

Drug Quality Assurance: Systems at ChemCon

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On February 13th, 2006, the FOOD AND DRUG ADMINISTRATION (FDA) implemented a revision to the "Compliance Program Guidance Manual" for active pharmaceutical ingredients (APIs). APIs are subject to the adulteration provisions of Section 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act. To assure the compliance with this act, this program provides guidance for the comprehensive regulatory coverage of all aspects of production and distribution under CGMP. No difference is made between APIs and finished pharmaceuticals. The ICH Q7A (Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients), implemented in 2001, represents the current thinking of the FDA on CGMP for APIs. While the strict compliance with the ICH Q7A guidelines is a given at ChemCon, it is of interest to take a closer look at the system approach which is described in the newly revised program and how it is realized at ChemCon. The system approach is a relatively new strategy to guide API manufacturers in evaluating compliance with CGMP by providing a comprehensive regulatory coverage of all aspects of production and distribution. Its strict implementation is fundamental to assure an adequate quality, identity and purity of the products, it expedites the approval process significantly and decreases costs by eliminating regulatory failures and delays. The FDA considers a manufacturer to be in a state of control if any one of these systems complies with CGMPs; or vice versa. It is important to mention, that the European Community applied a CGMP compliance system for APIs in October 2005, so it can be assumed that also the EDQM (European Directorate for the Quality of Medicines) will be focused on these systems at inspections for APIs for the European market.

The FDA approach defines the following systems:

1. Quality Assurance System: assures overall compliance with CGMPs and internal procedures and specifications.
2. Facilities and Equipment System: includes activities which provide an appropriate physical environment and resources used in the production of APIs.
3. Materials System: includes measures and activities to control starting materials, intermediates, and containers.
4. Production System: includes measures and activities to control the manufacture of APIs, including in-process sampling and testing, and process validation.
5. Packaging and Labeling System: includes measures and activities that control the packaging and labeling of intermediates and APIs.
6. Quality Control System: includes measures and activities related to laboratory procedures, testing, analytical methods development and methods validation or verification, and the stability program.

Based on these guidelines, ChemCon developed and implemented its Total Quality Management System (TQM), which assures the strict compliance with the ChemCon Quality Policy:

ChemCon GmbH commits that all API batches with a Certificate of Compliance issued and produced at the ChemCon facilities in Germany are manufactured in accordance with current Good Manufacturing Practices as set forth in 21 CFR Parts 210, 211 and ICH Q7A.

TQM consists of the Quality Assurance System (QA System) and several subsystems. The QA System contains two independent systems, the Production System and the Quality Control System. The Production System includes the appropriate systems which have an impact on production, the Production Facilities and Production Equipment System, the Production Materials System and the Packaging and Labelling System. The Quality Control System involves the Quality Control Facilities and Equipment System and the Quality Control Material System. This is visualized in the scheme below.

It includes validation of computerized and inventory control processes, storage, and distribution controls.



Each of these systems consists of a variety of executable subsystems, which are described in detail in appropriate documents and SOPs (Standard Operating Procedures).

The Quality Assurance System

As a typical example, the Quality Assurance System is discussed in more detail. Table 1 below shows the subsystems.

System	Instruments
Internal Audits	SOP including regular internal audits
Training	SOP including regular GMP-trainings
Change Control	SOP describing the change control procedures
Deviations	SOP describing the handling with deviations
Release/Rejection	SOP describing the procedures of release and rejection of materials and products
Complaints/Recalls/Returns	SOP describing the handling with Complaints/Recalls/Returns

Table 1: Subsystems in the Quality Assurance System

Internal audits:

Regular internal audits are the basis to assure that all other systems are in compliance with CGMPs. The accordant SOP describes the scope of the internal audits, which is the regular testing and monitoring of the ChemCon Total Quality Management System. The emphasis of the internal audits is the detection of a lack of execution, regulation or training, the detection of errors and the determination of the completeness of documentation.

In a regular time interval an audit program is created and released. This program defines at least the reason, the occasion, the range and the date of audits of different systems based e.g. on the significance of the system for the current processes and the results of former audits.

All internal audits at ChemCon are executed following DIN ISO 10011, Part 1 and the reports are stored for a fixed time period. The auditors have to be qualified by appropriate training. All internal audits are strictly confidential.

Training:

The SOP Training describes the intervals and scopes of training for employees. Fundamental is the CGMP training, which is conducted at least every six month or in case of special occasions. Additional training categories can be implemented and trained in defined intervals. Such categories are for example project related trainings, general SOP training, analytical method training etc.. In general there is training requirement for new personal, if personal is applied for new tasks, after occurrence of deviations or if personal from contractors must enter GMP facilities in operational affairs. The determination of training requirements and the scope of the training will be determined by the Head of Production and the Head of Quality Control Unit.

