

Quality Management System (QMS)

for Active Pharmaceutical
Ingredients (API) Manufacturers

integrating GMP (ICH Q7a) into ISO (9001:
2000)

September 2005

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I. Introduction

The changing regulatory environment

In a Science Board Meeting held in November 2001, FDA raised some concerns regarding the efficiency of the pharmaceutical industry. The factors contributing to this situation were identified as follows:

- Pharmaceuticals are complex, multivariate physicochemical systems that are
 - Often treated (during development) as univariate systems (one-factor-at-a-time, trial-and-error experimentation)
 - Physical properties of materials normally not well characterized
 - Equipment selection based on tradition
 - Process factors are not well understood
- Development is done under time crunch
- Post approval changes require regulatory oversight

It was said that a *higher efficiency* is required in order to provide high quality drugs to the market in a timely manner, to successfully take advantage of the new drug development opportunities offered by advances in chemistry and biology. In addition, one should also ensure the optimal utilization of public and private resources to meet the growing health care needs and, last but not least, to obtain global competitiveness for the pharmaceutical industry.

The consequences are that the status quo is no longer tenable and that the pharmaceutical manufacturing could be much better. Furthermore, it is claimed that traditional metrics hide poor performance, and that compliance infrastructures are not economic. Currently, utilization levels are judged to be down to 15 percent or less, and costs in terms of quality are in excess of 20 percent.

The agency's conclusions were that often processes are transferred that are neither fully understood nor capable of being so at commercial scales. Also, there is a lack of scientific basis for deeper process understanding. Further, the pharmaceutical manufacturers fall short in the ability of a process to be 'right the first time' (e.g. pro-active quality management, six sigma approach)

Under the umbrella of the GMP for the 21st century initiative, the FDA started an international co-operation to find answers to the current situation covering the following topics:

- A science based approach
- Risk management
- QSIT (Quality System Inspection Technique)
- PAT (Process Analytical Technology)

QSIT and PAT

The Quality System Inspection Technique moves the FDA from reviewing all documentation to a system-based inspection covering the following six subsystems:

- Quality system
- Facilities and equipment system
- Production system
- Packaging and labeling system
- Laboratory controls system
- Materials system

Scientific and technological advances in the area of process analytical chemistry, engineering, and multivariate data analysis offer new opportunities for improving the overall efficiencies of drug development, manufacturing and regulatory processes. Although for many years the pharmaceutical community has recognized the need for improvements in these areas, little progress has been made. Therefore FDA forced the development of PAT (Process Analytical Technology). PAT is a model to facilitate the discussion on of emerging regulatory science issues in pharmaceutical manufacturing. PAT provides an opportunity to move from the current "testing to document quality" paradigm to a "Continuous Quality Assurance" paradigm that can improve the ability to ensure quality that was "built-in" or was "by-design" - the ultimate realization of the true spirit of GMP.

It is the expectation of the industry that these initiatives will result in improved product quality, reduced manufacturing cycle times, reduced laboratory testing burdens and costs.

QMS combining ISO and GMP

Overall, there is a clear tendency of authorities towards Quality Management Systems (QMS), as already outlined in some new guidelines, e.g. in ICH Q7a, Section 2.11 *"Each manufacturer should establish, document, and implement an effective system for managing quality that involves the active participation of management and appropriate manufacturing personnel"*.

Finally, ISO 9002 already stated in the introduction: *"It is emphasized that the quality system requirements specified in this International Standard are complementary - not alternative - to the technical (product) specified requirements"*.

As early as 1997 a guideline on the integration of the GMP requirements with the QMS requirements, issued by CEFIC/APIC, was available for the API manufacturers.

Introduction to the old APIC version (excerpt)

Because the pharmaceutical industry has traditionally focused upon the application of Good Manufacturing Practice (GMP), it has been slow to consider the potential benefits to be gained by implementing an EN ISO 9001 Quality Management System (QMS).

Over the last few years the global pharmaceutical market has undergone significant change, forcing pharmaceutical companies, more than ever before, to focus on customer needs and upon their own internal efficiency in order to continue to compete effectively.

With this in mind CEFIC commissioned a working group of experts drawn from several major Active Pharmaceutical Ingredients (API) producers to prepare a practical, user-friendly guidance document integrating current GMP requirements into the EN-ISO 9001 QMS framework. To achieve this the working group have taken relevant features from the August 1996 CEFIC/EFPIA publication "Good Manufacturing Practice for Active Ingredients Manufacturers" and combined these with the relevant complementary requirements of EN-ISO 9001 "Quality Systems: Model for quality assurance in design, development, production, installation and servicing". It was intended that these Guidelines would be applicable to all APIs.

To facilitate understanding of this composite guidance document it is important for the reader to be aware of the following points:

- EN-ISO 9001 is a generic, business-focused standard that supports the effective management of quality to an internationally recognized level of best practice. It is flexible in that it specifies what is to be achieved, but allows each company freedom to determine, and justify, how these requirements are achieved. In contrast, GMP is an industry-specific standard prescribing what should be done to ensure product safety and efficacy. Thus, EN-ISO 9001 benefits the business by ensuring the quality of the management system, while GMP ensures that quality is built during the whole manufacturing and control process and that regulatory requirements are met.

- Although there is inevitably some overlap between the requirements of a QMS and GMP they are, in fact, highly complementary. This view is supported by a statement in the introduction to the PIC (Pharmaceutical Inspection Convention, now called PIC/S) GMP Guideline which refers to "... a correctly implemented system of Quality Assurance incorporating GMP ...", and by the wording of the introduction in ISO itself which points out that "..... this international standard is complementary - not alternative - to the technical (product) specified requirements".
- The interrelationship between EN-ISO 9001 and API GMP is illustrated in this guidance document by a matrix cross-referencing the main QMS elements and GMP requirements.
- To be effective the QMS should have the visible and ongoing support of top management.
- To fully benefit the company the QMS should involve all staff whose activities influence quality, have a clear and unambiguous continuous improvement focus, and incorporate relevant, realistic performance measures with emphasis on reducing failure costs, and satisfying (internal and external) customer needs.
- The quality manual occupies the highest level in the document hierarchy. It overviews and acts as a directory to the QMS, capturing the unique character of the company.
- An effective QMS has a minimum of paperwork, and should constantly question the need for the existing documents. In contrast, a bureaucratic and inefficient QMS will arise if the Standard is misinterpreted, and incorrectly applied.

Safety, health and the environment were not specifically addressed. However, it was widely acknowledged that implementation of a robust QMS provides a sound basis for the future development of such an Integrated Management System.

Changes of the relevant GMP/ISO requirements

In the meantime the GMP as well as the QMS requirements have changed. For this reason the 1998 APIC guideline needs to be updated.

Changes to the GMP requirements

API manufacturers no longer need to follow GMPs as defined in e.g. 21 CFR Part 210/211, or draft versions of API guidance documents. The new ICH guideline Q7a "Good Manufacturing Practice for Active Pharmaceutical Ingredients" has some fundamentally different GMP requirements, and specifically applies to the manufacture of APIs for use in drug (medicinal) products. The guide covers APIs manufactured by chemical synthesis, extraction, cell culture/fermentation, by recovery from natural sources, or by any combination of these processes.

Changes to the QMS requirements - ISO 9001:2000

The ISO 9001 series has changed fundamentally. The differences are outlined below.

ISO 9001:2000 is based (as is ISO 9004:2000) on the following eight quality management principles:

- Customer focus
- Leadership
- Involvement of people
- Process approach
- Systematic approach to management
- Continual improvement
- Factual approach to decision making
- Mutually beneficial supplier relationship

The fundamental difference between the ISO 9000:1994 series and the ISO 9000:2000 series is the change in scope from addressing an organization's "capability to design and supply conforming product

(where this) needs to be demonstrated” to “ability to consistently provide product that meets customer and applicable regulatory requirements, and aims to enhance customer satisfaction....”.

The new standard emphasizes the involvement of “Top Management”, (e.g. the Board) in the quality management process. In this context customer satisfaction and continual improvement are of particular concern.

The new standard promotes the adoption of a process-approach. Processes convert inputs into outputs. They have first to be identified, then managed and linked to other processes. They form part of a system and can extend beyond the boundaries of the organization. Once a process is identified and appropriately defined, the following points should be checked:

- are responsibilities assigned (e.g. process owners nominated)?
- are the procedures implemented and maintained?
- is the process effective and providing the required results?

Relationship with ISO 9004:2000

ISO 9001:2000 and ISO 9004:2000 are two stand-alone documents which were designed to be a consistent pair of standards.

ISO 9001:2000 defines the requirements which have to be fulfilled in order to accomplish compliance with customer needs and continual improvement of the Quality Management System. In addition, if considered necessary, this standard can be used to achieve third-party certification.

ISO 9004:2000 develops the concept in a more extensive and intensive manner as a roadmap for organizations on their way to excellence with links to:

- the EFQM Business Excellence Model
- the Balanced Score Card Approach

Compatibility with other management systems

The standard has been made compatible with ISO 14001:1996 “Environmental management systems - Specification with guidance for use” and should assist users in implementing (and certifying) both quality and environmental systems.

The common requirements in both standards (such as continual improvement of the processes, training, auditing and documentation) will facilitate auditing, and integration, if desired by an organization.

Conclusion

One can easily infer that the ISO 9001:2000 series are an excellent complementary fit to the GMP requirements, and additionally addresses the concerns of the authorities, e.g. as raised in FDA's GMP for 21st century initiative mentioned earlier.

II. Objective and Scope

The environment in which API manufactures operate is subject to constant changes. These changes require adaptation to new situations. A state-of-the-art QMS (Quality Management System) helps an API manufacturer respond to changes and be ready for the future developments.

The structure of the ISO 9000 series has moved from describing a QMS in 20 chapters to a process orientated approach. Furthermore, the emphasis has changed from preventing non-conformities of products to consistently providing customers with products or services that meet their needs. Customers can either be internal (e.g. other departments) or external. In addition health authorities demand compliance with GMP and regulatory requirements. As a consequence a QMS should cover both ISO and GMP/Regulatory requirements.

A QMS enables a company to implement effective, efficient, transparent and simple processes and structures to achieve continual compliance. In addition, this will benefit the company's business in terms of improved quality, optimized costs, inspection readiness and customer satisfaction.

This document gives detailed guidance for implementing a QMS. It provides a standard for API manufacturers and other parties involved, including official bodies.

III. Quality Management System for API Manufacturers

1. Quality Management System

This section relates to ISO 9001: 2000 chapter 4

1.1 General Requirements

Companies perform many activities besides manufacturing of APIs, such as development, marketing, purchasing, warehousing and distribution. All these activities are processes which are required to be managed in a systematic manner. Therefore, the company shall establish, document and implement within its organization a Quality Management System that is designed to continually improve its effectiveness as required in section 2 (Quality Management) of ICH Q7a. Top management is called to establish a customer oriented organization:

- by defining the systems and processes that can be managed and improved in effectiveness and efficiency,
- acquiring and using process data and information on a continuing basis,
- directing progress towards continual improvement,
- using suitable methods to evaluate process improvement.

Although ICH Q7a defines which part of the production process is subject to GMP (introduction of the 'API Starting Material') it is not advisable to limit the implementation of the QMS to these production steps; it should be extended to the entire company. From this perspective all regulatory and GMP activities of a company are captured by the Quality Management System.

An important part of the Quality Management System is made up of the Change Control procedures which represent the interface between the company, GMP, the authorities and customers, if applicable.

When a company decides to outsource activities it should ensure control over the outsourced process(es) and/or activities.

API material manufactured for use in clinical trials as described in section 19 of ICH Q7a (development) shall be fully integrated into the Quality Management System even if other GMP standards are to be applied.

The performance of the Quality Management System is the responsibility of every person involved in all activities related to the company's API business.

1.2 Documentation

1.2.1 General

A documentation system remains a fundamental component of a Quality Management System. The objective of such documentation is to identify and describe what should be in place. The documentation system is an essential tool to keep all processes in a state of control.

Top management should define the documentation required to run a Quality Management System and to support effective and efficient operation of the processes. It should include:

- top management's commitment to quality,
- a quality manual (see 1.2.2),
- documented procedures,
- documents and records needed for an efficient QMS.

The minimum extent of the documentation, especially regarding Master Production Instructions (section 6.4 of ICH Q7a) and laboratory documentation (section 11.1 of ICH Q7a), needed for compliance with GMP regulations is described in more detail in ICH Q7a.

