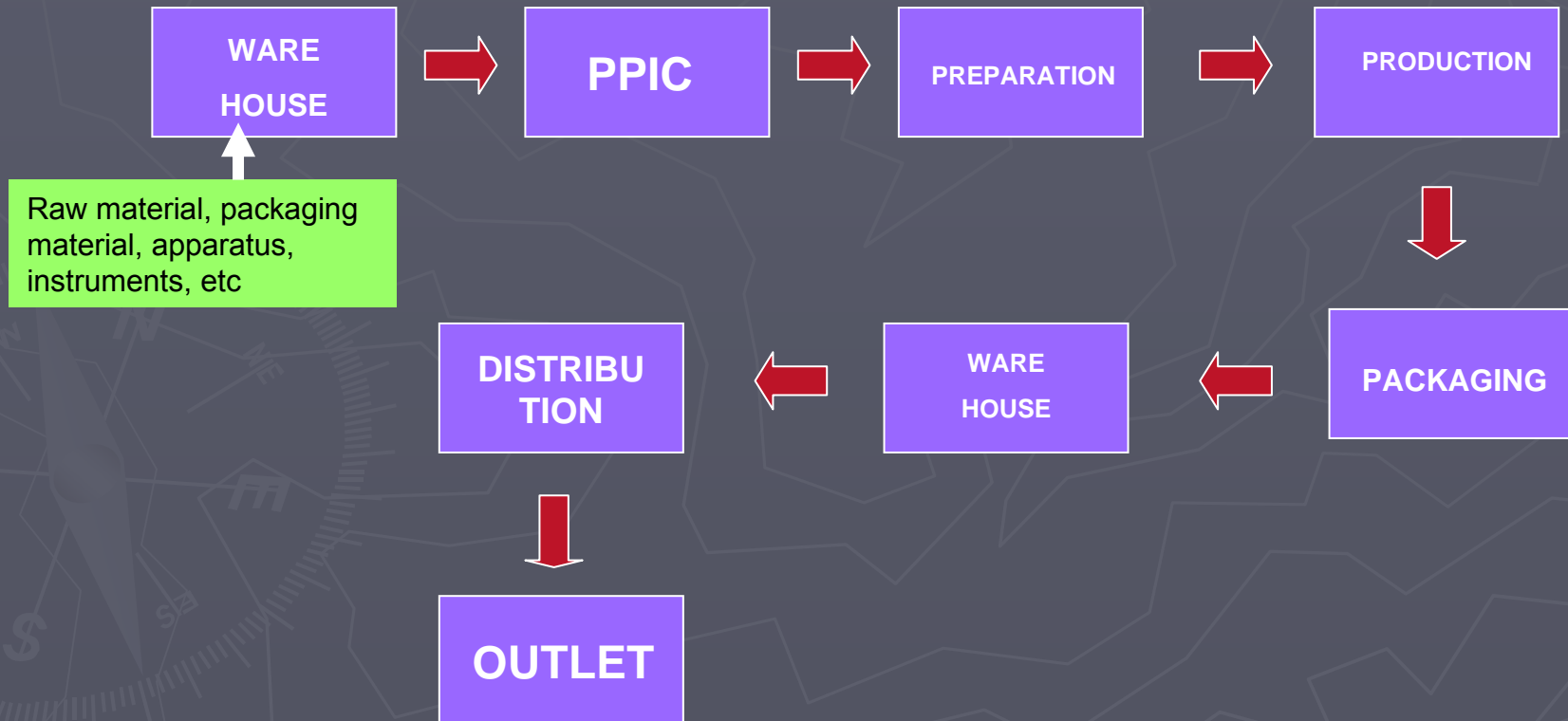




PRINCIPLES AND METHOD OF SAMPLING

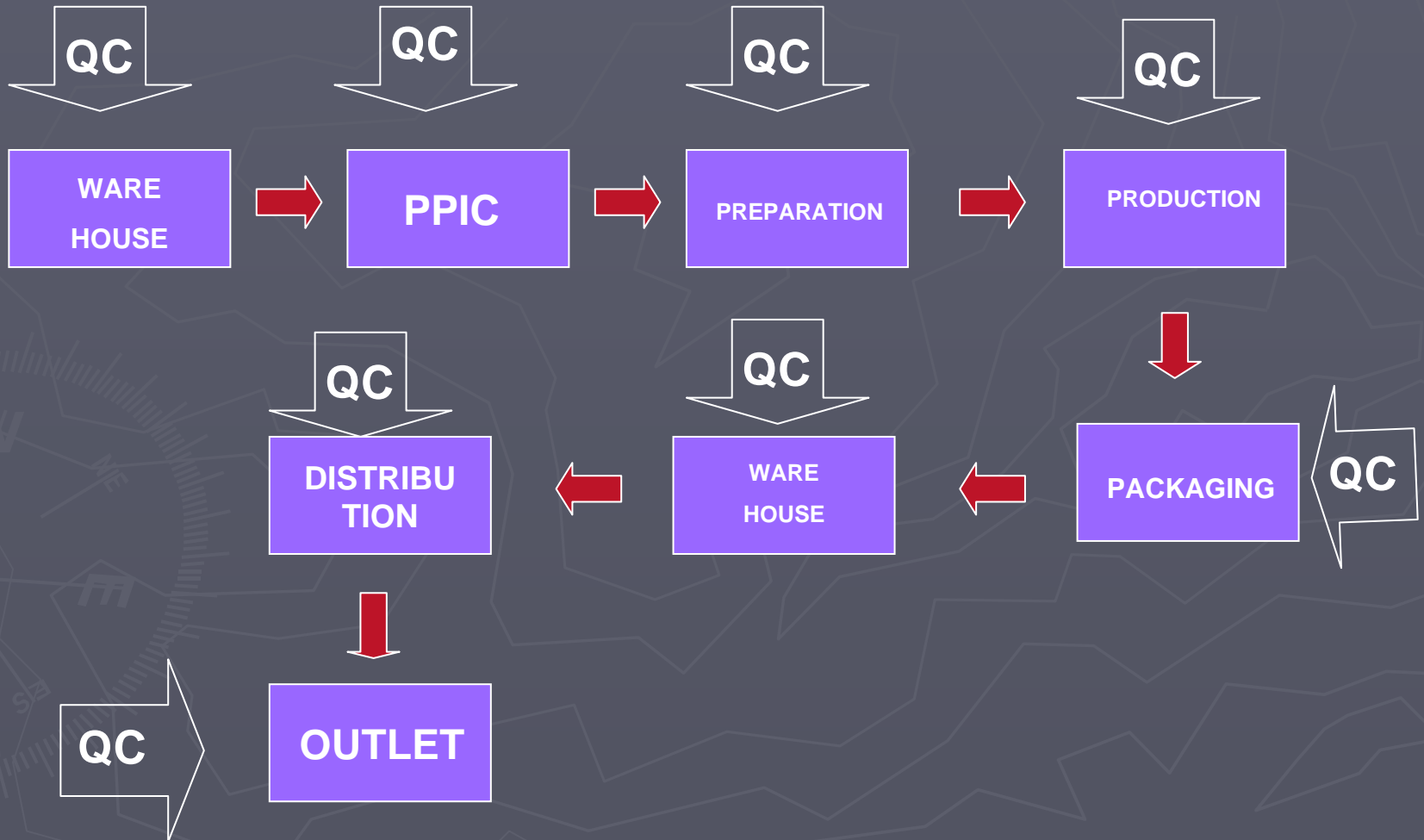
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GENERAL PROCESS IN PHARMACEUTICAL INDUSTRY



**WHERE AND WHICH STEP QC
SHOULD BE APPLIED?**

QC SAMPLING



General Principles

- ▶ Taking Sample (*Sampling*) is a first step in a process where data of characterisation results of one batch's products is collected to be evaluated
- ▶ Since only a part of a batch of products is taken as a sample to be evaluated, that "part" should be REPRESENTATIVE of batch
- ▶ Test Results will determine the "fate" of the batch (will be accepted or rejected), so that SELECTION PROCESS of sample is a critical/important step in Quality Assurance System

- ▶ In any sampling process, there is an indicator of quality → called "attribute"
- ▶ Some Attributes should be determined and it will show all characteristics in a certain batch
- ▶ In microbiological sampling, the requirements not only on homogeneity and random sampling, but also HACCP (Hazard Analysis and Control of Critical Points).

