

# In Process & Finished Products Quality Control

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# Introduction

- All Pharmaceutical Industry aims to make products with good quality products so this can be done by allowing In-Process Quality Control (IPQC) Approaches.
- The importance of IPQC to carry out complete testing before, after and during the manufacturing process is completed for the Products.
- To Monitor and improve effectively the whole applied process at the every stage of the finished pharmaceutical products by according to Standard Operating Procedures (SOPs).

Definition: IPQC is concerned with providing accurate, specific and definite description of the procedures to be employed from the receipt of raw materials to the release of the finished dosage form.

- Quality is not an accident this is the result of intelligent effort.
- IPQC tests are performed at regular intervals (generally each 1 hr later) during the manufacturing process.
- These tests are varied from dosage form to dosage form.
- In process quality control is a planned system to identify the materials, equipments , process and operators.

# OBJECTIVES

- To optimize the whole applied technological procedure.
- To monitor control and improve effectively the whole applied operations at the every stage of the finished pharmaceutical products.
- Inspection of raw material, equipment, environment, process, testing with respect to specification, packing and so on.
- Quality control & Process Control

# IPQC Involve

- Physical and chemical test:
  - Identity test
  - Quality test
  - Purity test
  - Potency test
  
- Biological and microbiological test:

# Physical and chemical test:

- **Identity Test**- These tests are qualitative chemical method used to confirm the actual presence of compound. E.g. color formation, precipitation.
- **Quality test**- These tests are physical method used to measure accurate the characteristics properties of drug. e.g.- absorbance, refractive index.
- **Purity test**- It is deigns to estimate the level of all known and significant impurities and contamination in the drug substances. E.g. test for clarity of solution, acidity/alkalinity.
- **Potency test**- these tests always estimate the quality of an active ingredient in drug.

# Biological and microbiological test:

- Biological and microbiological– It included macro and micro biological ways and test for safety , toxicity, pyrogenicity, sterility, antiseptic activities and antimicrobial preservative effectiveness test.
- Biological test of drug can be qualitative or quantitative in nature.
- It involves the animals preparation isolated by living tissues.

# In Process Checks Shall Includes

## Following Process Controls

- Cleanliness of the area and line clearance
- Checking of the status labels on the area and process containers.
- Equipment/instrument: Calibration, verification and checking of the status labels.
- Checking and verification of material used as Material Name, Material Code, Control No. or A.R. No.
- Time limits at all stages of process.
- Checking of sieve/filter integrity.
- Check vendor while goods are received and it should be according to approved vendor.
- Online review of batch record at every stage of process.
- Product attributes Like Weight, Hardness.
- Verification of yield at various stages of manufacturing process.
- Periodic check of control samples.
- Measured values obtained from the room environment like Temperature, Humidity.



# ➤ IPOC Before, After & During The Manufacturing

- At Sampling Stage : Planning of sampling should be done as per the Standard Operating Procedures (SOP)s which describes the sampling methods. Sufficient quantity of samples should be collected for Analysis.
- At Manufacturing Stage : Weighing or measuring of active pharmaceutical ingredients, excipients, diluents or vehicle should be done under the suitable conditions which do not affect their conformity of use. Appropriate and calibrated equipment / instrument should be used for the above purpose.
- In Process Test Stage: In-process tests should be performed on the sampled material. The quality control dept. will be responsible for the testing. Samples are tested by quality control personnel to verify conformance with specifications within the acceptable limits.

<b>Stage</b>	<b>Control Variables</b>
Granulation	Moisture, Blend Uniformity, Bulk & tapped Density, Particle size Distribution.
Solid Oral Products (Tablets, Capsules)	Appearance, Average Weight, Weight Variation, Hardness, Thickness, Friability, Disintegration
Semi-solids	Appearance, Viscosity, Homogeneity, pH,
Liquids Oral Products	Appearance, Clarity Of Solutions, pH, Specific Gravity, Weight Per mL
Parenterals- Injectables (liquid-SVP & LVP)	Appearance, Clarity, Fill Volume, pH, Filter Integrity Tests, Particulate Matter, Shape Of Container, Sealing Quality Of Container, Leak Testing Of Container, Pre-Filtration or Post-Sterilization, Bio-Burden Testing, Bacterial Endotoxin Tests.
Parenterals-Injectables (Dry powder Injection)	Appearance, Clarity after reconstitution, Weight, Average weight, Weight variation, Particulate matter, Shape of container, Sealing quality of container, Leak testing of container.
Dry powder inhalers	Assay of API-excipient blend, Moisture, Weight variation of individually contained doses.
Transversal dosage forms	Assay of API-adhesive mixture, Weight per area of coated patch without backing.
Metered dose inhalers	Fill weight or volume, Leak testing, Valve delivery.
Yield	Verification with the set target at every stage

