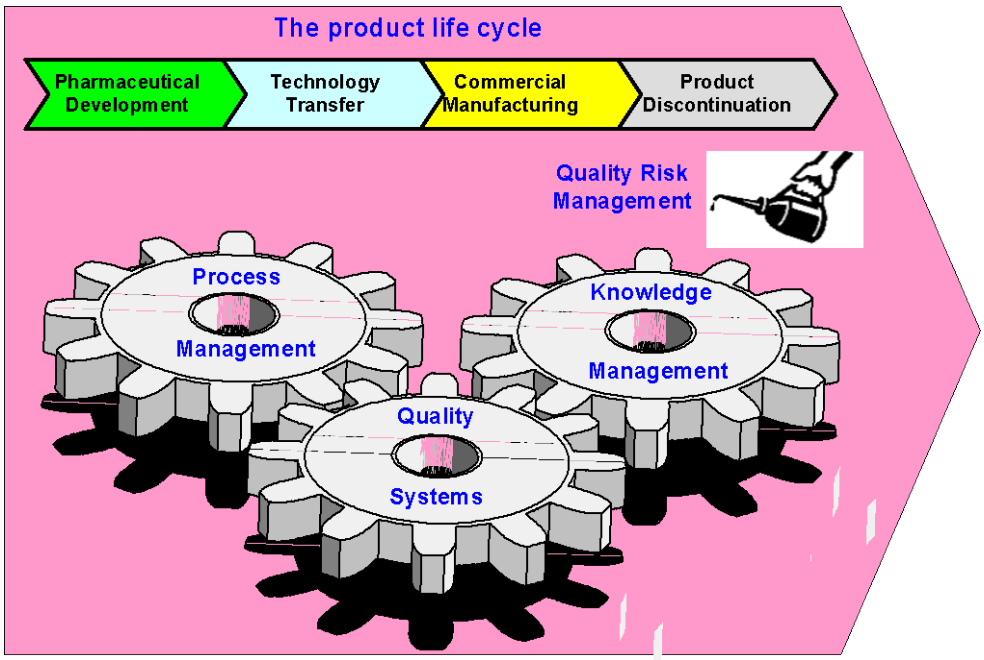
Parenteral Drug Association

Connecting People, Science and Regulation®

Paradigm Change in Manufacturing Operations℠

Dossier



February 2013

1. Life cycle approach

1.1. Specification Setting for IMPs (#L01)

Taking into account other Technical Reports on 'GMP Considerations for Manufacture of Investigational Drug Product', 'Quality Requirements for the Extemporaneous Preparation of Clinical Trial Materials' and 'Phase Appropriate cGMP and Quality Systems elements to the development (#L05)' this task force will provide practical guidance how to set specifications for Investigational Medicinal products (IMPs). This includes IMP specifications for all clinical phases (not for commercial license application), (Potential) critical quality attributes (CQAs) and non-CQA specifications, implementing current global regulatory expectations. In addition the overall control strategy, appropriate use of historical data and clinical experience will be considered.

1.2. Implementation of Quality by Design in Manufacturing (#L02)

This topic will discuss how to adopt the ICH Q8(R2)/Q11 concept of Quality by Design in the manufacture of Clinical Trials material throughout the different development phases. It will outline how this concept will influence the commercial manufacturing later on. The interface of manufacturing and CMC on compiling a dossier under the new concept will be elaborated as well as the handling of changes during commercial manufacturing under the new approach. Special attention will be given to implement QbD concepts into Clinical and Commercial Manufacturing. Assume the proper Process Development using QbD approach have been done and focus on how that information can be best utilized in the actual manufacturing process.

- Implementing appropriate control strategies in the manufacturing situation (i.e., in-process testing, parameter controls, spec testing, etc.)
- Using QbD information to help resolve NC investigations and assess potential change control initiated by manufacturing
- How one might implement controls over using an approved design space at the manufacturing level.
- How manufacturing supports process validation (including CPV) concepts (link to the PV TR) and DoE approaches
- Differences in preparing manufacturing site implementing these QbD concepts for a PAI inspection

1.3. Technology Transfer (incl. discontinuation) (#L03)

This topic covers best practices performed during technology transfer throughout the life cycle as well as transfers of manufacturing processes from one site to another during the commercial production phase. It also addresses manufacturing site changes of Clinical Trials material.

The following items will be discussed, at a minimum:

- How to best arrange sourcing decision
- Documentation transfer
- Change control
- Analytical transfer
- Production of test batches
- Bridging stocks
- Logistics

The aspect of product discontinuation is addressed as a transfer of a product to cessation.

1.4. From Warehouse to Patient (Supply Chain / Good Distribution Practice) (#L04)

The supply chain is currently most critical for patient safety. A reasonable supply chain that is best from the point of view of the patient will be identified/proposed (Good Distribution Practice). Different measures (RFID, 2D bar code, etc.) to secure product among the supply chain will be discussed and assessed.