Sampling in microbiology context

- ▶ **Contamination** should be concerned! Special treatment should be applied for certain raw material that highly risk in contamination.
- ▶ Kind of treatment can be varied depends on the sample's properties. For example, if the product should be manufactured **aseptically**, sterility test should be carried out in a special room with special facilities (**LAF cabinet class A in clean room class B**).
- ▶ For other products (non-sterile products), the sampling area no need to be in sterile-area.

SOP (Standard Operating Procedure) for sampling process

- ▶ SOP for sampling should be established because sampling Quality Assurance System
- ▶ SOP should contain several factors, such as :
 - **methods and apparatus used**
 - **Personnel allowed to do sampling**
 - Amount of sample should be taken
 - **Distribution of samples**
 - Container for samples
 - Storage condition
 - Time interval when sampling applied,
 - and other specific attention for certain samples

Single sampling (Sampling Tunggal)

- ▶ Classic sampling method : one sampling for one container
- ▶ The number of sample's container should be taken is depends on number of batch delivered.
- ▶ General principles of sampling : $\sqrt{n} + 2$
- ▶ n = number of containers in 1 batch
- ▶ Samples taken should be then mixed, and tested, and the result will determine the batch *reject or release*
- ▶ If the result cannot be determined due to uncertain datas, the samples can be resampling to be retested.
- ▶ The result of retesting should be evaluated to see the trend of the products

Attribute Sampling

- ▶ An alternative method of sampling involves the selection of attributes which must be met in full or part by predetermined number of samples taken from the delivery.
- ▶ It is widely adopted in cosmetic and food industries
- ▶ **Tolerance** : allowing a small proportion of samples to show slight deficiencies
- ▶ However, Clearly it is not for STERILE product!
- ▶ Level of assurance is higher than classic method

Two-class Attribute Scheme

- ▶ Important Parameters :
 - Number of samples taken , and
 - Maximum permitted number of positive result are defined (Symbol n and c).
- ▶ Example : Bacteriology test for drinking water: if > 5 samples taken ($n=5$), *E.coli* is not permitted in any sample, and only 2 of 5 samples may contain **Enterobacteriaceae**.
- ▶ Thus, two quality levels are defined :
 - No *E.coli* , and
 - A limited number of samples which may contain **Enterobacteriaceae**.

- ▶ In pharmaceutical term this scheme is suitable where 1 positive results are unacceptable. For example : a raw material of natural origin, such as thyroid powder, may have a specification requiring the absence of *Salmonella* in 25 gram ($n=5 \times 5$ g, $c=0$)

Parameter in Two attribute sampling

- ▶ n = number of sample to be tested
- ▶ m = maximum number of positive result that on the limit of reject/defect
- ▶ c = maximum number of positive result above "m" before the lot will be rejected
- ▶ Example : If $m = 10^4$ cfu/g, and the test result :
 - $9,8 \times 10^3 \rightarrow$ it is "acceptable" , but
 - $1,2 \times 10^4 \rightarrow$ it is "defective"

