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IN-PROCESS QUALITY CONTROL: A SYSTEMATIC APPROACH TO CONTROL CRITICAL STEPS IN FINISHED PHARMACEUTICAL PRODUCTS

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ABSTRACT

The main objective of pharmaceutical industry is to manufacture the quality products. Quality cannot be tested in the product it should be built- in by design and verified during the process with careful attention to the extent possible rather than depend alone on the end product testing. Many factors are responsible to give assurance of the quality of product. One of them is In-Process Quality Control Checks (IPQC). Critical points of all stages of the manufacturing process being checked by In-Process Quality Control according to standard operation procedures (SOPs). These applied SOPs vary from one finished dosage form to another. The acceptance criteria for the critical steps are also varying from product to product; it is close to the final release specification. The aim of In-Process Quality Control checks is to monitor and improve effectively the whole applied operations at the every stage of the finished pharmaceutical products. The In-Process Quality Control check ensures that the finished dosage form fulfills all quality requirements.

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INTRODUCTION

The quality of the product is the foundation of pharmaceutical industries and is achieved from careful attention to a number of factors including selection of materials, selection of product, manufacturing process design and development, control of the process variables, in-process control and end-product testing.

In-process quality control (IPQC) is the process that is carried out before, after and during the manufacturing of the finished pharmaceutical product[1] (FPP). The FPP are the products of all categories which has undergone all stages of manufacturing process, including packaging in its final container and labelling.

The function of In-process quality control is to monitor and if necessary modification and adjustment of the manufacturing process in order to comply with the specifications. In this check control of equipment, process and environment also included[2].

In-process control gives an assurance to the manufacturer that the finished pharmaceutical product fulfills all the quality requirements. All operations involved in the preparation of a pharmaceutical product, from receipt of materials, through processing, packaging and repackaging, labeling and re-labeling, to completion of the finished product are controlled.

A planned set of control strategy is followed for critical operations. The controls can include specifications parameters, associated methods and frequency of monitoring related to active pharmaceutical ingredient, excipients, finished pharmaceutical product, and equipment operating conditions respectively[3].

The control on the all operations should be established in the form of written procedure which clearly describes to follow the IPQCs and tests.

Written procedures are known as Standard operating procedures (SOPs)[4]. In-process control should be strict to follow SOPs.

Aim of In-Process Quality Control:

As already mentioned many operations are involved during the manufacturing of a finished product and it is understood that quality is the responsibility of all the persons involved in the manufacturing and also Quality cannot be tested into products; it should be built-in (i.e. by design) and verified during the process to the extent possible rather than depend alone on end product testing. Hence it is necessary to check and control the critical points of the product during the manufacturing and up to the final packing of the product.

Thus the main purposes of In-Process Quality Control checks (IPQC) are to monitor control and improve effectively the whole applied operations at the every stage of the finished pharmaceutical products. In-Process control includes inspection of raw material, equipment, environment, process, testing with respect to specification, packing and so on. The In-Process control is performed at regular intervals[5] of either one hour or half an hour later.

The Good Manufacturing Practices follow to eliminate the risks at every stage of manufacturing process Good Documentation Practices and Good Review Practices should be follow during the In-process checks[6] to maintain the records.

Controls of Critical Steps

The quality assurance (QA) dept plays an important role at the different stages of manufacturing of finished pharmaceutical product. One of them is IPQC checks of critical points.

Critical Process controls[7-9] is changes in the process step and methods. The changes are not permitted within pre-established limits; it must be approved by the QA dept. All tests and results should be fully documented as part of the batch record.

In-process controls and their acceptance criteria should be defined on the information obtained during the development stage or previous records. The acceptance criteria, type and extent of testing can depend on the nature of the process step being conducted, finished product being manufactured, and the degree to which the process introduces variability in the product's quality.

In process checks shall include following process controls.

- Cleanliness of the area and line clearance
- Environmental conditions and 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.
- Verification of yield at various stages of manufacturing process.
- Periodic check of control samples.

To check the variation in the quality of the products filled documents should be maintained for the above process steps to keep the record of progress, and control the performance of process steps.

At Manufacturing Operation 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.

Weighing, measuring, or subdividing operations should be done in presence of QA & production authorized personnel. Prior to use in manufacturing process, IPQC & production personnel should verify all the materials against the batch manufacturing record. Materials should be appropriately controlled to prevent unauthorized use. Following information being available on the label:-

- Material Name, Material Code, Control No. or A.R. No
- Weight or volume of material in the new container; and
- Re-test date if required.