Best practices as well as bad examples, pitfalls and regulatory recommendations will be shared in this document. It should be shown how a manufacturer could organise the distribution best, what has to been addressed in contacts with e.g. transporters and storage firms. A specimen for a GDP-agreement will be given.

1.5. Phase Appropriate cGMP and Quality Systems Elements to the Development (#L05)

This topic we will discuss a basic, science-based and compliant approach towards the technical development using the example of a Protein Bulk Drug substance (API). The scope covers the development path from R&D, through pre-clinical studies, process development and scale up to commercialization. It describes the minimum activities and quality systems considered appropriate for the support of effective GxP elements (e.g. GRP, GLP, GMP). Detailed examples will describe Quality Systems as applicable to cell culture development, references for recommended testing of mammalian cell lines and references for recommended testing of e. coli production strains.

See A. Earth et al., **Phase-Appropriate QS to the Development of Protein API**, *PDA Technical Report, 56*, **2012**.

1.6. GMP Considerations for Investigational Drug/Medicinal Products (IDP/IMP) (#L06)

This task force will focus on GMP for investigational drug product (IMP/IDP). Interpretation will be provided regarding incremental application of cGMPs in preparing material for use in the different phases of clinical trials through product development and concurrent registration process, taking into account basic and enhanced design concepts according to ICH Q 8 through Q11. Best practices will be shared including quality risk management case studies and knowledge management approaches in stage one of the process validation paradigm.

Industry practices appropriate for the different stages of manufacturing during development will be illustrated, addressing the supporting and evolving Quality System, Management of Outsourced Operations, , Facilities and Equipment, Materials Management, Laboratory, Production, Packaging and Labelling and Distribution , including comparator, placebo and blinding operations.

2. Quality Systems

2.1. Capture Knowledge Management during Commercial Manufacturing (#Q01)

Within commercial manufacturing, the scope of this section is the continuum of data collection through to understanding of both the process and the product, with the feedback loop of decision-making that engenders new data collection for the revised product/process. Aspects addressed include explicit knowledge, and converting tacit knowledge (non-written personal knowledge of employees) as well as the means of capturing knowledge, as knowledge originates from data which is interpreted and analyzed to become information which, when understood, becomes knowledge.

2.2. Management of Suppliers and Contractors (incl. Audit) (#Q02)

This topic addresses the interaction between a manufacturer and his suppliers and CMOs.

It will focus on what is needs to be addressed in such a relationship covering e.g. best practice procedures, identifying responsibilities and documents needed. Case studies are envisaged to be provided from API, Biological, laboratory contacting or re-packaging/re-labelling.

An template and examples for quality agreements will be worked out (e.g. outsourcing biologic manufacturing, API manufacturing, laboratory activities, Packaging Material and Medical Device suppliers). The most common pitfalls will be highlighted.

2.3. Establishing a Pharmaceutical Quality System (PQS) in a Company (#Q03)

The purpose of addressing the requirements of ICH Q10 is to provide a practical model / example for implementing a PQS within a company.

This model will cover all aspects of a PQS as described in ICH Q10. It will identify the major processes (production as well as business) in the pharmaceutical manufacturing, how processes can be mapped, management review is conducted, continual improvement is built into the system, etc. It will also address the impact of the size of a company for a PQS.

2.4. Concepts for Training towards Human Performance (#Q04)

A modern, effective quality system approach to training and qualification of personnel at all levels within an organization. Bearing in mind Management Responsibility – start at the top with a model for senior management and use a “drill down” approach based on Deming / Juran model used in Japan in 1950’s – 60’s.

3. Process Management

3.1. From Process Validation to Process Verification (#P01)

This topic outlines the new philosophy of the life-cycle approach to process validation. It includes the concepts patterned after ICH Q8-10 including upcoming Q11 and US FDA’s new guidance on process validation (Nov 2008). It will describe the validation-related activities needed in design/development, qualification and commercial manufacturing stages of products. The products included in the scope will be those in the FDA Draft Guidance (Introduction). The audience of the team’s activties and deliverables will be global in scope. This TR will be supplemented with a solid dose case study.

See S. Bozzone, H. Baseman, **Process Validation and Process Verification**, *PDA Technical Report, 60*, **2013**.

3.2. Concepts of Cleaning Validation (#P02)

The Technical report “Points to consider for cleaning validation” (TR 29) was updated. This includes a concept on how to handle cleaning validation in different manufacturing areas (API, drug product, sterile, biotech) and will take into account current information and techniques on pharmaceutical cleaning validation, approaches from ICH Q8, Q9 and Q10 as well as the reasoned published guidance from regulators (e.g. from FDA Nov 2008).

See D. LeBlanc, **Cleaning Validation**, *PDA Technical Report, 29 update*, **2013**.

3.3. How to Improve Robustness of a Manufacturing Process (#P03)

The pharmaceutical (manufacturing) process robustness of about 2 Sigma is behind the industry standard (approx. 4 Sigma). This situation needs to be improved.