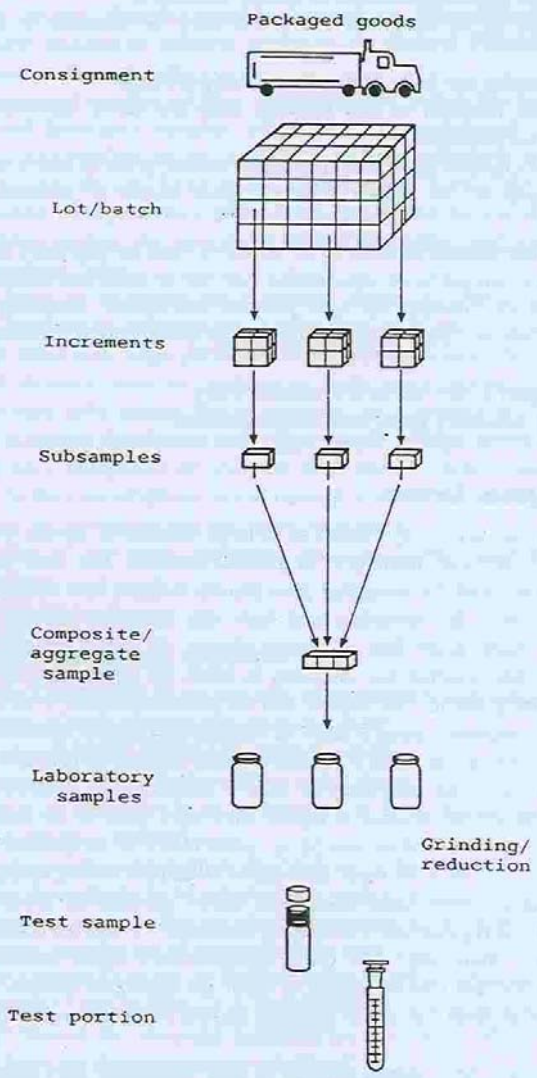


Figure 6 Sampling scheme for packaged goods

Three-class Attribute Scheme

- ▶ In this scheme, 3 quality levels are defined :
 - Fully acceptable (AQL=Acceptable Quality Level)
 - Marginally acceptable
 - Unacceptable
- ▶ This Method is widely used in food and cosmetic industries with the establishment and use of microbiological reference value. (Mosses 1995, CTPA 1996).
- ▶ In Pharmaceutical microbiology, the method is used very restricted for non-sterile products, and in-use testing of raw material

- ▶ Example : a viable count of less than 100 cfu, may be regarded as **acceptable**, while a count of more than 1000 cfu is **unacceptable**, counts between 100 – 1000 cfu may regarded as **marginally acceptable**, only in a defined number of samples.

Sampling from package/sacks/cans/bags

Number of package	min.number to be sampled
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100 or less

not less than 10

Above 100

$\sqrt{n + 2}$

Re-sampling

- ▶ If there is any doubt as to the validity of sampling, a second sampling must be taken.
- ▶ When the accuracy of the counting method has been questioned, or perhaps a non-homogeneous distribution of microorganisms is suspected, a re-examination may be justified.
- ▶ Microbial populations may be dynamic, changing over a period of time and reveal a different microbial profile on a second sampling.

Requirement of sampling method

- ▶ It should not introduce contaminants
- ▶ It should not stress the microbial population (example: shear forces, rising temperature, etc)
- ▶ It should provide reproducible results

Reference Samples

- ▶ Sample taken for reference material should be representative of the batch from which they were taken.
- ▶ The Samples should be labelled, with reference number, the content, batch no, date of sampling, and the container from which the samples are withdrawn.
- ▶ The reference Sample should be retained from each batch over 1 year after the expire date of the products. The amount of the samples should be sufficient to permit at least a full re-examination.
- ▶ Appropriate precaution should be taken to prevent damage to samples during storage which would invalidate the results.

HACCP

(Hazard Analysis of Critical Control Point)

- ▶ HACCP = a system to guarantee that the microbiological monitoring and control at critical points has been established in every production steps, and the number of samples taken are suitable.
- ▶ The production process must be monitored routinely and intensively
- ▶ If necessary, Corrective action should be taken to assure the quality at any time.

Monitoring in HACCP

- ▶ To limit contamination by selecting suitable raw material and applying appropriate hygienic measures during manufacture
- ▶ To minimize all opportunities for microbial growth throughout product manufacture, distribution, and storage
- ▶ Processing for safety (i.e. sterilization process) if a safe product cannot be ensured by the two previous system of defence.

