method parameters.

Robustness of a method is evaluated by varying method parameters such as percent organic, pH, ionic strength, temperature, etc., and determining the effect (if any) on the results of the method..

As in ICH guidelines, robustness should be considered early in the development of a method.

In addition, if the results of a method or other measurements are susceptible to variation in method parameters, these parameters should be adequately controlled and a precautionary statement included in the method documentation

System Suitability

According to the USP, system suitability tests are an integral part of chromatographic methods.

These tests are used to verify that the resolution and reproducibility of the system are adequate for the analysis to be performed.

System suitability tests are based on the concept that the equipment, electronics, analytical operations, and samples constitute an integral system that can be evaluated as a whole.

System suitability is the checking of a system to ensure system performance before or during the analysis of unknowns.

Parameters such as Plate count, Tailing factors, Resolution and Reproducibility are determined and compared against the specifications set for the method.

These parameters are measured during the analysis of a system suitability, "Sample" that is a mixture of main components and expected by-products.

USP chapter 1225 on validation of analytical methods specifically address terms and definitions, but leaves protocol and methodology open for interpretation

Conclusion

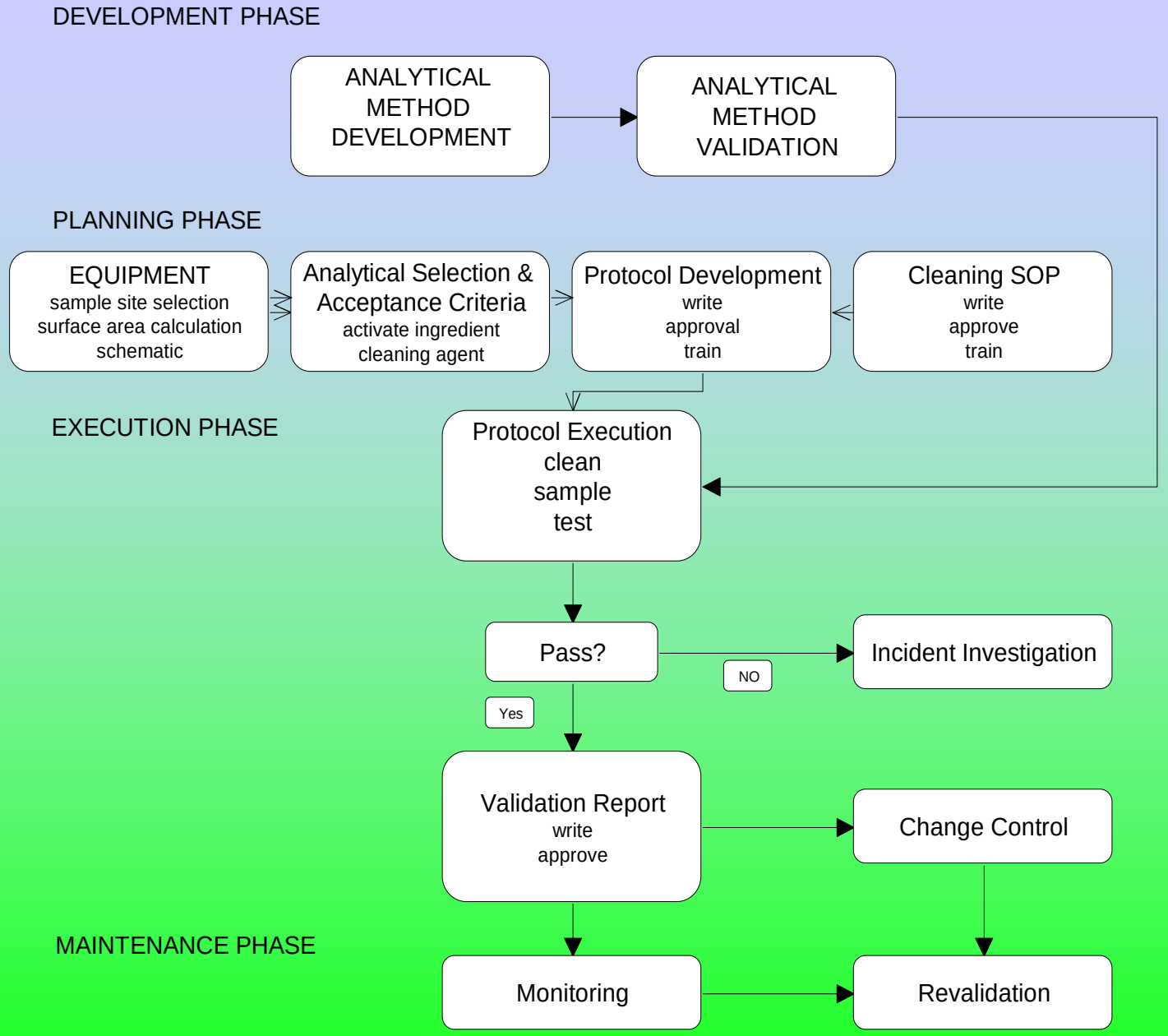
A well-defined and documented validation process provides regulatory agencies with evidence that system and method is suitable for its intended use.