**Table: In-process Control Parameters**

# IPQC & FPQC For Tablets

- ❑ **Size and Shape**: The size and shape of the tablet can be dimensionally described monitored and controlled. It is determined by the tooling during the compression process.
- ❑ **Color and Odor**: Many pharmaceutical tablets use color as a vital means of rapid identification and consumer acceptance. But it must be uniform within a single tablet, from tablet to tablet and from lot to lot. The presence of an odor in a batch of tablets could indicate a stability problem e.g. the characteristic odor of acetic acid in degrading aspirin tablets or could be characteristic of the drugs e.g. vitamins have a characteristic odor. Taste is important in consumer acceptance of chewable tablets.

- ❑ **Thickness** :The thickness of a tablet is the only dimensional variable related to the process. Thickness of individual tablets may be measured by a micrometer. Other techniques involve placing 5 or 10 tablets in a holding tray, where their total thickness may be measured by a sliding caliper scale. Tablet thickness should be controlled within a  $\pm 5\%$  variation of a standard. Thickness must be controlled to facilitate packaging. It is expressed in mm.
- ❑ **Unique Identification Markings** : Pharmaceutical companies often use some type of unique markings on tablets in addition to color, for rapid identification of their product these markings utilize some form of embossing, engraving or printing of the company name or symbol or a product code.

- ❑ **Moisture Content of Granules** : Granules should possess sufficient strength to withstand normal handling and mixing processes without breaking down and producing large amounts of fine powder. On the other hand, some size reduction during compaction into tablets is desirable to expose the areas of clean surface necessary for optimum bonding to take place so moisture content is the very important factor for producing good pharmaceutical product.
- ❑ **Assay** : In a tablet an active ingredient is present which is called API. So to prepare the tablet assay has to be done by using suitable analytical method to produce good finished product.



**□ Uniformity of Content :** A physically sound tablet may not produce the desired effects. To evaluate a tablet potential for efficacy, the amount of drug per tablet needs to be monitored from tablet to tablet and batch to batch.

- For this test according to BP using a suitable analytical method, determine the individual contents of active substance(s) of 10 tablets taken at random.
- The tablet complies with the test according to BP, if each individual content is between 85 percent and 115 percent of the average content.
- The tablet fails to comply with the test if more than one individual content is outside these limits or if one individual content is outside the limits of 75 percent to 125 percent of the average content.
- If one individual content is outside the limits of 85 percent to 115 percent, but within the limits of 75 percent to 125 percent, determine the individual contents of another 20 tablets taken at random.
- The tablet complies with the test if not more than one of the individual contents of the 30 tablets is outside 85 percent to 115 percent of the average content and none is outside the limits of 75 percent to 125 percent of the average content .

□ **Uniformity of Mass** : This test is applicable for uncoated and film coated tablets. For this test according to BP weigh individually 20 tablets taken at random and determine the average mass. As per BP the tablet complies with the test if not more than 2 of the individual masses deviate from the average mass by more than the percentage deviation as shown in Table 1 and none deviates by more than twice that percentage.

Table 1: BP limits for uniformity of mass

Average Mass (mg)	Percentage Deviation (%)
80 or less	10
More than 80 and less than 250	7.5
250 or more	5

## □ Weight Variation Test :

- According to the USP weight variation test is run by weighting 20 tablets individually calculating the average weights and comparing the individual tablet weights to the average.
- The value of weight variation test is expressed in percentage. The following formula is used.

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$$\text{Weight Variation} = (Iw - Aw)/Aw \times 100\%$$

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- where,  $Iw$  = Individual weight of tablet  
 $Aw$  = Average weight of tablet.
- As per USP the tablet complies with the test if not more than 2 of the individual masses deviate from the average mass by more than the percentage deviation as shown in Table 2 and none deviates by more than twice that percentage.