Specialized Sampling



Specialized Sampling

- ▶ Sterile Products
- ▶ Sampling for Bioburden test
- ▶ WATER
- ▶ Environment
- ▶ Medical Devices



Sampling for Sterile Products

- ▶ Probability of test results
- ▶ Number of samples for test
- ▶ Volume of samples for test

Sterile products

- ▶ When sampling for sterility, the level of assurance concerning the quality of the batch is a function not only of the homogeneity of manufacture condition, but also of the efficiency of the sampling plan
- ▶ In mathematical term, the proportion of container which are sterile and not-sterile in one batch can be defined as : q and p
→ $p + q = 1$ or $q = (1-p)$
- ▶ If "n" samples are taken, probability (P) of all of the samples being sterile, and the batch therefore passing the test is :

$$P = q^n \text{ atau } P = (1-p)^n$$

Probability in sampling of sterile product

- ▶ Example: Supposing 1% of the containers were contaminated, (means: $p = 0.01$), and ten samples were taken for test ($n=10$), then the $P = (1-0,01)^{10}$ or $P = 0,904$
- ▶ This means : in taking ten samples from the batch (with 1% not sterile) the batch will pass the test with probability 9 of 10 occasions when tested
- ▶ Thus, number of samples taken, will determine the probability of passing the sterility test

Probability of a batch passing the sterility test on various degree of contamination and sample size

Sample size	Percentage of contaminated items in the batch				
	0.1	0.5	1.0	3.0	5.0
10	0.99	0.96	0.91	0.74	0.60
20	0.98	0.90	0.82	0.54	0.35
50	0.95	0.78	0.61	0.22	0.08
100	0.91	0.61	0.37	0.05	0.01

Bioburden Sampling

- ▶ Bioburden testing is generally done to estimate number of microorganisms that may be present in : product before sterilization (pre-sterilization count), solid and liquid raw material, equipments, and gas components
- ▶ Aqueous Products : Assumed **homogeneously contaminated**
- ▶ Non-aqueous products : contamination may occur depends on the product properties
- ▶ Aerosol Products : air-borne contamination

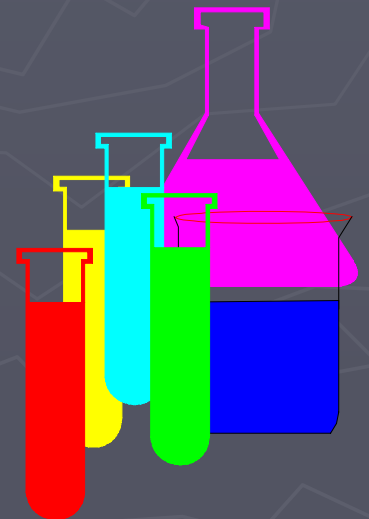
Sampling for water

- ▶ Method and number of sample are depend on its usage, preparation and storage.
- ▶ Water for production process, should be sampled at least 1x/week
- ▶ Deionized water should be sampling 1x/week, or at every regeneration cycle
- ▶ During validation process system, and should be guarantee that no contamination occurred before regeneration process

- ▶ The higher quality of water used, the fewer contamination allowed , and more volume of water should be sampled
- ▶ According to FDA :
 - Water for cleaning and washing : 3x100 mL
 - Water for production or rinsing process : 3x250 mL or more than 1 same sampling point
 - Water for cooling process after sterilization : 3x1 L or more than 1 same sampling point
 - Water for endotoxin test : < 1 mL, taken from depyrogenized containers
- ▶ Sampling of water should be carried out at the outlet and the water is allowed to drain for 2 minutes before sampling