The documentation created to run a Quality Management System and to comply with GMP requirements should fulfill criteria in respect of:

- functionality,
- user friendliness,
- structure of company's documentation system,
- managing knowledge,
- interfaces with other departments and, if applicable, with customers.

It is necessary to designate and document a rationale for the point at which production of the API begins ('API Starting Material'). In addition critical production steps should be identified, as should critical control points and parameters within the production of APIs. The company's overall approach to validation and change control procedures should be documented.

All quality-related activities should be recorded at the time of performance.

Deviations from established procedures should be documented and explained and/or investigated, a complaint and recall procedure has to be in place.

Contract manufacturing (including laboratories) needs to be carefully managed, e.g. evaluation, assessment and documentation (including quality agreement). All (GMP) activities and responsibilities have to be defined in writing.

1.2.2 Quality Manual

The basic document of a Quality Management System is the quality manual. Although it is up to the company to decide the level of detail, the quality manual should be made as comprehensive as possible.

The main elements to be incorporated include:

- the scope (see section IV, 3. Structure of a Quality Manual, section 4.1),
- the quality commitment,
- a description of the main processes,
- their interactions and
- the description of major responsibilities.

1.2.3 Control of documents

All documents and records required by the QMS are subject to an appropriate control. A documented procedure shall be established to define the controls:

- drafting, review, approval (Quality Unit at a minimum for GMP related documents) and up-date of documents,
- handling and control of changes to documents (version control) including P & ID (Piping & Instrumentation Diagram) schemes,
- handling, control and internal distribution of external documents,
- withdrawal and prevention of unintended use of obsolete documents.

Details of a documentation system needed from a GMP perspective are given in ICH Q7a, section 6.1.

It is a regulatory expectation that the impurity profile is checked at appropriate intervals against the registration dossier, e.g. as part of the Product Quality Review.

1.2.4 Control of records

Records provide evidence of conformity to requirements. They should be legible, readily identifiable and retrievable. A documented procedure should define the control needed for identification, storage, protection, retrieval, retention time and disposition.

The control of records includes hard copies as well as electronically stored data.

Records should be established, at least for raw materials, intermediates, labelling, packaging materials, batch production, laboratory data, including Certificates of Analysis and stability data, calibration, distribution, complaints and returns.

A procedure for the review of batch production and laboratory records is required.

2. Management Responsibility

This section relates to ISO 9001: 2000 chapter 5

2.1 Management commitment

Top management should provide evidence of its commitment to the development and implementation of the Quality Management System (QMS) and continual improvement of its effectiveness by:

- communicating to the organization the importance of meeting customer as well as regulatory (GMP) and legal requirements, including environmental, health and safety aspects,
- *applying risk management*,
- establishing the quality policy,
- ensuring that quality objectives are established,
- conducting management reviews,
- maintaining appropriate conditions throughout the organization for processes and systems,
- ensuring the availability of resources, particularly enough manpower, suitably trained.

2.2 Customer focus

Top management should make sure that customer (external and/or internal) needs and requirements are clearly understood so that, when fulfilled, they will lead to customer satisfaction.

Consequently, this calls for close communication with the customer throughout the whole co-operation including, at least, notification to the customer (e.g. dosage form manufacturer) of significant process changes (see also QMS 5.3) in a timely manner before implementation of the change and appropriate complaint management.

2.3 Quality policy

Top management should ensure that a clear commitment to complying with (regulatory and GMP) requirements and to continually improve the effectiveness of the Quality Management System is a key element. This should be explained in the quality policy. Furthermore, criteria affecting the efficiency of the system should be identified and evaluated.

Quality objectives should be based on the quality policy which is closely coupled with company operational planning. This should include a statement addressing environmental, health and safety obligations.

Measures have to be initiated to ensure that the key statements of the quality policy become part of the daily business. Therefore, the quality policy needs to be communicated to and understood at all levels within the organization. Quality is the responsibility of all persons involved in a process.

To cope with inevitable changes that occur in and around the organization, the quality policy should be reviewed for continuing suitability. The responsibility for these activities is clearly allocated to top management.

2.4 Planning

2.4.1 Quality objectives

Top management should make sure that quality objectives are known and widely used at all levels within the organization. By doing so, employees will identify with and become fully involved in reaching the agreed objectives. The quality objectives should be measurable and consistent with the quality policy. The "SMART" criteria (S=Specific, M=Measurable, A=Achievable, R=Relevant, T=Time-framed) should be applied to establish quality objectives.

2.4.2 Quality Management System planning

Top management should ensure that the planning of the QMS is carried out in order to meet the requirements as defined in 4.1 (ISO) as well as the quality objectives. They should ensure that the integrity of the Quality Management System is maintained. Changes for system improvement should not impair the effectiveness and efficiency of the QMS.

Planning may be driven by e.g. strategies and organizational objectives, by customer needs, by regulatory requirements, by the intended use of the API, or by risk management. This may give rise to, e.g. skill and knowledge requirements, allocation of task responsibilities, resources (financial and infrastructure), performance metrics, contingency plans.

2.5 Responsibility, authority and communication

2.5.1 Responsibility and authority

Top management should make sure that responsibilities and competences (authorities) are defined for all profiles and communicated to all levels within the organization. There should be a quality unit (QU) independent of production, and that fulfills both quality assurance (QA) and quality control (QC) responsibilities.

2.5.2 Management representative

Top management should appoint a member of management who, irrespective of other responsibilities, is responsible and authorized:

- to make sure that processes needed for the Quality Management System are established, implemented and maintained,
- to report to top management on the performance of the Quality Management System and any need for improvement,
- to ensure the promotion of awareness of customer requirements throughout the organization.

The responsibility of a management representative can include liaison with external parties on matters relating to the Quality Management System.

2.5.3 Internal communication

Top management should ensure that appropriate communication processes are established within the organization and that communication takes place regarding the effectiveness of the Quality Management System. This should include the communication of GMP and regulatory requirements as appropriate to each level in the organization.

Quality issues should be considered as a standard topic on the agenda of all appropriate meetings as well as on the company's intranet website(s).

Procedures should exist for notifying responsible management in a timely manner of quality critical situations.

2.6 Management review

2.6.1 General

Top management should review the organization's Quality Management System at predefined intervals, to ensure its continuing suitability, adequacy and effectiveness. This review has to include assessing opportunities for improvement and the need for changes to the QMS, including the quality policy and the quality objectives.

The review should also cover environmental, health and safety aspects. Records of management reviews are to be maintained.

2.6.2 Review input

The input to top management review comprises a consolidation of the available data as a basis for their decision-making process. These data include, but are not limited to:

- audit observations / results (internal and external audits as well as inspections by authorities),
- supplier qualification,
- product conformity (product quality review),
- customer feedback,
- process performance, e.g. key performance indicators (KPI),
- status of corrective and preventive actions (CAPA),
- follow-up actions from previous management reviews,
- changes that could affect the Quality Management System,
- recommendations for improvement.

2.6.3 Review output

The output from the management review should include any decisions and actions taken relating to:

- continual improvement of the effectiveness of the QMS and its processes,
- continual improvement of product relating to customer requirements,
- resources (in relation to time, money and manpower) needed.

3. Resource Management

This section relates to ISO 9001: 2000 chapter 6

Resource management comprises provision of resources, infrastructure, human resources and the work environment.

3.1 Provision of resources

The top management has to determine and provide the resources needed:

- to implement and maintain the Quality Management System and continually improve its effectiveness,
- to enhance customer satisfaction by meeting defined requirements and specifications (including compliance with regulatory requirements),
- to maintain equipment and facilities and
- to adequately train and educate the employees.

Provision of resources is the responsibility of top management and has to be included into the budgeting and investment processes. These processes have to be defined in writing.

When using external resources such as contract manufacturers (including laboratories), they are expected to provide sufficient resources as described in this chapter. The external provision of resources should be ruled by contract.

3.2 Human resources

3.2.1 General

The top management has to provide an adequate number of personnel qualified by appropriate education, training, and/or experience to perform work and meet the requirements.

If the company's performance indicators (such as timelines for calibration due dates, deviation / investigation handling, testing, release) can constantly not be achieved in such a way as to run the QMS processes properly, the adequacy of the human resources should be reconsidered.

3.2.2 Competence, awareness and training

Competence, awareness and training are ensured through top management by:

- implementing an adequate and effective organization,
- determining the necessary competence and education for personnel performing work affecting quality of product and processes,
- issuing job descriptions and qualifications for all functions throughout the organization,
- training provided regularly by qualified individuals covering, at a minimum, the particular operations the employee performs and GMP as it relates to the employee's functions,
- evaluating the effectiveness of the training periodically, such as by
 - testing on the content of procedures
 - observing the employee performing the task(s)
 - checking the accuracy of the work and results
- ensuring that personnel are aware of the relevance and importance of their activities and how they contribute to the achievement of the quality objectives,

- maintaining appropriate records of education, training, skills and experience.

3.3 Infrastructure

Top management has to ensure that the organization determines, provides and maintains the infrastructure needed to conduct operations (e.g. manufacturing, testing and support) according to contemporary standards.

Infrastructure comprises buildings (including utilities and workspaces), equipment and computerized systems.

Buildings have to:

- be located, designed, and constructed to facilitate cleaning, maintenance, and operations as appropriate to the type and stage of manufacture,
- provide adequate space for the orderly placement of equipment and materials to prevent mix-ups and contamination,
- provide adequate cleaning, washing and toilet facilities,
- provide laboratory facilities separate from production,
- provide adequate lighting in all areas to facilitate cleaning, maintenance, and proper operations,
- provide areas for the storage of all materials under appropriate conditions (e.g., temperature and humidity),
- provide adequate laboratory facilities for the quality unit,
- be properly maintained and repaired,
- provide separate areas for eating, drinking and smoking,
- contain the necessary utilities (such as HVAC, water, gases etc.) in order to perform the relevant production operations.

Equipment should be:

- of appropriate design, adequate size and suitably located for its intended use in order to facilitate cleaning, sanitization (where appropriate), and maintenance,
- constructed so that surfaces that contact raw materials, intermediates, or APIs do not alter the quality of the intermediates and APIs beyond the official or other established specifications.

Computerized systems should be:

- of appropriate design and adequate capacity,
- equipped with the necessary software programmes,
- maintained (such as programme updates or exchange of hardware components),
- safe against loss of data.

The infrastructure has to meet all legislative requirements laid down by regulatory authorities (safety issues, occupational health problems, environmental aspects, etc.).

3.4 Work environment

Top management should ensure that the work environment has a positive influence on motivation, satisfaction and performance of people in order to enhance the performance of the organization.

Elements to be considered for a suitable work environment are:

- creative work methods to enhance the potential of the employees,
- use of protective equipment,
- ergonomics,
- sufficient workspaces as well as a suitable location,
- opportunities for social interaction,
- suitable heat, humidity, light and air flow,

- hygiene, cleanliness, noise, vibration and pollution.

Full account should be taken of regulatory requirements.

4. Product Realization (Manufacturing Operations)

This section relates to ISO 9001: 2000 chapter 7

The product realization includes all the different value adding activities for the realization of product, starting from customer requirements up to shipment of product to the customer in the mutually agreed quality.

The realization process consists of different activities such as planning of the product realization, customer-related issues, design and development, purchasing, production, service provision and control of monitoring and measuring devices.

This chapter is the part of the document where most of the requirements of ICH Q7a related to manufacturing are applicable.

4.1 Planning of the product realization

The planning of the product realization should be in line with the QMS requirements of the other processes.

All responsibilities of the different production activities should be defined in writing (ICH Q7a: 2.30).

Process equipment, including laboratory equipment, is an important part in the planning of product realization. Equipment should be of adequate design and appropriately qualified before use in manufacturing of APIs or intermediates (ICH Q7a: 5.16). Schedules and procedures should be established for the preventive maintenance of equipment (ICH Q7a: 5.20). In addition, established cleaning procedures prevent contamination or carry-over (ICH Q7a: 5.21-5.25). Where computerized systems are used in a GMP relevant process, hardware and software should be appropriately qualified and validated on the basis of the criticality of the system (ICH Q7a: 5.40-5.42). Changes to any equipment (including computer systems and laboratory equipment) should be done under a defined change control system to maintain the qualified status (ICH Q7a: 5.45, 5.47). All activities described above are subject to risk management.