## USP limits for weight variation test for uncoated tablets

Average Weight (mg)	Percentage Deviation (%)
130 or Less	10
130 – 324	7.5
More than 324	5

- ❑ **Hardness Test:** For this test one of the earliest testers was Ketan tablet hardness tester, which is a type of the Monsanto hardness tester to evaluate tablet hardness tester.
- The tester consists of a barrel containing a compressible spring held between two plungers. The lower plunger is placed in contact with the tablet and zero reading is taken.
  - The upper plunger is then forced against a spring by turning a threaded bolt until the tablet fractures.
  - As the spring is compressed, a pointer rides along a gauge in the barrel to indicate the force. The force of fracture is recorded in kilogram.

- ❑ **Friability Test** : Friability of a tablet can determine in laboratory by Roche friabilator.
- For this test twenty tablets are weighed and placed in the friabilator and then operated at 25 rpm for 4 minutes. The tablets are then dedusted and weighed.
  - The difference in the two weights is used to calculate friability and the value of friability is expressed in percentage.
  - It is determined by the following formula.

$$\text{Friability} = (Iw - Fw)/Iw *100\%$$

where, Iw = Total Initial weight of tablets;

Fw = Total final weight of tablets.

As stated by USP if conventional compressed tablets that loss less than 0.5 % to 1 % (after 100 revolutions) of their weight are generally considered acceptable.

## ❑ Disintegration Test :

- The USP disintegration apparatus consist of 6 glass tubes that are 3 inches long, open at the top, and held against a 10-mesh screen at the bottom end of the basket rack assembly.
- To test for disintegration time, one tablet is placed in each tube and the basket rack is positioned in specified medium at  $37 \pm 2$  ° C such that tablet remains 2.5 cm below the surface of the liquid on their upward movement and descend not closer than 2.5 cm from the bottom of the beaker.
- A standard motor driven device is used to move the basket assembly containing the tablets up and down through distance of 5 to 6 cm at a frequency of 28 to 32 cycles per minute.
- Perforated plastic discs may also be used in the test.
- These are placed on the top of tablets and impart an abrasive action to the tablets.
- The discs may or may not be meaningful or impart more sensitivity to the test, but they are useful for tablets that float. Operate the apparatus for the specified time (15 minutes for uncoated tablet unless otherwise justified and authorized).

- The tablet complies with the test, if the tablets disintegrate, and all particles pass through the 10-mesh screen in the time specified.
- If any residue remains, it must have a soft mass with no palpably firm core.
- The tablet complies with the test according to USP, if all of the tablets have disintegrated completely.
- If 1 or 2 tablets fail to disintegrate completely, repeat the test on 12 additional tablets.
- The requirement is met if not less than 16 of the total of 18 tablets tested are disintegrated.
- The BP and IP limits for disintegration times of tablets are given in Table 4 and Table 5 respectively.

<b>Categories of Tablets</b>	<b>Disintegration Time (min)</b>
Uncoated tablets	15
Coated tablets	60
Enteric-coated tablets	60
Film-coated tablets	13
Effervescent tablets	5
Soluble tablets	3
Dispersible tablets	3

IP limits for disintegration times of tablets

# □ Dissolution Test :

- Temperature inside the vessel at  $37 \pm 0.5$  ° C during the test and keeping the bath fluid in constant, smooth motion.
- Place 1 tablet in the apparatus, taking care to exclude air bubbles from the surface of the tablet.
- Operate the apparatus at the specified rate.
- Within the time interval specified, or at each of the times stated, withdraw a specimen and replace with equal volumes of fresh dissolution medium at 37 ° C.
- Verify the temperature of the medium at suitable times.
- Perform the analysis using a suitable assay method as directed in the individual monograph. Repeat the test with additional tablets.
- Unless otherwise specified in the individual monograph, according to BP, USP, PhEur, JP the requirements are met if the quantities of active ingredient dissolved from the tablets tested conform to the following acceptance criteria.

Stage	Number of Tablet Tested	Acceptance Criteria
S1	6	Each unit is not less than $Q + 5\%$ .
S2	12	Average of 12 units (S1 + S2) is equal to or greater than $Q$ , and no unit is less than $Q - 15\%$ .
S3	18	Average of 24 units (S1 + S2 + S3) is equal to or greater than $Q$ , not more than 2 units are less than $Q - 15\%$ , and no unit is less than $Q - 25\%$ .

Table: BP, USP, PhEur, JP acceptance criteria for dissolution test of tablet

Continue testing through the 3 stages unless the results conform at either S1 or S2. The quantity  $Q$ , is the specified amount of dissolved active substance, expressed as a percentage of the labeled content; the 5 percent, 15 percent, and 25 percent values in the table are percentages of the labeled content so that these values and  $Q$  are in the same terms.

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**Thank You**