Product Quality Review and Annual Product Review

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Introduction

One of the primary functions in any Quality Management System is the regular assessment of the current status of a subsystem (such as industrial hygiene). This makes it possible to retrospectively verify conformity to rules and observance of limits. It also enables prospective actions based on trend analyses to be defined for protection from possible risks. Whereas the Code of Federal Regulations has long been calling for an Annual Product Review (APR), the EU GMP Guide did not include a similar demand until the ICH Q7A was implemented as Annex 18 for the area of active substances. Now that the EU GMP Guide has been updated, the call for a Product Quality Review can be found in Part II, Basic Requirements for Active Substances Used as Starting Materials. However, Part I of the EU GMP Guide also includes the demand for a product quality review for drug products (chapter C.4.1, section 1.4). In addition, the revised version of Chapter 1 which has become official in January 2013 places greater emphasis on the significance of supply chain security for active substances.

Implementing a review can be considered part of the continuous improvement process. Various subtargets can be achieved here as well, such as:

- reducing the risk of complaints, returns and product recalls
- reducing the risk of OOS (out of specification) results
- preventing errors and the resulting costs
- increasing productivity
- extending calibration and maintenance intervals
- improving communication between Production, Engineering, Quality Control, Quality Assurance, Regulatory Affairs
- checking the validation status
- updating limits and requirements (e.g. yield limits)
- checking the conformity of the marketing authorisation and the supply chain in good time

An ideal real-time assessment would contain a constant, ongoing system review that is available to the person granting the release. This person can take it into consideration when a batch is released. However, from today’s perspective this vision is confronted with practical challenges to the system such as the different natures and the frequency of change in historically developing quality management systems (paper-based vs. electronic). In some partial aspects, appropriate IT systems already make a system-based assessment possible.

Some examples of these systems are:

- Electronic Batch Recording (EBR)
- Electronic Document Management Systems (EDMS)
- Electronic Quality Management Systems (EQMS)
- Laboratory Information Management Systems (LIMS)

The purpose of an APR or PQR is not only to assess the quality of products, processes and systems, but also to offer the possibility of checking the current state of the marketing authorisation with regard to conformity of the following to the data submitted:

- manufacturing and testing requirements
- specifications of starting materials, intermediate and finished products
- CEP version numbers
- registered manufacturers of starting materials
- registered contract laboratories or contract manufacturers.

This gives businesses and authorities a quick overview of the particular status. Intervals of one year are scrutinized both in APRs and in PQRs, but cyclical reviews are also allowed for PQRs. Shorter intervals are possible, but not necessarily useful as far as trends statements and work input are concerned. The aspects that have to be considered in both types of review are similar, but not identical. Fundamentally, in terms of content the APR can be considered to be a precursor to the PQR.
Product Quality Review (PQR)

The EU GMP Guide Part I, Chapter 1.10, lists exactly which data must be evaluated in a PQR for drug products.

Requirements for the Product Quality Review (Chapter 1.10 EU GMP Guide Part I)

- Evaluation of the starting materials and packaging materials, especially with regard to new supply sources (particularly the traceability of the supply chain of active substances)
- Evaluation of critical in-process controls and results of release analyses
- Evaluation of all batches not conforming to specifications and of pertinent investigations
- Evaluation of all significant deviations, investigations and corrective actions, evaluation of the effectiveness of the corrective and preventive actions
- Evaluation of all changes in the production process and testing methods
- Evaluation of the marketing authorisation and change notifications (including export)
- Evaluation of the stability test results and trend analyses
- Evaluation of all complaints and product recalls
- Evaluation of all corrective actions regarding processes and equipment
- Evaluation of fulfilment of conditions agreed to as part of marketing authorisations and change notifications
- Qualification status of rooms and equipment, e.g. HVAC, water supply, compressed gases
- Evaluation of technical agreements with regard to current status
- Evaluation of results

Annual Product Review (APR)

The significance of the APR becomes clear if we keep in mind that the relevant APRs are generally requested in advance in preparation for every FDA inspection. The review offers a simple point of entry for every inspection. 21 CFR 211.180(e) describes the requirements for creating an APR. Other chapters are also cited in 21 CFR (e.g. Section 211.192 Production Record Review, Section 211.198 Complaint Files, Section 211.204, Returned Drug Products etc.). Because of this, it is not always clear exactly what is expected. It is presently standard FDA practice to make additional, quite reasonable demands that make it possible to improve the evaluation possibilities for products. This development is consistent with the requirements of the Guidance for Industry Quality Systems Approach to Pharmaceutical CGMP Regulations published in September 2006.

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