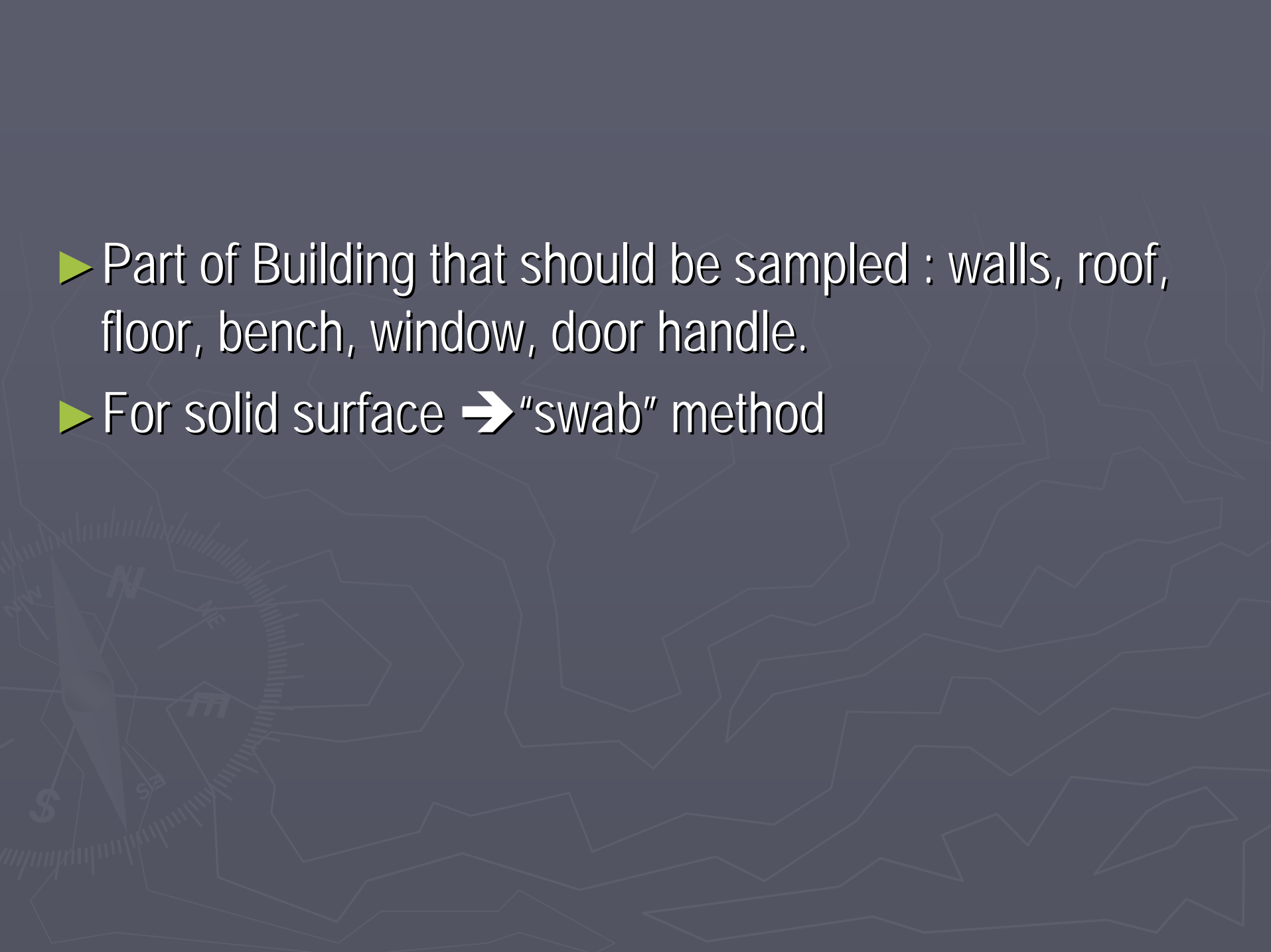
Sampling of Environment

- ▶ Sampling method used to monitor contamination in air inside the laboratory can be done by placing a petri dish contains medium for microbial growth in certain areas.
- ▶ Apparatus for sampling can be varied



Analysis of quality of air in laboratory or other rooms

- ▶ Evaluation was based on normal activities
- ▶ Sampling apparatus : i.e. SAS = Surface Air System Sampler, or Sieve Sampler
- ▶ Determination of microbial number in the air sampled per square metre or other value.
- ▶ Parameter measured : Total Plate Count (Angka Lempeng Total) of microorganisms (aerob bacteria and mould/yeast)

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- ▶ Part of Building that should be sampled : walls, roof, floor, bench, window, door handle.
 - ▶ For solid surface → "swab" method

Sampling of medical devices

- ▶ In contrast to raw material, the component of medical devices are not normally tested for microbial contamination on a routine basis.
- ▶ Sterility testing only conducted on final product, and before sterilization.
- ▶ Medical devices : Syringe, Pacemaker, orthopaedic implant, dressing, tapes, patch raw material , etc.