This topic will identify the possible tools available for increasing the process robustness (e.g. 6 Sigma, CPK, Kaizen) and will elaborate on how these tools can be utilized in pharmaceutical manufacturing area.

3.4. Utilization of Statistical Methods for Production & Business Processes (#P04)

In current manufacturing environment statistical tools are not utilized widely. It is the aim to compile the most common and easy to use statistical tools on the front end of data input. These tools such as X-bar chart, histogram, statistical tolerance intervals, CuSum Charts, process capability (cpk) can be applied in the manufacturing environment. Multivariate models and DoE will not be in the focus.

We are focusing on the tools and do not differentiate between Total Quality Management (TQM) with focus using statistics to improve quality and Six Sigma with focus on a short projects. They should be easy to implement in a standard IT environment (e.g. MS-Excel).

The deliverable reflects the pros and cons of each tool, opportunities and provide case studies of success and non-success i.e. threats of over interpretation of statistical results and trends.

See G. Flexman et al., **Utilization of statistical methods for production monitoring**, *PDA Technical Report, 59*, **2012**, 1-65.

4. Quality Risk Management

4.1. Risk-based Manufacturing (#R01)

This task force provided guidance for application and implementation of Quality Risk Management principles for various types of manufacturing operations and define how to integrate Quality Risk Management (QRM) into the Quality System and routine manufacturing operations. PDAs existing Technical Report No. 44 is the basis for this topic.

See E. Ramnarine, J. Hartman, **Implementation of Quality Risk Management for Pharmaceutical and Biotechnology Manufacturing Operations**, *PDA Technical Report, 54*, **2012**.

The basic overview is provided in the parent document TR 54. It is extended to other areas of manufacturing, such as

- **Biotech manufactured APIs (#R02)**
- **Drug products (liquids and solids) (#R04)**
  See W. Harclerode, **Implementation of Quality Risk Management for Pharmaceutical and Biotechnology Manufacturing Operations Annex 2: Case study in the manufacturing of pharmaceutical drug** *PDA Technical Report, 54-3*, **2013.**
- **Packaging and Labelling (#R05),**
  See G. Haddad, **Implementation of Quality Risk Management for Pharmaceutical and Biotechnology Manufacturing Operations Annex 1: Case study of QRM in Pacakging an labelling** *PDA Technical Report, 54-2*, **2013.**

which are using different techniques and technologies described in case studies.

4.2. Risk-based Scheduling of Audits (#R06)

The purpose of this task-force is to develop and describe a risk based approach to auditing. The scope of this project relates to the following types of audits: GMP, GLP, GCP, GPvP (Good Pharmacovigilance Practice), GDP, GCLP (Good clinical laboratory practices).

The task-force applies the risk based model as described in ICH Q9. The different audit types identified above will be addressed and discussed individually. The similarities between audits and specifics inherent to a particular audit type will be described and discussed. The task-force will establish a generic or basic example of an audit plan, which will become a living document because updates to the audit plan will take into account new knowledge, changed needs, and changes in the business environment on a continuing basis. The audit plan will be the output from a risk management process, which will address a variety of factors specific to each audit type. These factors will include regulatory and business circumstances and requirements.

See S. Rönninger, et al., **Considerations on auditing and GxP requirements along the product life cycle**, *PDA J Pharm Sci and Tech*, **2012**, 66, 396-402.

4.3. Risk based Approach for Ensuring Sustainable Supply (#R07)

The basis for the risk based approach to prevent drug shortages is a triage driven by categorization of drug products (generic, medically necessary, only product on market etc.), patient impact, supply and inventory considerations to determine the criticality of the drug shortage event. The article will present strategies and methods such as supply chain value stream mapping and risk management tools to identify weak links in the overall demand to supply process for drugs. A decision making approach to determine action/rigor to manage drug shortages based on criticality will be explained.

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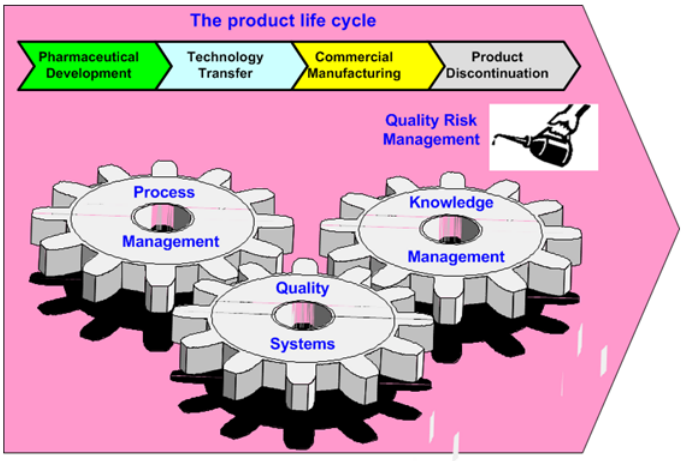

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