Material in product realization should be defined by appropriate specifications, especially if the quality of the API is affected. Acceptance criteria should be established (ICH Q7a: 6.17 and 8.10-8.14) to control processes. All activities from material receipt to sampling and testing against defined specification and storage and release for use or rejection should be well defined (ICH Q7a: 7.10).

To prove the capability of the product realization process, the equipment should be qualified and the production process validated, where appropriate, following the requirements given in ICH Q7a Chapter 12.

Activities not covered by the manufacturers QMS, such as contract manufacturing (incl. laboratories), activities of brokers or distribution, a written contract should define in detail Quality responsibilities of each party (ICH Q7a: 16.10, 16.12). All companies involved in the product realization process should comply with the GMP requirements as defined in Q7a.

4.2 Customer-related processes

The responsibilities for all production activities should be defined in writing (ICH Q7a: 2.30).

Critical changes in the realization process of the intermediate or the API should be evaluated and customers should be notified before implementation of significant changes (ICH Q7a: 13.16/17, see also QMS 5.3) if mutual agreed.

A written procedure should ensure the investigation of all quality related customer complaints (ICH Q7a: 15.10).

4.3 Design and development

The design and development process comprises planning, determination, review and verification of inputs and outputs and the control of changes. To achieve a robust manufacturing process it is mandatory to perform all of the above-mentioned steps.

For all further details and activities regarding GMP for new chemical entities see ICH Q7a, section 19 (APIs for Clinical Trials).

4.4 Purchasing

Purchased items which could impact final product quality should be purchased to defined requirements according to written procedures from an approved supplier. There should be written procedures describing receipt, initial visual check of labels and containers, identification, quarantine, storage, handling, sampling, testing and approval or rejection of materials.

Suppliers should be selected on the basis of their ability to supply the items and their performance. Supply chain and/or manufacturer qualification for critical raw materials, utilities and services is mandatory. Particular attention should be paid to:

- Changes to the supply chain and/or the manufacturing processes which could impact the organization's final product, e.g. changes in method might impact product purity or performance.
- Purchasing documentation, which may include data relating to the suppliers and/or manufacturer's Quality Management Systems e.g. Good Manufacturing Practices (GMP), Hazard Analysis Critical Control Point (HACCP). Purchasing data would also be expected to include Certificates of Analysis / Conformity.
- Verifying that the product is as ordered, so as to prevent cross-contamination or product disruption.

Receipt of a material prompts the following actions:

- Initial visual check of labels and containers to verify correct material and that there is no evidence of damage, tampering or contamination.
- Assignment of a distinctive code or batch number.
- Identification of the status.
- Bulk deliveries in non-dedicated tankers require assurance of the absence of cross-contamination.
- Materials are kept under quarantine and should not be mixed with existing stocks until approved.

Sampling and testing:

- Sampling is to be performed at defined locations and by procedures designed to prevent contamination.
- Containers from which samples have been withdrawn should be marked.

- Samples should be representative of the batch of material from which they are taken.
- Each batch should be tested for conformance with specifications unless the supplier's Certificate of Analysis has been verified as accurate.
- As a minimum requirement an identity test on each batch is mandatory.
- Processing aids, hazardous or highly toxic raw materials, and other special materials do not need to be tested if a Certificate of Analysis shows that these materials conform to established specifications or are shown to be suitable for the intended use.

Approval or rejection of material:

- Material that conforms to specifications may be approved by the quality unit.
- Rejected material should be identified and controlled under a quarantine system designed to prevent their unauthorized use in manufacturing.

Storage and handling:

- Materials should be handled and stored in a manner to prevent degradation, contamination, and cross-contamination.
- Placement of stored material should allow easy cleaning and inspection.
- Stored material should be used on the basis of the first-in first-out principle.
- Materials should be re-evaluated after prolonged storage to determine their suitability for use.

4.5 Production and service provision

Production and service provision should be systematically planned and controlled to predetermined conditions derived from comprehensive process understanding (e.g. specifications, process parameters, contents and scope of service, operating procedures). Operating under these conditions would reduce the potential for non-conformities, deliver material that is fit for use in the customer's application and provide the basis for continual process improvement.

In order to reduce costs of failure and to control the production process, all steps (if necessary) should be adequately monitored. The requirement of process validation applies only to critical production steps and is documented evidence that the process can be performed effectively and reproducibly.

Product conformity should be continually maintained throughout the entire supply chain by appropriate measures for identification, handling, packaging, storage and protection.

Traceability depends on the nature of the processing, e.g. bulk silos and storage tanks, continuous processing and requires appropriate concepts (e.g. batch, time or volume based). Identification and traceability are imperative by regulatory requirements.

In the special case of contract manufacturing specified control conditions should be observed and deviations notified to the customer according to the agreement.

ICH Q7a items to be considered for production and service provision are listed below:

- document control, pre-approved manufacturing procedures, batch record review and handling of deviations,
- qualification, process, analytical and cleaning validation,
- change control,
- production activities (chemical as well as biotech) such as in-process controls, blending, recovery of materials, hygiene, calibration, cleaning, sanitation, maintenance, contamination control as well as packaging and labelling of APIs and intermediates,
- utilities (e.g. air, piping), water treatment and containment,

- design and construction of facilities and process equipment,
- sampling (including retention samples), testing and release of materials, intermediates and APIs,
- storage and distribution of materials, intermediates and APIs,
- stability of APIs and intermediates, where appropriate,
- returns,
- APIs for clinical trials and their appropriate controls.

4.6 Control of monitoring and measuring devices

The suitability of devices used to monitor product characteristics for the intended purpose should be confirmed, and they should be checked, calibrated and regularly maintained.

This includes computerized systems, laboratory instruments, reference materials, standard analytical solutions and buffer solutions used for process controls.

5. Measurement, Analysis and Improvement (Evaluation Activities)

This section relates to ISO 9001: 2000 chapter 8

5.1 Deviation Investigation

The Quality Management System should ensure that deviations from established procedures are identified and recorded. Incidents that could affect the quality of API or the reliability of records or test results should be investigated. The Quality Unit is responsible for making sure that critical deviations are investigated and resolved. The Quality Management System should specify the responsibilities for all functions involved in the investigation and resolution of deviations.

5.2 Product Quality Review (Annual Product Review)

The Product Review itself is a GMP requirement and should be conducted annually, or on another routine basis, as justified, to evaluate process consistency through reviews of:

- critical in-process control and critical API test results (Q7a 2.50);
- all batches that failed to meet established specification(s) (Q7a 2.50);
- all critical deviations or non-conformities and related investigations (Q7a 2.50);
- any changes made to the processes or analytical methods (Q7a 2.50);
- results of the stability monitoring program (Q7a 2.50);
- all quality-related returns, complaints and recalls (Q7a 2.50);
- adequacy of corrective actions (Q7a 2.50);
- the current impurity profile versus the established impurity profile.

The cumulative effects of changes to systems and processes should also be reviewed periodically to determine if there is a need to revalidate. The Product Review may be used to evaluate process performance with respect to validation.

5.3 Change Management

A continual improvement-focused QMS is, by definition, a dynamic entity. The introduction to this publication stresses the need to adequately document quality critical systems to ensure uniformity and understanding. Changes are, therefore, intimately linked with documentation and its control. Quality critical changes should be comprehensively planned, carefully controlled, and fully documented. All relevant stakeholders, including regulatory authorities and customers where appropriate, should be involved and/or notified, depending upon the nature and significance of the proposed change.

Change control procedures

- Evaluation and approval of proposed changes to specifications, test procedures, production processes, production equipment, etc., should be controlled by written procedures.
- Evaluation of a proposed change should include consideration of the following:
 - significance of the proposed change
 - effect on quality of final API
 - impact on dosage form subsequently manufactured from API (e.g. through changes to impurity profile, crystal form, particle size, residual solvents, stability etc.)
 - need for operator training

- need to involve regulatory authorities
- need to inform customers
- need to revalidate processes.
- Proposed changes should be reviewed and approved by the relevant departments and the Quality Unit.

Implementation of changes

- All documents affected by the change should be identified and revised accordingly.
 - Changes to documents should be reviewed and approved by the same functions that performed the original review and approval, unless specifically designated otherwise. The designated functions should have access to pertinent background information upon which to base their review and approval.
 - Where appropriate, the nature of the change(s) should be identified in the revised document or attachments. However, it is advantageous to incorporate a brief summary of previous changes in the current version of the document.
 - Relevant changes in documents previously submitted to regulatory authorities and/or customers should also be notified.
- Any operator training needed should be satisfactorily completed (and recorded).
- Several batches of API produced following implementation of the change should be extensively evaluated.
- Changes resulting from corrective and/or preventive action should be documented and adequately controlled.
- Changes to existing quality critical activities should only be introduced once validation is completed, documented and approved.

Periodic Review of Cumulative Changes

Validated processes (including computerized systems) should be monitored and/or periodically evaluated, and previous changes assessed, to determine whether there is a need for revalidation.

5.4 Audits

Internal quality audits, incorporating ISO and GMP requirements, provide a regular and systematic way of obtaining objective evidence about how the QMS is functioning. They are an effective means of highlighting activities requiring attention and are, therefore, a means of driving continual improvement. This approach should be achieved through the use of documented procedures for planning, implementation and follow-up of internal quality audits to verify compliance with documented QMS activities, quality manual claims, and GMP and other regulatory requirements. Since many GMP deficiencies are the result of a weakness in, or failure of, part of the QMS, an effective internal quality audit system will go a long way towards ensuring regulatory compliance, and will facilitate continual inspection readiness.

- Internal quality audits should be scheduled as part of an ongoing QMS internal audit programme covering the scope of the quality system documented in the quality manual. The frequency with which different parts are audited should be determined on the basis of importance to overall QMS performance, i.e. activities with known weaknesses should be audited more frequently.
- Internal quality audits should be planned, performed, recorded and followed up by suitably trained staff who are independent of the area being audited. Internal quality auditors should be experienced in QMS and GMP in order to perform audits which benefit the organization.
- It is the responsibility of the Quality Unit to make sure that internal quality audits are performed.
- Internal quality system audit findings should be discussed with the management unit responsible. Agreed, time-limited remedial actions should be recorded and followed up to completion and sign-off.

- The follow-up activities should verify the effectiveness of the corrective action taken.
- Output of the internal quality audit programme should be summarized and periodically submitted to top management as an integral part of the management review process.
- Further guidance for conducting quality system audits is provided in ISO 19011: 2002 (Guidelines for Quality Audit and/or Environment Management Systems Auditing)

5.5 Complaints

All customer complaints should be recorded, promptly investigated and reported in accordance with a written, approved procedure. Quality related complaints have GMP significance, and it is the responsibility of the Quality Unit to assure that these complaints are investigated and resolved. Records of complaints should be reviewed as part of the product quality review (annual product review) in order to identify trends and corrective and preventive actions.

5.6 Data Analysis

An integral part of successfully implementing an effective QMS is the need to identify, agree and use realistic criteria for routinely monitoring performance trends (KPI - Key Performance Indicators). These kinds of data are needed to support the Balanced Scorecard approach. Some general examples are provided below. The nature and emphasis of performance measures will, inevitably, vary from one company to another. Examples given below are not all-inclusive:

- Improvement initiatives ongoing and/or completed
- Quality failures e.g. cost of production failures per month
- Percentage on-time delivery to customer
- Failure costs per development project as % of project costs
- Controlled documents overdue for review
- Internal audit observation trends
- Customer complaints (numbers, response times)
- Recalls and other market withdrawals
- Laboratory errors and OOS results
- Process deviation frequency
- Staff training status
- Equipment breakdowns per month

At defined intervals top management should review the adequacy and performance of the QMS to ensure that GMP and regulatory requirements, ISO quality management principles and quality manual claims are being routinely satisfied. The measures listed above and other sources of relevant information such as product reviews and external inspections should be used. This information can be used to realign resources in order to improve the QMS.

Another application of data analysis is in the control of processes. Appropriate statistical techniques should be identified, documented and implemented to control quality critical processes.

Identification of needs

- The main activities for the application of statistical techniques in all areas are likely to be trend analysis and identifying process capabilities. In the manufacturing and control area, statistical techniques would apply e.g. to validation, sampling plans, stability testing and interpretation of analytical data. A statistical perspective is essential when planning a complex investigation if maximum benefit is to be derived.
- API manufacturers should identify and document the need for, and application of, appropriate statistical techniques.