When the product from one process is transferred to other process, the yield should be compared with set targets, if problems or deviations are observed the remarks and reasons are mentioned. If the deviation is not within the acceptable limits further manufacturing process should be continued only after QA / QC clearance and proper records should be maintained either by computer control systems, or alternative means[10].The processing status should be appropriately documented,

At Sampling stage

Planning of sampling should be done as per the Standard Operating Procedures (SOP) which describe the sampling methods. Sufficient quantity of samples should be collected for Analysis. Sampling plans and procedures will be changed for in-process materials, intermediates, bulk products or products of different category, it should be based on the required testing parameters for different dosage forms. Sampling procedures should be established to ensure the quality of the samples after collection[11]. Samples are tested to verify conformance with specifications by quality control personnel.

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.

These tests are only used for the purpose of adjusting process parameters within an operating range, e.g., hardness and friability of tablet cores which will be coated, individual tablet weights are not included in the specification. Some tests conducted during the manufacturing process, (e.g., pH of a solution), the IPQC limit of pH is also within the appropriate range. The examples of applicable in-process controls testing are [12] given in the table-1.

Table -1.: In-process Control parameters.

Stage	Control variables
Granulations	Moisture (limits expressed as a range), blend uniformity (e.g. low-dose tablets), bulk and tapped densities and particle size distribution.
Solid Oral Products (Tablets, Capsules)	Appearance, average weight, weight variation, hardness, thickness, friability, disintegration checked periodically throughout compression and weight gain during coating.
Semi-solids	Appearance, viscosity, homogeneity, pH.
Liquids Oral Products	Appearance, clarity of solutions, pH, specific gravity, volume.
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 and/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

The acceptable limit comply to specifications for above stage will be set by the manufacturing site which should be establish according to available data of development stage, validation stage, stability studies and compendia.

The limit set for the in-process tests are only for the purpose of monitoring and/or adjusting the process. Out-of-specification (OOS) investigations are not necessary for the in-process tests.

At Packing stage

QA Personnel should give clearance for the finished dosage forms at all the critical points of packing operation stages according to the written procedure. The packing of batch should be performed in following sequence:-

- Check environmental monitoring it should be performed and record must be maintained.
- Check the area of cleanliness, all unwanted material of previous batches should be absent.
- Check that the blisters are free from knurling defects, strips for alignment defects & empty pockets.
- Check that the packing materials are received from approved vendors.
- Check that the packing material should be tested by quality control dept and status labels.
- Check the status labels on equipment, area & in-process containers.
- Check the Name, Strength, Volume and Composition on the printed packing material.
- Check the over printing quality on the primary & secondary packing material
- Check the Batch coding details on primary and secondary pack (B. No, Mfg./date, Exp./date, M.R.P. /bar code, etc.)
- Check the Text matter on the printed label, foil, carton & shipper etc.
- Check the Pharmacopeial status of the material used in the preparation of product.
- Check the Mfg. License number printed on the packing material.
- Check the mandatory information printed according to drugs act and rules on pre-printed packing materials.
- Check and confirm that the Storage condition details are available in the packaging materials are according to particular product and same condition should be available on all printed items.
- Check the directions for use are available on the packaging items and warnings or caution against wrong administration is provided in the packing items.
- Ensure checkers are performing their activity in a proper way.
- Verify the records for online entries.
- Sampling should be done according to SOPs.

Testing must be completed by Quality Control Personnel before packing and record should be maintained.The above In-process control checks, and interpretations of the results of all stages become the part of Batch Manufacturing Record. These records should be maintained by authorized IPQC and Production person with their initials and become the part of Batch Manufacturing Record. The final packed finished control samples are kept as representative sample

The packed Finished Goods transfer to quarantine area and submit the filled BMR, BPR and Finished Goods Transfer Note to QA Personnel for verification.QA authorizes to release the batch for dispatch after reviewing all the records.

CONCLUSION

Monitoring the In-process checks with filled written records at all stages of finished dosage form, improve the assurance level at the time of product release. These in-process controls are necessary to ensuring the quality of the product. This article proposes to establish clearly written in-process methods for critical points at all stages of the product their documentation and review. By the in-process checks QA gives assurance that the product conforms to its specification and ensure that the quality of product is built up within the product.

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Abbreviations

Finished Pharmaceutical Product	:	FPP
In-process Quality Control	:	IPQC
Quality Assurance	:	QA
Quality Control	:	QC
Standard Operating Procedure	:	SOP
Batch Manufacturing Record	:	BMR
Batch Production Record	:	BPR
Out of Specification	:	OOS
Small Volume Parenteral	:	SVP
Large Volume Parenteral	:	LVP

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