By approaching method development, optimization and validation is logical, stepwise fashion, laboratory resources can be used in a more efficient and productive manner

Thank U

CLEANING VALIDATION FLOW DIAGRAM

Dr.K.Kathiresan,M.Pharm., Ph.D.,M.B.A.,
Associate Professor
Department of Pharmacy
Annamalai University


DEVELOPMENT PHASE
ANALYTICAL METHOD DEVELOPMENT
ANALYTICAL METHOD VALIDATION
PLANNING PHASE
EQUIPMENT
sample site selection
surface area calculation
schematic
Analytical Selection & Acceptance Criteria
activate ingredient
cleaning agent
Protocol Development
write
approval
train
Cleaning SOP
write
approve
train
EXECUTION PHASE
Protocol Execution
clean
sample
test
Pass?
NO
Incident Investigation
Yes
Validation Report
write
approve
Change Control
MAINTENANCE PHASE
Monitoring
Revalidation

Thank You

STERILE AREA VALIDATION

Dr. K. Kathiresan,M.Pharm.,Ph.D.,M.B.A.

Associate Professor

Department of Pharmacy

Annamalai University

GENERAL REQUIREMENTS

Sterile products, being of very critical and sensitive nature, a high degree of precautions, preventions and preparation are needed, dampness, dirt and darkness are to be avoided at all cost to ensure aseptic conditions in all areas. There should be no let up in the prescribed standards specially in the matter of water supply, air, active materials and the maintenance of hygienic environment.

Buildings

The buildings should be built on a proper foundation with standardized materials to avoid cracks in critical areas like aseptic solution preparation, filling and sealing rooms, there shall be no drains, doors shall be made of non-shedding material.

Air handling system

Air handling units for sterile product manufacturing area should be different from those of other areas, Critical areas ,such as aseptic filling area, sterilised components unloading area, change rooms conforming to grades D,C and B respectively should have separate Air handling units. The filter configuration in the air handling system shall be according to the grade of air as given below.

Grade	Maximum number of permitted particles per cubic meter equal to or above		Maximum No. of viable microorganisms permitted per cubic meter of air
	0.5 – 5 μ	> 5 μ	
A (Class 100) Laminar Air – flow Work station	100 – at rest and 3500 - in operation	None	Less than 1
B (Class 100)	3,500	None	5
C (Class 10,000)	3,50,000	2,000	100
D (Class 1,00,000)	3,50,000	20,000	500

Types of operations to be carried out in the various grades of aseptic preparation

Class	Types of operations for aseptic Preparations
100 (Grade A & B)	Aseptic Preparation and Filling
10,000 (Grade C)	Preparation of solution to be filtered
100,000 (Grade D)	Handling of components after weighting

LAF

Laminar air flow is the controlled air flow in which the entire volume of air within a designated space moves at a uniform velocity in a single direction along parallel flow lines.

HEPA filters

High Efficiency Particulate Air Filters are 99.99 % efficient in removing particles 0.3 micron and larger. HEPA filters utilize glass fiber rolled into a paper like material. This material is pleated to increase the fiber surface area and bonded, or potted, into a frame. Hot melt is used to hold the pleats far enough apart to allow air to flow between them.

Types of operations to be carried out in the various grades of Terminally Sterilized Products

Class	Types of operations for Terminally Sterilized Products
100 (Grade A & B)	Filling of Products
10,000 (Grade C)	Preparation of solution when usually at risk
100,000 (Grade D)	Preparation of solutions and components for subsequent filling

Environmental Monitoring

1. Particulate monitoring in air - 6 monthly
2. HEPA filter integrity testing (smoke testing) – yearly
3. Air change rates – 6 monthly
4. Air pressure differentials – daily
5. Temperature and humidity – daily
6. Microbiological monitoring by settle plates and / or swabs in aspectic areas / at decreased frequency in other areas – daily

Recommended limits for microbiological monitoring of clean areas “ in operation”

Class	Air sample Cfu/m^3	Settle plates (dia 90mmcfu/4 hrs)	Contact plates (dia.55 mm cfu/plate)	Glove points (five fingers)cfu per glove.
100 A	<1	<1	<1	<1
100 B	10	5	5	5
10,000	100	50	25	-
100,000	200	100	50	-

THANK YOU