Procedures

- Documented procedures and adequate training should be used to control the application of statistical techniques.
- Whenever possible, recognized published statistical techniques should be selected for use. If alternatives are applied, their use should be justified through traceability to basic statistical theory.

5.7 Risk Management

The principles of risk management as laid down in draft ICH Q9 should be incorporated into the QMS as a means of focusing resources on priority issues and areas of improvement. For example, while all deviations should be noted and recorded, those deviations involving critical steps or critical-to-quality parameters should be investigated. Also, the QMS should take into consideration that operations require careful planning, execution and monitoring to reduce risk and costs of failure. Some major operations where risk management could be applied are listed below:

- Control should be exercised over labels used during the manufacture and filling of the API, including label reconciliation, to absolutely minimize the risk of label mix-ups or the use of incorrect or out-of-date labels.
- Weighing or subdivision of material prior to use should be performed in an appropriate area to minimize the risk of cross-contamination.
- Pure and final API should be handled in an environment giving adequate protection
- Equipment should be designed, constructed, located, and used so as to minimize the risk of contamination or mix-ups arising during manufacture of API.
- Whilst clean-up between successive batches of the same API is not mandatory, equipment should be cleaned at appropriate intervals when the risk of contamination from microbiological growth or non-acceptable material build-up becomes too great.
- Pipework and valves should be designed to minimize the risk of contamination. Permanent pipework should be labelled with the name of the material therein and the direction of flow, and should be located so that rusting, surface condensation, or leakage will not lead to contamination.
- Prospective validation should apply to all relevant new or modified processes. It is usually the result of a risk analysis performed on the proposed new or modified production process.
- Computerized systems should be designed, implemented and operated so as to minimize the risk of failures. This includes supporting computerized systems such as Enterprise Resource Planning (e.g. SAP®) and/or Document Management Systems (e.g. Documentum®) as well as systems used in manufacturing (e.g. SPS, DCS, LIMS).

Other examples of integrating risk management into current operations are given in chapter 6 of draft ICH Q9.

5.8 Corrective and Preventive Actions (CAPA)

The QMS should aim to prevent occurrence of non-conformities, but when they do occur, it should allow for implementation of corrective measures. A planned and structured approach to corrective and preventive action increases the likelihood that the root cause of actual or potential quality problems will be identified and lasting remedial action taken. When failures occur, the true underlying cause(s) should be established if learning points are to be identified and appropriate corrective measures applied.

The cause(s) of actual and potential non-conformities in product, process or the quality system itself should be identified and eliminated. Action should be appropriate to the severity of the non-conformities. Changes resulting from corrective and/or preventive action should be documented and adequately controlled.

Corrective action

- Corrective action is intended to both rectify an existing non-conformities and avoid a recurrence. It is, therefore, necessary to identify the underlying cause of the problem.
- Corrective action may arise e.g. from customer complaints, recalls, audit findings, management reviews and other situations (see also section 5.2) where non-conformance is likely to be identified.
- A carefully planned and timely investigation should be carried out to determine the reason(s) for the non-conformities and agree appropriate action.
- Details of the non-conformities, the associated investigation and agreed actions should be recorded.
- Progress with agreed actions resulting from the non-conformities investigation should be closely monitored until all are satisfactorily completed.
- Top management should be notified about the costs of failure including the respective corrective actions.

Preventive action

- Preventive action is intended to avoid the initial occurrence of a non-conformities.
- Preventive action may include analysis of trends in process, product, analytical data and equipment as well as operator performance. Sources of information could include audit reports, product quality reviews (annual product reviews), recalls, customer complaints and any other data likely to assist in identifying areas of potential non-conformities.
- As with corrective action, preventive action should be authorized, carefully planned, implemented in a controlled manner and adequately monitored to ensure the desired outcome.
- Information relevant to preventive (and corrective) actions including costs and cost savings should be regularly collated and presented for management review in support of maintaining and improving the effectiveness of the QMS.

5.9 System for Suggesting Improvements

To fully benefit the company, the QMS should involve all staff whose activities influence quality, have a clear and unambiguous continual improvement focus, and incorporate relevant, realistic performance measures with emphasis on reducing failure costs, and satisfying (internal and external) customer needs.

If the QMS is designed and implemented to emphasize continual improvement (being driven by the effective use of internal quality audits, corrective and preventive action, and management review), then internal efficiency will rise, leading to a sustainable reduction in failure costs. Similarly, the effective control of nonconforming product helps to identify the root cause of quality problems, and in so doing provides an important improvement opportunity. A comprehensive internal quality audit system is a vital health check and provides a means of identifying issues in need of attention, while a planned and structured approach to corrective and preventive action increases the likelihood that the basic cause of actual or potential quality problems will be identified and lasting remedial action taken.

In addition, the QMS should encourage the employees to make suggestions for improvements by incorporating a system which makes it easy for employees to communicate suggestions and which provides for timely review of these suggestions.

5.10 Control of Non-Conforming Product

Product which does not conform to specification (OOS) and established processing requirements is usually identified by inspection and/or testing, customer complaint or internal quality audit. A non-conforming product should be recorded, clearly identified as non-conforming and physically segregated (unless an alternative, equally effective procedure is available) to prevent unintended use until its

disposition (i.e. reworking, reprocessing, release on conditional status, disposal) can be agreed. Relevant staff should be notified and an investigation performed to determine the extent and cause of the nonconformity and to agree appropriate action. The process for investigating and controlling non-conforming product should be described in written procedures.

- Responsibility for reviewing information relevant to, and authority to decide the disposition of non-conforming product should be clearly documented.
- Subsequent use of non-conforming material should be approved by the Quality Unit after full review of the non-conformities or deviation, including results that are out of specification, and the investigation.
- The likely effect upon related batches of product should be assessed.
- Any decision to reprocess returned non-conforming product should take into consideration the fact that the product has been outside the control of the manufacturing company.
- Reworked product should be retested in accordance with documented procedures incorporating appropriate controls agreed between production and the Quality Unit. Special consideration should be given to the impurity profile of a reworked batch, including the use of non-routine measurements if necessary. The release of reworked product has to be agreed with the relevant authority.
- Reprocessing and reworking should be documented and included in the batch records. A new batch number should be assigned following reworking.
- The nature of the non-conformities together with details of the associated investigation and justification for disposition of the non-conforming product should be recorded.
- If reprocessing becomes a regular occurrence, the adequacy of the original manufacturing process should be re-evaluated.
- A written, approved procedure should clarify the circumstances in which recall of an intermediate or API should be considered. This document should also indicate responsibilities and actions in the event of a recall. The distribution system should permit prompt determination of the location of each batch.
- In the event of a serious and potentially life-threatening situation, the (local and national) authorities should be informed and their advice sought.

5.11 Measurement of Customer Satisfaction

To fully benefit the company, the QMS should incorporate relevant, realistic performance measures with emphasis on satisfying (internal and external) customer needs. Methods for collecting information on customer satisfaction should be developed, and the results used as part of the continual improvement process of the QMS.

5.12 Measurement of Employee Satisfaction

A concisely documented QMS, having the full visible support of top management, will lead to better understanding of employee roles, responsibilities, authorities, and working interfaces. It will avoid confusion, and reduce the risk of omission and /or duplication. Less staff time will be absorbed by fire-fighting and crisis management, allowing more time to be devoted to improving operating efficiency.

Continually improving operations should result in measurable improvements in employee satisfaction with their work and working conditions. Management should periodically survey employees to measure their satisfaction as well as to identify opportunities to improve the QMS.

IV. Supplementary Information

1. Identification of system approaches in ICH Q7a

ICH Q7a was not just developed during a time when Quality Management was gaining increasing acceptance within the pharmaceutical industry; it was developed specifically to incorporate Quality Management Principles. Thus it is not surprising that the first sentence of the document states that its objective is:

“to provide guidance regarding good manufacturing practice (GMP) for the manufacturing of active pharmaceutical ingredients (APIs) under an appropriate system for managing quality.”

The large number of specific correlations between requirements in ICH Q7a and those in ISO (9001:2000) can be appreciated by reviewing the compilation in part IV. **7 Matrix GMP (Q7a) / ISO (9001: 2000)**. In this appendix we examine where ICH Q7a describes systems that are part of a QMS.

It is not surprising that the first chapter following the Introduction is titled “Quality Management” and begins with a listing of Quality Management Principles (section 2.1). This chapter summarizes many of the elements of a QMS, and in part 2.12 defines a QMS in terms readily recognized by those familiar with ISO 9001. This chapter on its own contains QMS elements of management responsibilities (2.11, 2.18, 2.2, and 2.3), organizational structure (2.13, 2.20-2.22, and 2.3), product realization (2.3), and measurement, analysis, and improvement (2.2, 2.4, and 2.5). Furthermore, there are multiple references to the procedures and records that are necessary for the effective functioning of a QMS.

Chapter 6 “Documentation and Records” does not just give a detailed description of the documents required for manufacturing under GMP: it also describes the system under which those documents should be managed. In addition, one can find references to the procedures needed for meeting the GMP requirements throughout ICH Q7a (e.g. 8.30, 9.10, and 11.11 to name just three).

Systems for the design and development of products and processes are found in several parts of ICH Q7a. Chapter 12 “Validation” incorporates into the validation system required by GMP the systems for critical product attribute identification. The system for process controls to ensure that critical product attributes are achieved is described in part 8.3 “In-process Sampling and Controls.”

The system for change control, including notification of customers, is the subject of all of Chapter 13 (“Change Control”). Chapter 15 “Complaints and Recalls” describes the system for handling quality-related complaints, and the system for managing contractors is described in Chapter 16 “Contract Manufacturers (Including Laboratories).”

Chapter 7 “Materials Management” describes the system for control of materials and the role of interactions with suppliers within that system (parts 7.11, 7.12, and 7.31).

As a consequence of the system approaches incorporated into ICH Q7a, compliance with ICH Q7a necessarily requires that an API manufacturer implements many elements of a QMS.

2. Description of Processes

2.1 Introduction

The purpose of the process approach, as outlined in the previous section (1. Identification of system approaches in ICH Q7a) or in Appendix A, is to enhance an organization's effectiveness and efficiency in achieving its defined objectives.

Benefits of the process approach are:

- Integration and alignment of processes to enable achievement of planned results.
- Ability to focus effort on process effectiveness and efficiency.
- Giving customers, and other interested parties, confidence about the consistent performance of the organization.
- Transparency of operations within the organization.
- Lower costs and shorter cycle times, through the effective use of resources.
- Improved, consistent and predictable results.
- Providing opportunities for focused and prioritized improvement initiatives.
- Encouraging the involvement of people and the clarification of their responsibilities.

2.2 Definition

A "Process" can be defined as a "Set of interrelated or interacting activities, which transforms inputs into outputs". These activities require allocation of resources such as people and materials. Fig. 1 shows the generic process.

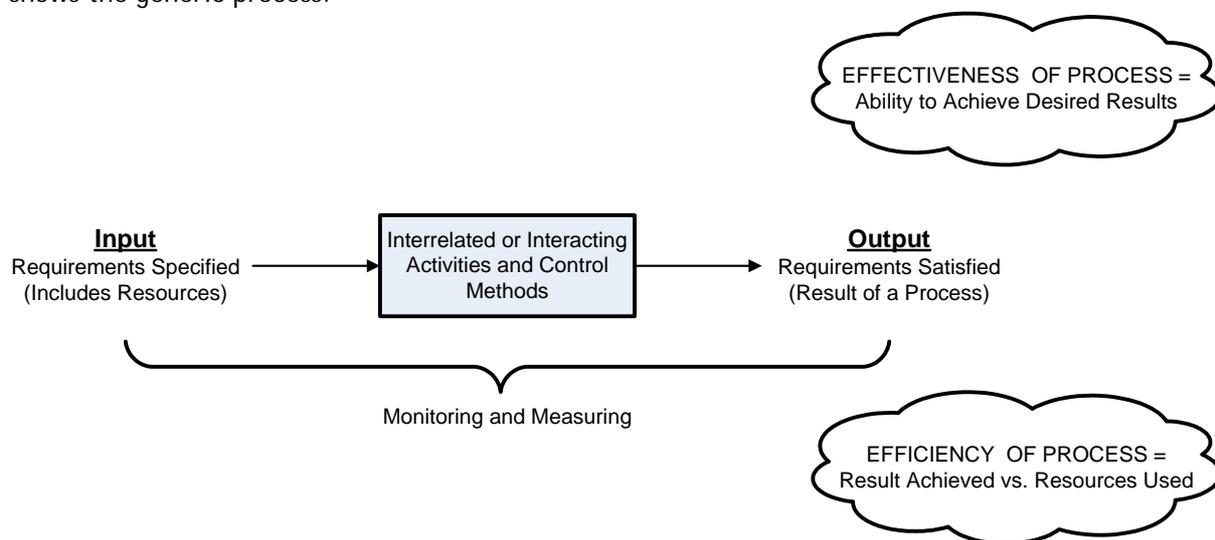


Figure 1 - Generic process

A major advantage of the process approach, when compared to other approaches, is in the management and control of the interactions between these processes and the interfaces between the functional hierarchy of the organization (as further explained in this appendix, section 2.4: Understanding the process approach).

