ANNUAL PRODUCT REVIEW

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What is APR?

An organized and comprehensive review of all production, analytical, stability, complaints, changes, deviations, recalls and customer data associated with a pharmaceutical product so as to monitor the drug product quality and improve where necessary.

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Why are APR’s’s required?

GMP Requirement-Requirements for APRs are found in 21 CFR 211.180(e) and include:

- Written procedure
- Review of every batch (or representative) to determine the need for changes in specifications or manufacturing or control procedures
- Review of complaints
- Review of recalls
- Review of returned or salvaged products
- Review of investigations

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OBJECTIVE

- To assess drug product performance annually and to determine need for any change in drug product specification and or manufacturing process and control procedures.

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Benefits

- Assess needed changes in product specifications.
- Assess needed changes in manufacturing or control procedures.
- Determine if validation or revalidation is needed.
- Identify product improvement or cost reduction opportunities.
- Confirm change control systems.
- Provide a preparation tool for FDA inspections.
- Communicate product and process status to management.

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Content of APR

- Analytical and Inspection data
- Critical process parameters.
- Review of Yield
- Market complaints and related investigations.
- All rejected batches / product failures and related investigations.
- All deviations, incidents, OOS and related investigations.
- All change controls.
- Results of the stability monitoring program.
- Any product recall and related information.
- Returned goods and salvaged goods.

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Content of APR

- Control sample review of the product.
- Batches taken for reprocessing/reworking, if any.
- Different pack size of the product offered in the market.
- If any experiment is conducted to improve yield or quality of product in consultation with R&D
- Purified water & environmental monitoring
- Status of Technical agreement

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Content of APR

- Status of process & Cleaning validation
- Status of TSE / BSE Certification (For Hard gelatin capsule)
- Adverse Drug Events

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Analytical and Inspection data

Finished product & in process analytical data of relevant critical parameters as mentioned below, but not limited to, shall be evaluated for all the batches.

**Tablets:**

- Water Content / Moisture Content
- Dissolution/Dissolution Profile
- Hardness
- Disintegration Test
- Impurities/Related Substances
- Residual Solvent
- Assay
- Total Microbial Count.
Analytical and Inspection data

Capsules:
- i) Water Content / Moisture Content
- ii) Dissolution
- iii) DT
- iv) Impurities / Related Substances
- v) Assay

Pellets:
- i) Water Content / Moisture Content
- ii) Drug Release in Acid Phase
- iii) Drug Release in Buffer Phase
- iv) Assay
- v) Impurities/Related Substances
- vi) Dissolution
Analytical and Inspection data

Soft Gel Capsules

- i) Water Content / Moisture Content
- ii) LOD of shell
- iii) DT
- iv) Impurities / Related Substances
- v) Assay
- vi) Total Microbial Count.

Powder

- i) Water Content
- ii) Assay
- iii) Impurities/Related Substances.

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Analytical and Inspection data

Gel :-
- i) pH
- ii) Density
- iii) Assay
- iv) Impurities/Related Substances
- v) Viscosity
- vi) Total Microbial Count.

Ointment/ Cream :-
- i) pH
- ii) Assay
- iii) Impurities/Related Substances
- v) Total Microbial Count.

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Analytical and Inspection data

Liquid :-

- i) pH
- ii) wt. /ml or Specific Gravity
- iii) Viscosity
- iv) Assay
- v) Impurities/Related Substances
- vi) Total Microbial Count.

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Analytical and Inspection data

**Injectables**:

- i) pH
- ii) wt./ml or Specific Gravity
- iii) Viscosity
- iv) Assay
- v) Impurities/Related Substances
- vi) Particulate matter
- vii) Colour
- viii) Sodium Chloride content (if any)
- ix) Bacterial Antitoxin Test.

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Critical Process Parameters

Example of Tablet

Critical Process Parameters During Granulation Stage :-

Mixing :-
- Impeller (amperage) final
- Chopper (amperage) final

Drying :-
- Duration of drying
- Inlet temperature
- Outlet temperature
- Loss on drying

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Critical Process Parameters

Critical Process parameters during Compression stage:
- Hardness
- Thickness
- DT
- Individual weight variation
- Average weight

Critical Process parameters during Coating Stage:
- Inlet temperature
- Outlet temperature
- Atomisation pressure
- Spray gun distance
- Pan RPM
- Weight buildup per tablet

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**Review of Yield**

- For each batch compile the percentage yield obtained at all critical stages and total percentage yield of the batch.

- Statistical graphs for Analytical data, Inspection data and Yield shall be prepared.

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Market complaints & related investigations

- In this section if any market complaints are came during this review period and related investigation to be mentioned.

All rejected batches / product failures & related investigations.

- In this section if any market complaints are came during this review period and related investigation to be mentioned.

All deviations, incidents and OOS

- Summary of all deviations, Incidents and OOS during the time frame of the APR.
- All change controls.
  - Summary of all change controls during the time frame of the APR.
- Results of the stability monitoring program.
  - The APR also covers all stability parameters of all batches on stability, which represents the manufactured batches for distribution. These data is trended, reviewed and compared from previous years APRs to assure that no negative trend has developed and the expiry period is still appropriate.

- Product recall and related information
  - Any Batches withdrawn or recalled or regulatory alerts made for the marketed product during the time frame of the APR are listed along with the reason for the withdrawal or recall.

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- Returned goods and salvaged goods.
  - Summery of Returned goods and salvaged goods, if any

- Control sample review of the product.
  - Summery of Control sample of the product.

- Batches taken for reprocessing/reworking
  - Summery of Batches taken for reprocessing or reworking, if any.

- Different pack size of the product offered in the market.
  - Summery of different pack size of the product.
If any experiment is conducted to improve yield or quality of product in consultation with R&D

- Purified water & environmental monitoring
- Status of Technical agreement
- Status of process & Cleaning validation
- Status of TSE / BSE Certification
- Adverse Drug Events

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Summary & Conclusion

- Which shall detail the actions based on the review, comments and recommendations made in each section.
FDA Inspections: Expectations for Annual Product Reviews

The following can sum up current FDA expectations for APR programs:

- Develop a comprehensive SOP – the SOP should be comprehensive and specific.
- Follow the SOP – failure to follow the SOP will almost always result in concerns from investigators.
- Include all required and “expected” elements in the APR.
- Identify and implement corrective or improvement actions – the routine assignment of corrective or improvement actions signals that you take the process seriously, and as originally intended by the authors of the GMP regulations.
- Follow-up on actions – a system to assure that actions occurred and were effective is essential.
- Assure that the quality unit reviews and approves the APR – most firms require QA approval on APRs.
- Involve management in the process – the higher the level of involvement and interest in the process, the more APRs can be used as a tool for process control and product improvement.
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THANK YOU