PathWise

Proper Execution of Annual Product Reviews

Overview:

Annual Product Quality Review (APR) is an evaluation conducted annually to determine if there are any possible changes in the process or manufacturing of the pharmaceutical product or any change in the specifications of the product or any change in the manufacturing process. It is designed to minimize the product defects and also the risks associated with the manufacturing of the pharmaceutical product. If done properly, the Annual Product Review (APR) report can be a highly valued administrative tool by upper management. "Reviews" are a critical element of any Quality Management System. Regular reviews of process and quality system performance is necessary to ensure product quality. All regulatory authorities require "reviews" which may be called:

"Annual Product Review" (US GMP term)

"Product Quality Review" (EU GMP term)

Expectations regarding contents and objectives are more or less the same.

Rationale:

Formally reviewing product quality and compliance related information on a regular basis is a mechanism to:

- Monitor process performance and product quality.
- Identify product and manufacturing process improvements and any product quality and compliance risks.
- Identify the need for any changes to manufacturing or control procedures and/or product specifications.

Annual Product Reviews (APRs) may also be used to confirm maintenance of the validation and regulatory compliance status of products and their associated manufacturing processes. Application of this APR process will lead to a deeper understanding of the product and process

and informed assessment of the potential cumulative impact of process changes on product quality. This improved knowledge will assist in improving manufacturing processes and reducing the number of deviations associated with the product line.

An Annual Product Review must be conducted for each commercial product. The purpose of this annual review is to verify the consistency of the process, to assess trends, to determine the need for changes in specification, production, manufacturing and/or control procedures and to evaluate the need for revalidation. Annual Product Reviews (APRs) are important for communication between manufacturing, quality and regulatory Affairs, to enable quality improvement processes. Lastly, content and management of Annual Product Reviews must be established.

APR Requirements:

Each site must have written procedures, which must be followed when conducting Annual Product Reviews. The Annual Product Review must cover a one-year rolling period, but does not have to coincide with a calendar year The review should normally be completed within sixty (60) calendar days of the period close and must in all cases be completed within ninety (90) calendar days of the period close If the production is less than 3 batches per year, an annual product review must still be conducted and this review can include a review performed on the 2 or 3 preceding production years.

Periodic review of the product's production documents, release data, stability data, product complaints, etc. to establish trends and determine any issues. A final report must be issued to Senior Site Management on an annual basis.

Annual Product Reviews are applicable to commercial products [such as API, intermediate for API, pharmaceutical product (i.e. drug product) and medical devices]. The Annual Product Review must:

- Include all batches of product whether they were accepted or rejected or destroyed during manufacture
- Address the assessment of data, documents and electronic records reviewed
    - For active pharmaceutical ingredients, the Annual Product Review includes the manufacturing critical steps

- Take into account previous reviews.

An Annual Product Review must be prepared for each water quality grade produced at each site. If one quality of water is only used for one product, the data concerning this water can be included in the APR of the corresponding APIs. For critical utilities, it is recommending either to perform a separate APR or to include a specific chapter in the APR of the corresponding APR.

What Should be Reviewed?

A review of any recommendations and actions taken from prior report should be considered first and foremost. Next, basic statistics must be reviewed, such as:

- Number of batches manufactured, including partially completed batches and corresponding yields
- Number and percentage of batches rejected and related reasons
- Number and percentage of batches reworked or reprocessed and related reasons
- Critical in-process controls, finished product results and critical API test results

Any deviations from a "validated state" for the product line must be analyzed. This includes:

- A review of all batches that failed to meet established specification(s) and their investigation
- Significant/critical deviations, Out of Specification Results and related failure investigations (review of adequacy and effectiveness of corrective and preventative actions taken)
    - A review of the adequacy of all corrective actions
    - Product quality complaints
    - Product Recalls
    - Critical regulatory issues
    - Quality related issues for returned, and/or salvaged goods

- Changes effected (change control) and variations during the period (e.g. process, suppliers, equipment)
- Changes of product specifications or methods (e.g. analytical changes, and results)
- Process Validation Status

In addition, data from trend analysis must be considered. Trend analysis on key in-process and release testing with graphic representation and basic statistics recommended. This includes a review of the results of the stability monitoring program and trend analysis on stability data. Lastly, observations and recommendations are routinely analyzed as part of the product line summary. This data includes:

- Observations/Recommendations from any official inspectorate which directly concern and relate to the product under review (i.e. not observations/ recommendations which relate to general quality system issues)
- New recommendations from this review

Finalizing the Report:

Annual Product Reviews will be reviewed, assessed, and approved by Senior Site Quality Management, Site Production Management and Senior Site Management. The approved documents must be archived for a minimum of 11 years and made available (upon request) during internal or external audits by Regulatory Authorities.

Always remember to make the report meaningful, such as:

- Focusing on evaluation and assessment of data and information.
- Creating a meaningful list of facts and data

Reviews should focus on mid- and long-term trends (e.g. intra- and inter-batch) because these trends are not obvious from single batch data:

- Therefore, make a connection to the previous report

- One element of a meaningful review is the verification of selected original records (e.g. batch record, test records)

In conclusion, it is important to group as much as is scientifically justified, differentiate between Product and Module specific information, use teams to develop the APR information, plan to compile information throughout the year – impossible task otherwise, collect efficiently, and link APR to ongoing validation program, CAPA and risk management.

About the Author: *Danielle DeLucy, MS, is owner of ASA Training and Consulting, LLC which provides Pharmaceutical and Biologics based companies with training and quality systems assistance to meet Regulatory compliance. Prior to this role, Danielle has been in the industry for 15 years serving in numerous Quality Management Roles, such as the Director of Product Quality, the oversight of Sterility Assurance practices and provided QA oversight of numerous filling and packaging operations. Danielle began her QA career as a Quality Control Pharmaceutical Microbiologist at a contract laboratory where she performed various tests for their clients. In the years after, she has held positions in the Quality management arena while increasing her responsibility. She has helped to lead many Regulatory Health Inspections and was instrumental in the coaching process of her peers prior to any inspection. Currently, Danielle assists companies who are faced with warning letters, consent decrees and those wishing to improve compliance establish more robust quality systems so that the company can succeed.*

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