Inputs and intended outputs may be tangible (such as equipment, materials or components) or intangible (such as energy or information). Outputs can also be unintended; such as waste or pollution.

Each process has customers and other interested parties (who may be either internal or external to the organization) that are affected by the process and who define the required outputs according to their needs and expectations.

A system should be used to gather data, which can be analyzed to provide information about process performance and to determine the need for corrective action or improvement.

All processes should be aligned with the objectives of the organization and be designed to add value, in relation to the scope and complexity of the organization.

Process effectiveness and efficiency can be assessed through internal or external review processes.

2.3 Types of Processes

The following types of processes can be identified (ISO model):

- *Processes for management of an organization.*
These include processes relating to strategic planning, establishing policies, setting objectives, providing communication, ensuring availability of resources needed and management reviews.
- *Processes for managing resources.*
These include all those processes for the provision of the resources that are needed for the processes for managing an organization, for realization, and for measurement.
- *Realization processes.*
These include all processes that provide the intended output (products (i.e. APIs), documents, customer services) of the organization.
- *Measurement, analysis and improvement processes.*
These include those processes needed to measure and gather data for performance analysis and improvement of effectiveness and efficiency. They include measuring, monitoring and auditing processes, corrective and preventive actions and are an integral part of the management, resource management and realization processes.

The realization process is often referred to as "main (manufacturing) process", whereas the other three types of processes are referred to as "supporting (or enabling) processes".

2.4 Understanding the Process Approach

A process approach is a powerful way of organizing and managing how work activities create value for the customer and other interested parties.

Organizations are often structured into a hierarchy of functional units. Organizations are usually managed vertically, with responsibility for the intended outputs being divided among functional units. The end customer or other interested party is not always visible to all involved. Consequently, problems that occur at the interfaces are often given less priority than the short-term goals of the units. This leads to little or no improvement to the interested party, as actions are usually focused on the functions, rather than overall benefit to the organization.

In contrast, the process approach introduces horizontal management, crossing the barriers between different functional units and unifying their focus to the main goals of the organization. It also improves management of process interfaces (see Fig. 2).

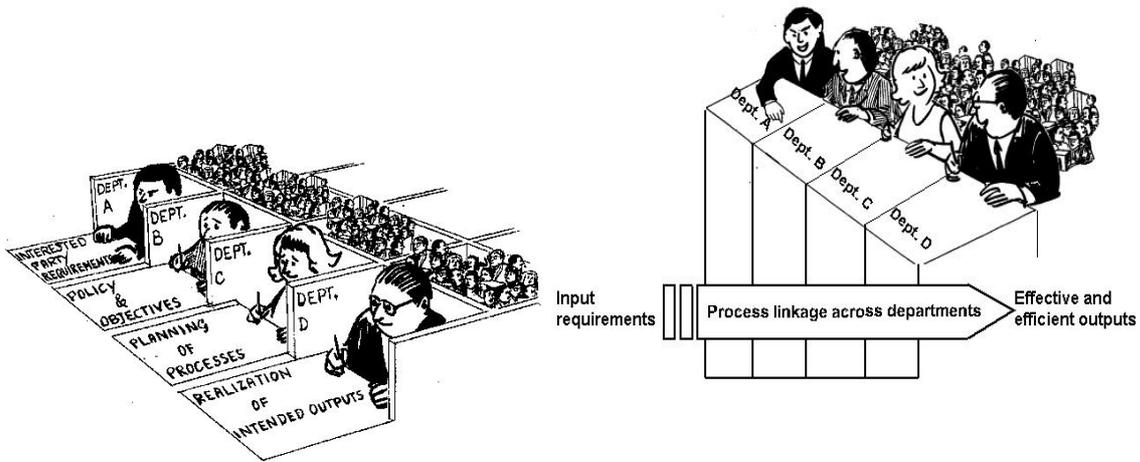


Figure 2 - Example of Process linkages across departments in an organization.

The performance of an organization can be improved through the use of the process approach. The processes are managed as a system, by creating and understanding a network of the processes and their interactions. The consistent operation of this network is often referred to as the “system approach” to management.

The outputs from one process may be inputs to other processes and interlinked into the overall network or system (for generic examples see Fig. 3 and Fig. 4).

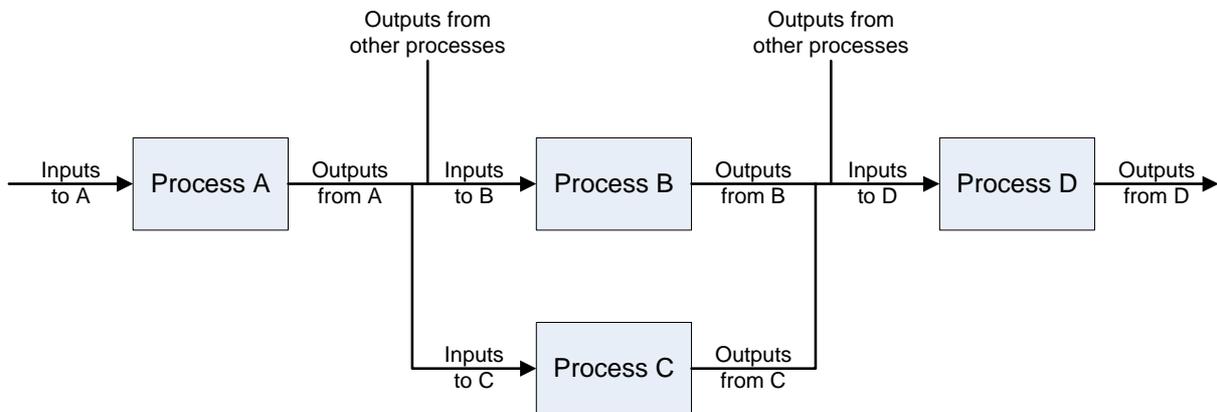


Figure 3 - Example of a generic process sequence

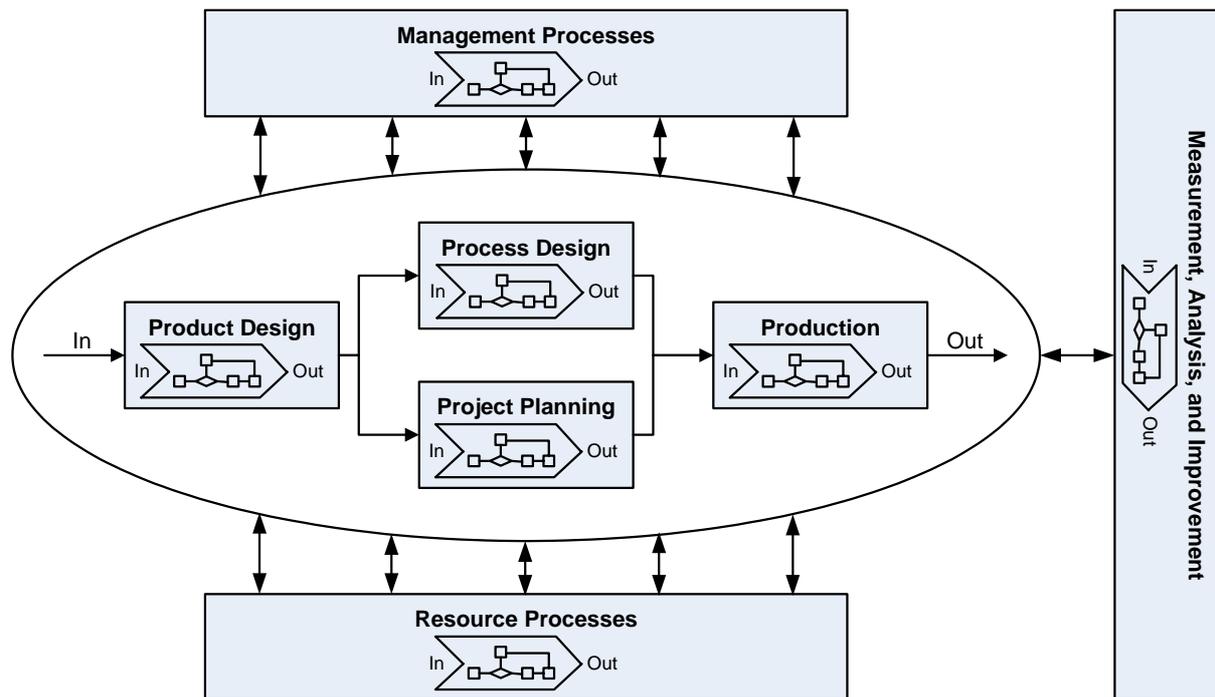


Figure 4 - Example of a process sequence and its interactions

2.5 Implementing the Process Approach

The following implementation methodology can be applied to any type of process.

Identification of processes of the organization

Steps in the process approach may be:

- Definition of the purpose of the organization
- Definition of the policies and objectives of the organization
- Determination of the processes in the organization
- Determination of the sequence of the processes
- Definition of process ownership
- Definition of process documentation

Planning of a process

The planning may be subdivided into the following steps:

- Definition of the activities within the process
- Definition of the monitoring and measurement requirements
- Definition of the resources needed
- Verification of the process and its activities against its planned objectives

Implementation and measurement of the process

Implement the processes and their activities as planned. The organization may develop a project for implementation that includes, but is not limited to:

- communication,
- awareness,
- training,
- change management,
- management involvement,
- applicable review activities.

Perform the measurements, monitoring and controls as planned.

Analysis of the process

Evaluate process data obtained from monitoring and measuring, in order to quantify process performance. Where appropriate, use statistical methods.

Compare the results of process performance measurements with the defined requirements of the process to confirm process effectiveness, efficiency and any need for corrective action.

Identify process improvement opportunities based on process performance data. Review the performance of the processes with top management on a regular basis.

Corrective action and improvement of the process

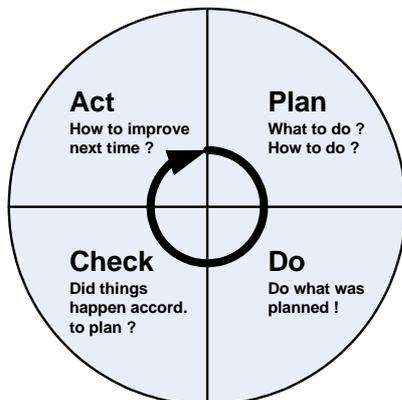
The method for implementing corrective actions should be defined, to eliminate the root causes of problems (e.g. errors, defects, lack of adequate process controls). Implement the corrective action and verify its effectiveness.

Once the planned process requirements are achieved, the organization should focus its efforts on actions to improve process performance to higher levels, on a continual basis.

The method for improvement should be defined and implemented (e.g. process robustness, enhancement of efficiency, improvement of effectiveness, reduction of process cycle time). Verify the effectiveness of the improvement.

Quality risk management as defined in draft ICH Q9 may be employed to identify potential problems. The root cause(s) of these potential problems should also be identified, documented and corrected, preventing occurrence in all processes with similarly identified risks.

The PDCA methodology (Plan-Do-Check-Act, see Fig. 5) could be a useful tool to define, implement and control corrective actions, and improvements. The methodology applies equally to high-level strategic processes and to simple operational activities.



- | | |
|--------------|---|
| Plan | Establish the objectives and processes necessary to deliver results in accordance with customer requirements and the organization's policies; |
| Do | Implement the processes; |
| Check | Monitor and measure processes and product against policies, objectives and requirements for the product and report the results; |
| Act | Take actions to continually improve process performance |

Figure 5 - The PDCA methodology (Plan-Do-Check-Act)

2.6 Graphical Representation of a Process

There are many different ways to visualize a process. One example relating to equipment qualification is given below (see Fig. 6).