Change Control:

The Change Control is fundamental to assure the authorities and the customer that no change is implemented which may affect the quality of the product without prior information of and release by the different parties. ChemCon defines four types of changes to categorize the actions to be taken. The first two types of changes do not have any impact on quality or process reliability and a notification of the customer is not necessary. The third type requires a notification but no release and type four requires a notification and a release by the customer.

Examples of the changes are:

- Type 1 (minor): Replacement of service parts by parts of the same quality and qualification
- Type 2 (major cat. 1): Change of QM-documents which have no impact on a Drug Master File.
- Type 3 (major cat. 2): Change of QM-documents which have an impact on a Drug Master File, but are not classified as major cat. 3. Minor process changes with no impact on quality.
- Type 4 (major cat. 3): Process change with a possible impact on quality, change of specifications of starting materials or product, changes in validation documentations, change on analytical release methods.

Every change must be done following the defined change control procedure. Major changes require a risk analysis by a qualified team and a release from the Head of Quality Control Unit. Regulatory actions following the change are determined.

Deviations:

All deviations, past, actual or planned, must be documented. Deviations are categorized in minor and major deviations. Major deviations, e.g. an Out of Specification result (OOS), require a deviation research and a risk analysis by a qualified team. The exact procedure of the risk analysis and all aspects which have to be considered for the research is described in detail in the according SOP. A deviation report must be created. This report describes the impact of the deviation and specifies the corrective actions to be taken. Each deviation report requires a release by the Head of Production and the Head of Quality Control Unit.

Release/Rejection:

The release and rejection process is described in detail in the according SOP. The Head of Production and the Head of Quality Control Unit are responsible for the release or rejection of starting materials, intermediates or final products. They have to prove all parameters following a check list before signing the release and the Certificate of Analysis in case of a final product:

1. Conditions of production (e.g. log-books, equipment qualification documentation).
2. Production process (e.g. batch record, cleaning record).
3. Results of in-process control (analytical protocols, monitoring reports).
4. Results of release testing and conformation with specifications.

Complaints/Recalls>Returns:

Two SOPs are describing the actions following a complaint, a recall or a return. The SOP customer complaint defines two different types of complaints. All complaints must be documented. Type 1 is a complaint about all aspects related to service but it is not product related. This type does not require regulatory action from the Head of Quality Control Unit but from the customer service department. Type 2 is a product related complaint which requires the Head of Quality Control Unit to create an investigation plan following the SOP "Deviations".

In case a recall or a rejection is the result of the customer complaint investigation, the appropriate SOP must be followed.

The Production System

Equal to the Quality Assurance System the Production System consist of several subsystems. These are summarized in table 2:

System	Instruments
Production documentation system	A set of documents is created for each production (Batch records, Cleaning records etc.)
Facilities and Equipment System	SOPs, qualification documentation (DQ, IQ, OQ, PQ) and log books
Material Flow	SOP describing the material flow
Material System	SOP describing the release and storage of material, test plans
Packaging and Labelling System	SOP describing the procedures for packaging and labelling, packaging qualification documentation.
Validation	A set of three documents is created for each validation (Process Validation Master Plan, Process Validation protocol, Process Validation Report)

Table 2: Subsystems in the Production System

The Quality Control System

The third fundamental system at ChemCon is the Quality Control System (QC). The subsystems are summarized in table :

System	Instruments
Documentation system in the QC	SOP, Raw data package
Facilities and Equipment System	SOPs, qualification documentation (DQ, IQ, OQ, PQ) and log books

Analytical Sample Flow	SOP describing defined sample flow
Reference Standards	SOP describing the procedure of handling, qualifying and managing reference standards
Out of Specification Results (OOS)	SOP defining and determination of procedures how to handle a OOS
Stability studies	SOP describing the performance of Stability Studies according to ICH Q1A and Q1B

Table 3: Subsystems in the Quality Control System

Summary

The Total Quality Management System outlined above was developed and implemented by ChemCon in the last years. It is in fully effect and the number of 7 approved Drug Master Files within the last years demonstrates its regulatory power. With this system in effect we can guarantee our customers a successful inspection and fast approval with respect to the manufacturing part of the API, both by the FDA and EDQM. This reduces time to market and saves significant costs from regulatory issues. ChemCon also implemented the CTD-format for Drug Master Files, so also from this point of view a fast, cost effective and smooth approval process can be assured. In case you are a small Pharmaceutical or Biotech company with innovative drug products, please do not hesitate to contact us. We also offer consulting with regard to regulatory affairs as well as CGMP process development.

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