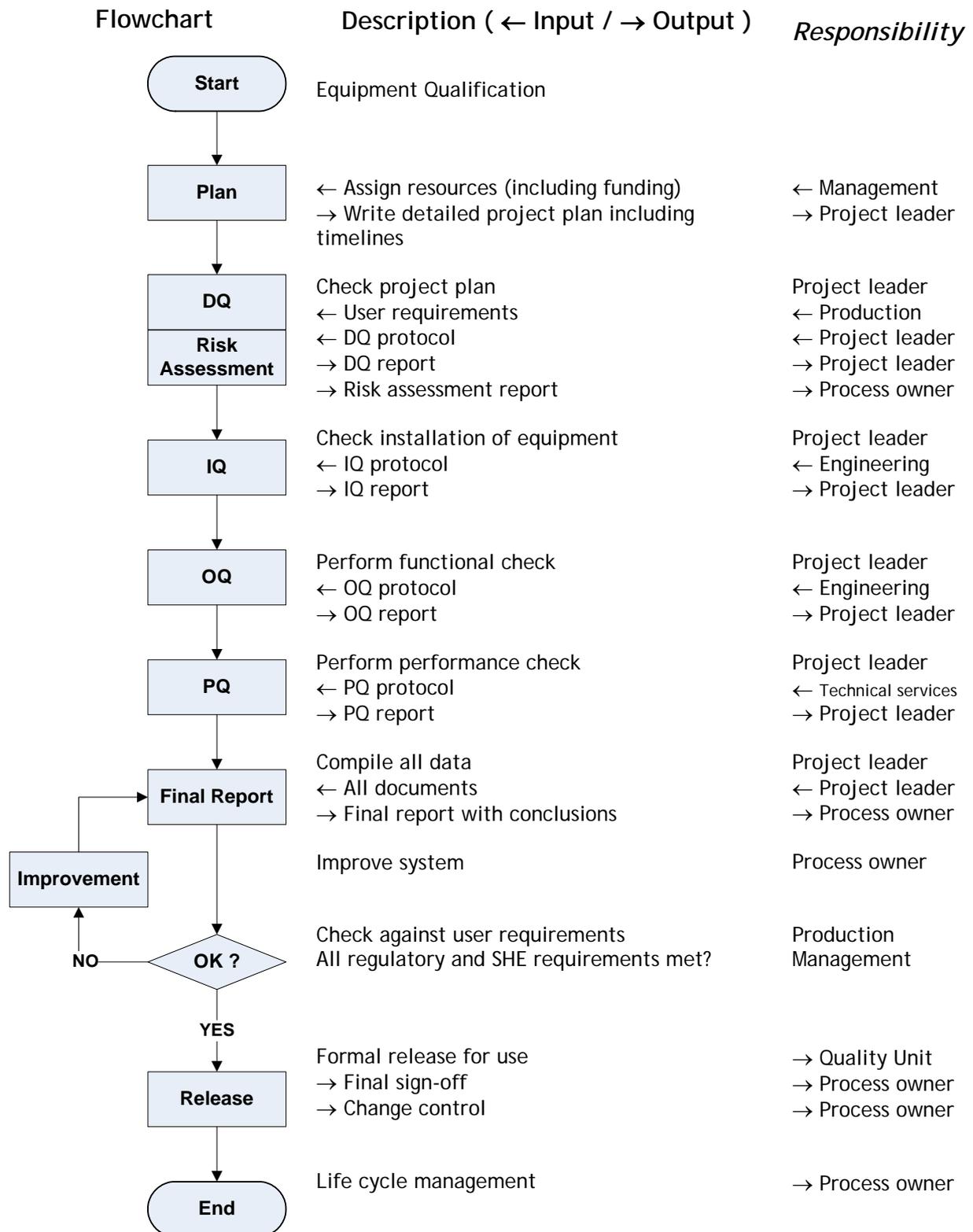


Figure 6 - Process Flow Chart including short description and responsibilities assigned

3. Structure of a Quality Manual

In this section an example for a table of contents for a Quality Manual is given. It reflects the process orientated ISO 9001: 2000 description and identifies the relevant GMP requirements that should be addressed. While in the first part of this section the pure table of contents is presented a more detailed description of the content (in form of bullet points) gives the information needed to facilitates the writing of a manual.

1	Title page
2	Control of Version Numbers
3	Table of Contents
4	General Part
4.1	Objective and scope
4.2	Profile of the company
4.3	Design of the QMS
4.4	Regulatory environment and requirements
5	Management Processes (corresponds to ISO Chapter 5)
5.1	Commitment of top management
5.2	Quality policy
5.3	Organization and responsibilities
5.4	QMS responsibilities
5.5	Assessment and review processes of the QMS by top management
5.6	Financing
5.7	Planning processes
5.8	Controlling processes
5.9	Communication and Information
5.10	Knowledge management
5.11	Project management
6	Resources Management (corresponds to ISO Chapter 6)
6.1	Management of personnel
6.2	Training and Education
6.3	Infrastructure
6.4	Outsourcing
6.5	Information technology
7	Customer Relations (internal and external customers)
7.1	Marketing of products
7.2	Information exchange and support
7.3	Recalls
7.4	Relationship with authorities

8	Product Realization (corresponds to ISO Chapter 7)
8.1	Development processes
8.2	Supply chain
8.2.1	Planning of realization processes
8.2.2	Procurement, distribution, transportation
8.3	Manufacture
8.3.1	Production
8.3.2	Analysis
8.3.3	Control of monitoring and measuring devices
8.3.4	Release
8.3.5	Hygiene
8.3.6	Cleaning procedures
8.3.7	Storage and warehousing
8.3.8	Environmental aspects
9	Measuring, Analyse, Improvement (MAI) (corresponds to ISO Chapter 8)
9.1	QC / QA (QU)
9.2	Product Quality Review (Annual Product Review)
9.3	Change Management
9.4	Audits
9.5	Complaints
9.6	Data analysis
9.7	Risk Management
9.8	Corrective and Preventive Actions (CAPA)
9.9	System for suggesting improvements
9.10	Control of non-conforming products
9.11	Measurement of customer satisfaction
9.12	Measurement of employee satisfaction
10	Documentation Management
10.1	Organization of documents
10.2	Document and data control
10.3	Regulatory files (Dossier)
11	Annexes
11.1	Corporate policies and guidelines (corporate level)
11.2	Abbreviations
11.3	Definitions

2 Control of Version Numbers

In total there are ____ originals in existence. This document has been identified as No. _____.
The original documents are subject to change control.

The Quality Handbook contains confidential information about the company and should therefore be treated with confidentiality.

Chapter concerned	New Version No.	Effective date	Reason of change

4 General Part

4.1 Objective and scope

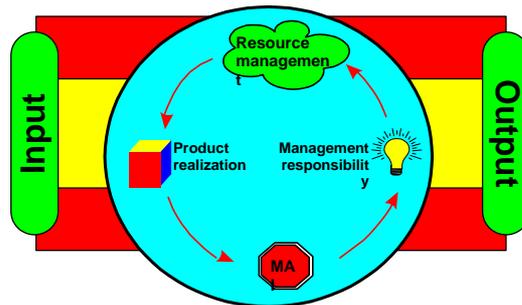
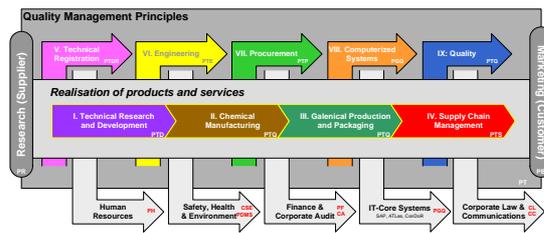
- Which parts (departments) of the company are covered, unless the entire company is affected
- Q7a applicable
- ISO 9001: 2000
- Specify if only QMS or if integrated Management System (i.e. including safety, health and environment (SHE) such as ISO 14000)

4.2 Profile of the company

- Brief description of company (product portfolio, locations)
- Elements of the Site Master File
- Vision, mission
- Ethical aspects
- Culture and philosophy

4.3 Design of the QMS

- Description of the identified processes (main and supporting); see example
 - examples of main processes: development, production, supply
 - examples of supporting processes: quality management, change management, human resources, data management, registration,
- QMS described in the (quality) management handbook
 - specify if only QMS or integrated management system will be covered; if SHE applies additional chapters are to be integrated in the Quality Manual - this is not covered by this example
- Describe the continual improvement process



4.4 Regulatory environment and requirements

- Description of applicable regulatory requirements such as ICH (e.g. stability, impurities), local laws and guidance
- Inspection readiness
- Commitment to comply with (local) regulatory requirements

5 Management processes (corresponds to ISO Chapter 5)

5.1 Commitment of top management

- Provide necessary resources in form of time, money and employees
- Fulfill all tasks required by the QMS
- Compliance with regulatory and GMP requirements

5.2 Quality policy

- Describe understanding and philosophy of top management
- Obligation towards quality awareness
- Compliance with pre-defined (company) standards
- Top down

5.3 Organization and responsibilities

- Organization charts
- Independence of the Quality Unit(s)
- Departments
 - identification of various functions to be covered by the organization
- Matrix organizations
- Tasks and responsibilities of the departments
 - including financial decisions

5.4 QMS responsibilities

- Description who is in charge (person or organizational unit)
- How organized and how ensured that top management will be provided with the relevant information

- Co-ordination, development, optimization, adaptation, implementation and maintenance of the QMS (covering all activities)

5.5 Assessment and review processes of the QMS by top management

- How data are compiled for top management for assessment

5.6 Financing

- How financial decisions are made in the company
- Cost centers
- Budgeting process

5.7 Planning processes

- Identify business of company in line with the company's philosophy (which products, services and/or activities)
- Cover all aspects from development, product portfolio, infrastructure
- Providing capacity, manpower, time, and financial resources
- Execution is described in chap 8 (product realization)
- Identify skills and knowledge requirements needed

5.8 Controlling processes

- Surveillance of financial processes
- Surveillance of QMS processes

5.9 Communication and Information

- Internal
 - formalized structure of informing the employees about developments, changes and news of the company
 - media: newsletter, intranet websites, e-mail, notice boards, meetings, face-to-face, tele- and videoconferences
 - reporting channels
 - effective use of IT technology (e-mail)
 - formalized feedback from employees
 - identify information and the frequency with which top management is going to inform employees
- External
 - customers relationship
 - press
 - neighbourhood
 - authorities
 - all contacts to be formalized with respect to responsible person, frequency and media

5.10 Knowledge management

- Ensuring that knowledge of the entire company - starting from research and development to production and including all other functions and activities - is captured (documented) in a suitable way
- Identify the media (electronic or paper or whatever)
- Switchboard: archive and distribution of available information/knowledge to functions and persons that need it
- Ensure transfer of knowledge in case of changes, i.e. personnel and/or site

5.11 Project management

- Identify milestones
- Clear definition of goals and tasks of project
- Timetable
- Resources
- Team

6 Resources management (corresponds to ISO Chapter 6)

6.1 Management of personnel

- Recruiting of new employees (criteria)
- Participation in benefit programmes of the company
- Job descriptions (per function or personalized)
- Regulatory aspects (e.g. health checks, safety training)
- Regular training and education programmes and activities, including documentation
- Assessment of employees performance
- Goal setting process

6.2 Training and education

- Identify the needs of the employees for training activities - systematic approach
- In-house training vs. external training courses
- Training on the job
- Frequency
- Failure rate during working as an indicator

6.3 Infrastructure

- Facilities
 - suitable for intended use
 - concept for pest control
- Utilities
 - HVAC
 - compressed air
 - water
 - gases (e.g. nitrogen)
 - electrical power
- Equipment
 - avoid contamination
 - ensure apparatus needed are available
- Maintenance
 - preventive maintenance programme
 - emergency handling/plans

6.4 Outsourcing

- Identify what kind of outsourcing is needed (GXP, specific equipment); prerequisites
- Identify in-house procedure to be followed when selecting a contract manufacturer
- Departments/functions involved
- How to set up a contract
 - interfaces
 - responsibilities
 - activities
 - information exchange
 - quality agreement
- Routine assessment of co-operation
 - identify areas for improvements

6.5 Information technology (IT)

- Ensure that suitable hard-and software for the employees is available
- Measures that ensure no loss of data occurs
- Archiving system
- Change management

- Access control
- Audit trail
- Maintenance and support
- Routinely evaluation of needs and resources
- Training of users

7 Customer Relations

7.1 Marketing of products

- Evaluate the market needs including competitors
- Establish / summarize product characteristics (data sheet)
- Ensure supply capability / demand chain management
- Educate marketing staff (product related and techniques used)
- Pricing policy

7.2 Information exchange and support

- Close co-operation with customer in terms of product design, as needed
- Providing customer support
- Developing the contract including responsibilities and specifications
- Provide information about changes (process and analytics) and process deviations as agreed
- Complaints
- Information about new development(s)
- Feedback from the market
- Provide CEP or open part of (E)DMF
- Communication with the press and other official bodies
- Policy on releasing (sensitive) information

7.3 Recalls

- System to identify and notify all customers within reasonable timeframe
- Internal evaluation procedure to assess the potential risk for the patient and/or impact for the customer
- Help customer to identify the risk
- Increase level of communication accordingly

7.4 Relationship with authorities

- Submit all necessary information for obtaining an CEP and/or (E)DMF
- Provide necessary information to pharmacopoeias for preparing monographs
- Actively communicate incidents with potential impact to market action
- Full support in case of market action (i.e. recall)
- Accept and support inspections
- Procedures for non-crisis communication with regulators

8 Product Realization (corresponds to ISO Chapter 7)

8.1 Development Processes

- Identify the chemical entities of interest
- Identify milestones throughout the development
- Establish project team(s)
- Inform authorities about new product
- Establish specifications, synthetic route and analytical methods
- Provide quantities of clinical trials material the customer requests
- Define level of GMP

- Generate data for identifying critical process steps, parameter limits (PAR - proven acceptable ranges), initial stability, retest date, storage conditions, validation and cleaning validation
- Scale-up process from laboratory to production
- Compiling data for registration

8.2 Supply Chain

8.2.1 Planning of realization processes

- Evaluation of demand for products
- Ensure source, price and quality of purchased materials
- Process for supplier qualification
- Allocate internal resources (capacity planning, timelines)
- Defining sequence of production in multi-purpose equipment
- Training of procurement staff in terms of GMP
- Ensure that contracts have a GMP/quality part
- Procedure for filling unused capacity (in-sourcing)
- Strategy for selecting and using suppliers

8.2.2 Procurement, Distribution, Transportation

- Selecting, instructing and monitoring carriers with respect to transportation conditions
- Import/export restrictions
- Identify set of documents needed for receipt and distribution
- Procedure for placing orders (way of communication)
- Procedure for receipt of materials (e.g. inspection, sampling)
- Procedure for accepting deliveries
- Procedure for preparing goods for transportation
- Procedure for handling returned goods
- Maintaining records of distribution

8.3 Manufacture

8.3.1 Production

- Operating instructions to be in place
- Qualification of equipment and facilities
- Validation of processes
- Procedures for handling labels and other identification
- Procedures for handling of packaging materials in the production areas
- Procedures for packaging goods
- Equipment use logs
- Procedure for transfer of production
- Assigning status of equipment
- Pest control measures

8.3.2 Analysis

- Qualification of laboratory equipment
- Validation of analytical methods
- Procedure for transfer of analytical methods
- Programme for stability testing
- Laboratory testing methods / procedures in place
- Handling of reference standards
- Preparation, review, approval and archiving of laboratory records

- Establishing sampling plans
- Evaluation of in-process control data

8.3.3 Control of monitoring and measuring devices

- Calibration procedures
- Traceable standards to be available
- Programme for calibration (frequency)
- Acceptance criteria
- Procedure for assigning status of devices (sticker or electronically)
- Procedure for cases when calibration acceptance criteria were not met

8.3.4 Release

- Procedure for release of goods
 - identifying the responsible person
 - evaluations to be conducted before release
 - analytical data assessment
 - production information assessment
 - ensure that deviations/investigations are completed
- Identification of status of goods
- Procedure for change of status of goods (labels or electronically)
- Issuing a certificate of analysis

8.3.5 Hygiene

- Zone concept
 - identify areas where specific hygiene aspects have to be applied
 - flow of material and persons
 - cleaning materials containers
 - specify use of pallets (wooden vs metal vs plastic)
- Establish hygiene monitoring programmes
- Acceptance criteria
- Analytical methods for testing
- Determine protective clothing of operators
- Gowning procedures (including training)

8.3.6 Cleaning Procedures

- Concept for cleaning facilities (including warehouses) and equipment
 - manual vs CIP / SIP
 - frequency and lag time
 - different concepts for dedicated and multi purpose equipment
 - cleaning materials used
 - cleaning verification vs validation
 - acceptance criteria
 - storage of cleaned equipment
 - assigning status of cleaned equipment
- Cleaning validation, where needed
 - validation of analytical methods
 - reference to APIC/CEFIC guidance

8.3.7 Storage and Warehousing

- Assign storage conditions for materials, intermediates and APIs
- Monitoring storage conditions (e.g. temperature, humidity)
- Distribution principle (FIFO, FEFO)
- Identifying material status
- Concepts for storage (computerized systems vs manual)
 - separate area for returned and rejected goods, where needed
- Access control and security measures

- Pest control measures

8.3.8 Environmental aspects

- Procedures for handling waste
- Identify local regulations for environmental controls
- Monitoring of environmental parameters
 - emissions, waste, run-off
- Waste water treatment
- Air pollution treatment

9 Measuring, analyse, Improvement (MAI) (corresponds to ISO Chapter 8)

9.1 QC / QA (QU)

- Procedures for deviation / investigation handling
- System of batch record review
- OOS procedure
- Involvement in: complaints, recalls, returns, outsourcing, supplier qualification, qualification and validation projects, changes, Quality Product Review, establishing audit plan
- Reference to 2.22 ICH Q7a

9.2 Product Quality Review (Annual Product Review)

- Procedure for establishing a Product Quality Review
 - frequencies
 - responsibilities
 - format
 - follow up measures, where needed
- Defining data to be evaluated
 - reference to 2.50 ICH Q7a

9.3 Change Management

- Procedure for handling changes
 - identify departments involved
 - regulatory impact
 - evaluate impact on quality and costs
 - classification of changes (e.g. major/minor)
 - decision process
 - documentation
 - follow up activities (e.g. stability)
 - implementation of change
 - evaluate whether customer needs to be notified
- Establish change control committee(s)
 - approval of change
- System for notification of authorities
 - track approvals

9.4 Audits

- Procedure for carrying out audits
 - frequencies
 - responsibilities
 - confidentiality of audit reports
- Establish plan for internal and external (supplier) audits
 - justification for audits not conducted
- Identify auditors
 - qualification of auditors
- Observations in writing (audit report)

- Classification of observations (e.g. serious, major, minor)
- Follow-up activities
- Inform top management (escalation strategy)
- Procedure for handling customer audits and inspections by authorities

9.5 Complaints

- Procedure for handling complaints
 - responsibilities
 - timelines
 - documentation
 - conclusion
- Departments involved
- Batches involved
- Follow-up measures
- Respond to complainant
- Notify authorities, if applicable

9.6 Data analysis

- Trend analysis
 - analytical and process data
 - impact on costs
 - indicators: e.g. complaints, OOS, deviations, stability
- Use of statistical tools / techniques
- Format
- Conclusions and resulting actions
- Consolidation process for top management
- Preparation of data for benchmarking
- Identify key performance indicators (KPI)

9.7 Risk Management

- Reference to draft ICH Q9
- Integration of risk management into existing processes and decision making processes
 - examples are shown in chapter 6 of draft ICH Q9
 - labelling errors, contamination control, mix-ups

9.8 Corrective and Preventive Actions (CAPA)

- The key element for continual improvement
- Assessing available data for improvement
- Systematically evaluate preventive actions after corrective actions have been taken
- Monitor preventive actions if improvements are achieved
- Link together with KPIs
- Inform top management

9.9 System for suggesting improvements

- Address all employees and all areas
- Timely response to suggestion
- Award system and/or compensation
- Evaluation committee
 - decision on suggestion
 - communication of approved suggestion
- Monitor approved suggestion
 - reassess impact/efficiency after a certain time limit
- Monitoring of system effectiveness

9.10 Control of non-conforming products

- Procedure for handling non-conforming products
 - responsibilities
 - timelines
 - decision making process (e.g. reuse, disposal)
- Follow up actions (e.g. inform customer, authorities)
- Identification and tracking (e.g. manually or electronically)
 - OOS, reworking, reprocessing, recalls, complaints
- Assess impact on other batches (materials) and potential recall
- Link with KPIs and Product Quality Review, where applicable
- Investigation of root cause (link to CAPA)

9.11 Measurement of customer satisfaction

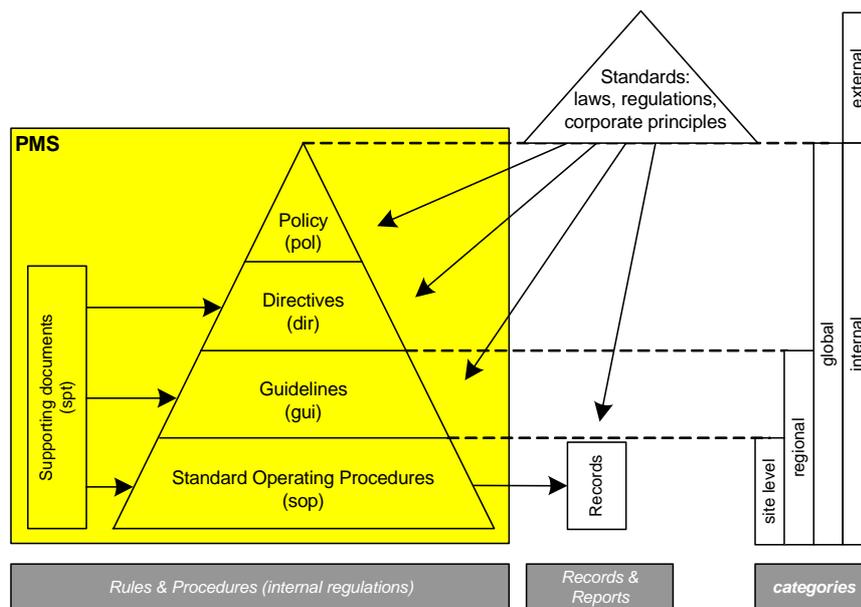
- Number of complaints (KPI)
- Time delays
- Out of stock
- Questionnaire
- Costs
- Repeat business (right first time)

9.12 Measurement of employee satisfaction

- Yearly interview with employee
 - performance evaluation
 - feedback of employee
- Questionnaire
- Employee turnover

10 Documentation Management

10.1 Organization of Documents



- Define policy, directive, guideline, SOP and other supporting documents
- Integrate Quality Management Handbook into documentation system
- Describe documentation hierarchy/structure
- Identify documents resulting from directives and guidelines (e.g. quality agreement)
- Define term 'controlled document'
 - in terms of controlling / describing / supporting processes
 - in terms of regulatory requirements
- Identify documents to be controlled
- Formatting issues
- Confidentiality aspects
- Handling of electronic documents
 - verify hidden information in documents (delete)
 - ensure accurate distribution
 - protection of documents

10.2 Document and data control

(Handling of documents)

- Define documentation requirements (Master document)
 - drafting, reviewing and approval processes
 - training and distribution (manually or electronically)
 - withdrawal
- Maintenance of documentation system
 - review / revision process for documents
 - up-dates of documents
- Archiving, storage and retention time
- Handling of raw data
 - laboratory
 - production (e.g. batch record)
 - maintenance (e.g. calibration)
 - use logs
 - correction procedures in records
 - identify raw data to be retained (electronic systems)

10.3 Regulatory files

- Procedure for compiling data for registration files
- Departments / sites involved
- Responsibilities
 - who is sending file out to authority
 - identify contact for authorities
- CTD format (hard copy and/or electronically)
- Up-date of regulatory files
- Link to change management process
- Communicating regulatory approval
- Accessibility of approved files

11 Annexes

11.1 Company policies and guidelines (corporate level)

- Ethic, sustainability, etc.

11.2 Abbreviations

- List of abbreviations used in the company

11.3 Definitions

- List of definitions used in the company

4. Cross-reference of API QMS documents (from 'old' to 'new')

In this chapter a comparison of APICs new QMS document with the previous one (Quality Management System for Active Pharmaceutical Ingredients Manufacturers - integrating GMP into ISO 9001: 1994, published 1998; 8) is made. The column in the middle is identical with the Table of Content that is given in section before of this document (IV, 3; Structure of a Quality Manual) and the right column reflects the numbering system within the chapters of the previous document.

	Structure of a Quality Manual according to ISO 9001: 2000 as described in section IV. 3 of this document	Reference chapter numbers of APICs previous QMS document (basis: ISO 9001) published in 1998 (8)
1	Title page	
2	Control of version numbers	
3	Table of contents	
4	General part	
4.1	Objective and scope	
4.2	Profile of the company (Brief description, strategy, goals, ethic)	
4.3	Design of the QMS (Illustration of processes, (quality) Management Handbook; to be combined (or not) with environmental (ISO 14000, safety and health; this document not provides assistance to SHE)	2.1, 2.2
4.4	Regulatory environment and requirements	
5	Management processes (=Chap. 5)	
5.1	Commitment of top management	
5.2	Quality policy	1.1
5.3	Organization and responsibilities (Organizational diagrams)	1.2, 1.310.1
5.4	QMS responsibilities	1.3
5.5	Assessment and review processes of the QMS by top management	1.4
5.6	Financing (global view; product and process related)	
5.7	Planning processes (executing is described in chap. 8: product realization; providing resources)	2.3, 4.1
5.8	Controlling processes (review, adjustment; not limited to finance)	
5.9	Communication and Information	
5.10	Knowledge management	2.3
5.11	Project management	

6	Resources management (= Chap. 6)	
6.1	Management of personnel (Resources, job descriptions, regulatory aspects, health issues, leadership, goal setting, assessment processes, benefit programmes; hygiene?)	9.4
6.2	Training and education	9.4, 18, Annex B (B5)
6.3	Infrastructure (Facilities, utilities, equipment, maintenance)	9.5, 11, Annex B (B1, B4, B5)
6.4	Outsourcing	3.1, 3.2, 3.3, 3.4
6.5	Information technology (IT) (Equipment (hard-/software, maintenance, training)	Annex B (B2), Annex C (C5)
7	Customer relations (internal and external customers)	Chap 7
7.1	Marketing of products (Description of process to sell products)	
7.2	Information exchange and support (including contract (part of: change management, specifications, quality agreement), if applicable)	
7.3	Recalls	2.3
7.4	Relationship with authorities	
8	Product realization (=chapter 7)	
8.1	Development processes (Determination of product requirements)	4.1, 4.2, 4.3, 4.4, 4.5, 4.6, 4.7, 4.8
8.2	Supply chain	8.1
8.2.1	Planning of realization processes (realization of <i>technical</i> process to provide product (capacity) and/or service)	2.3
8.2.2	Procurement, distribution, transportation	6.1, 6.2, 6.3, 8.1, 10.2, 12, 15.1, 15.5
8.3	Manufacture (refer to Chapter 10: documentation management)	9.3, 10.1, 15.1
8.3.1	Production (Qualification, validation, labelling, packaging and identification; transmitting information other than batch records)	8.1, 8.2, 8.3, 9.2, 9.3, 10.3, 12, 15.3, Annex C (C1, C2, C3, C6, C7)
8.3.2	Analysis	10.1, 10.2, 10.3, 10.4
8.3.3	Control of monitoring and measuring devices (Calibration)	11
8.3.4	Release	10.2, 10.4
8.3.5	Hygiene	Annex A (A1, A2)
8.3.6	Cleaning procedures	Annex A (A2), Annex B (B3), Annex C (C6)
8.3.7	Storage and warehousing	15.1, 15.2, 15.4
8.3.8	Environmental aspects (waste handling; laws to be followed)	
9	Measuring, analyse, improvement (MAI) (=Chap. 8)	

	(target: continual improvement)	
9.1	QC / QA (OU) (Deviation /investigation)	10.1, 10.2, 10.3, 10.4, 10.6
9.2	Annual Product Review	
9.3	Change Management	Annex D
9.4	Audits	17
9.5	Complaints	
9.6	Data analysis (Statistics, data compression)	20
9.7	Risk Management (draft ICH Q9)	
9.8	Corrective and Preventive Actions (CAPA)	14.1, 14.2
9.9	System for suggesting improvements	
9.10	Control of non-conforming products	13
9.11	Measurement of customer satisfaction	
9.12	Measurement of employee satisfaction	
10	Documentation Management	
10.1	Document hierarchy and structure (Describe the system)	5.1
10.2	Documents (Rules & procedures, records, external documents (with other companies), others like fax, memos, e-mail, etc.) (Describe execution of system; identify kinds of documents; decide if to be integrated into 10.1)	9.1, 10.5, 11 (11.5), 12 (12.3), 15.5, 16, 18 (18.3), Annex C (C4)
10.3	Document and data control (Handling of documents, instrument logs, approval and change procedures, distribution, archiving, destruction)	5.1, 5.2, 16
10.4	Regulatory issues (Dossier)	
11	Definitions (Specific company terms)	
12	Annexes	
12.1	Corporate policies and guidelines (Ethic, sustainability, etc.)	
12.2	Abbreviations	

5. Assistance for implementation of a QMS

5.1. Introduction

The implementation of a Quality Management System should be a top down approach. A very important success factor in this process is the visible commitment and full support of top management.

Basically the implementation of a QMS takes place in 4 different phases

- Analysis of status quo
- To-be analysis (identification of requirements)
- Variance comparison (gap analysis)
- Management of Change/Implementation

The first 3 phases can be considered as the preparation of the real implementation phase. Typically, too many resources are used for the analysis in relation to the implementation. 25% of the total resources should be sufficient for the first 3 phases.

Realization speed of the implementation of the QMS correlates with the size of the organization but not necessarily with the number of the main process (e.g. manufacturing), support processes and their related sub-processes.

The implementation of a QMS is the most resource-intensive phase of the whole project and will cost approximately 75% of the total resources. For the Project Leaders and their facilitators in the different departments (Change Agents) this is a full time job throughout this phase. It will be highly beneficial to have these key persons focused only on the implementation work.

5.2. Analysis of status quo

During this analysis the main focus is set on the review of documents (e.g. policies, SOP, guidelines, master production instructions) as well as the corresponding records. Other effective tools to analyze processes are interviews with the employees involved in these processes and physical audits in the different departments. All current activities of the company are of interest at this stage (e.g. old ISO 9001:1994 structure with 20 chapters).

Tools like VAT Analysis (value added time analysis), integrated resource planning or flow charting are helpful to prioritize the different activities and the extent of the corresponding process analysis.

5.3. To-be analysis (identification of requirements)

This document (APIC/CEFIC-QMS integrating GMP into ISO) can be used for the QMS to be implemented. Additionally, the regulatory environment (i.e. local laws, international guidelines like ICH etc.) has to be considered.

The outcome of this to-be analysis should be a description of the proposed structure of the QMS.

5.4. Variance comparison (gap analysis)

The comparison between the current activities (as described in 10.2) and the proposed QMS (as described in 10.3) reflect the main areas for adaptations.

More emphasis should be placed on planning the closure of major gaps than in comprehensive identification of minor gaps.

Since the management of the change/implementation phase is the most resource-intensive step, careful planning in this phase of the project will enable a smooth and successful implementation and will lead to saving resources.

5.5. Management of the change/implementation phase

It is advisable to work out a detailed project plan with appropriate milestones to follow and control the implementation.

5.5.1 Prioritization

Variance comparison shows different areas for improvement but not all of them are equally critical in respect to product quality and the effectiveness of the QMS. The Quality Risk Management document of draft ICH Q9 can be used to prioritize the changes to be made.

5.5.2 Road Map / Implementation plan

- Based on the prioritization (10.5.1) a road map is established clearly addressing responsibilities, timelines, milestones and resources.
- All individual activities should finally lead to the QMS as proposed before.
- Criteria for the kick-off the QMS have to be defined. The operational phase of a QMS may start before all gaps are closed. Those gaps still open are included in the continual improvement process.
- Address how the implementation is controlled (Change Management)

5.5.3 Approval of the Road Map

The road map needs to be signed off by top management to make available necessary resources.

5.5.4 Diversification of the Road Map into projects

- Detailed description of the activities that have been prioritized on the top level.
- Identify the interfaces to other processes.
- Distribute these activities into projects and assign responsibilities and timelines.
- Define how the effectiveness and efficiency of the QMS will be measured (e.g. KPIs)
- Train the project team members and employees involved.

5.5.5 Management of implementation

- Monitoring of costs and milestones by the Project leader.
- Monitoring of implementation by audits and measuring KPIs.

- Report to top management status of implementation.

5.5.6 Documentation

- Document transition from existing to new design.
- Prepare and issue all necessary documentation for the new system.
- Document the training performed on all levels.

5.5.7 Operate the new system

When the predefined criteria (10.5.2) are fulfilled top management can declare the operational phase of the QMS by signing the Handbook.

Chapter 3 of ICH Q7a (Personnel)

ISO PROCESSES: 4 (QMS), 5 (Management), 6 (Resources), 7 (Product realization), 8 (MAI)

	4		5					6					7					8					
	4.1	4.2	5.1	5.2	5.3	5.4	5.5	5.6	6.1	6.2	6.3	6.4	7.1	7.2	7.3	7.4	7.5	7.6	8.1	8.2	8.3	8.4	8.5
3	Personnel																						
3.1	Personnel Qualifications																						
3.10						X				X													
3.11							X																
3.12									X														
3.2	Personnel Hygiene																						
3.20									X		X												
3.21											X												
3.22											X												
3.23									X	X	X												
3.24									X		X												
3.25							X		X														
3.3	Consultants																						
3.30						X			X														
3.31	X																						

Chapter 4 of ICH Q7a (Buildings and Facilities)

ISO PROCESSES: 4 (QMS), 5 (Management), 6 (Resources), 7 (Product realization), 8 (MAI)

	4		5					6					7					8					
	4.1	4.2	5.1	5.2	5.3	5.4	5.5	5.6	6.1	6.2	6.3	6.4	7.1	7.2	7.3	7.4	7.5	7.6	8.1	8.2	8.3	8.4	8.5
4	Buildings and Facilities																						
4.1	Design and Construction																						
4.10											X												
4.11											X												
4.12											X												
4.13											X	X											
4.14											X	X											
4.15											X												
4.16											X												
4.2	Utilities																						
4.20																	X						
4.21																	X						
4.22																	X						
4.23											X						X						
4.24											X												
4.3	Water																						
4.30																	X						
4.31											X												
4.32											X						X						
4.33											X						X						
4.34																	X						
4.4	Containment																						

Chapter 7 of ICH Q7a (Materials Management)

ISO PROCESSES; 4 (QMS), 5 (Management), 6 (Resources), 7 (Product realization), 8 (MAI)

	4		5					6					7					8					
	4.1	4.2	5.1	5.2	5.3	5.4	5.5	5.6	6.1	6.2	6.3	6.4	7.1	7.2	7.3	7.4	7.5	7.6	8.1	8.2	8.3	8.4	8.5
7	Materials Management																						
7.1	General Controls																						
7.10													X			X							
7.11																X							
7.12																X							
7.13																X							
7.14																							
7.2	Receipt and Quarantine																						
7.20																X							
7.21																X							
7.22																X							
7.23																X							
7.24																X							
7.3	Sampling and Testing of Incoming Production																						
7.30																X							
7.31																X							
7.32																X	X						
7.33																X							
7.34																X							
7.35																X							
7.4	Storage																						
7.40																X							
7.41																X							
7.42																X							
7.43																X							
7.44																X	X			X		X	
7.5	Re-evaluation																						
7.50																X				X		X	

Chapter 8 of ICH Q7a (Production and In-Process Controls)

ISO PROCESSES; 4 (QMS), 5 (Management), 6 (Resources), 7 (Product realization), 8 (MAI)

	4		5					6					7					8					
	4.1	4.2	5.1	5.2	5.3	5.4	5.5	5.6	6.1	6.2	6.3	6.4	7.1	7.2	7.3	7.4	7.5	7.6	8.1	8.2	8.3	8.4	8.5
8	Production and In-Process Controls																						
8.1	Production Operations																						
8.10													X				X						
8.11													X				X						
8.12													X				X						
8.13													X				X						
8.14													X				X						
8.15								X															X
8.16																	X						

9.4 Packaging and Labelling Operations																				
9.40																			X	
9.41																			X	
9.42	X																		X	
9.43	X																		X	
9.44	X																		X	
9.45	X																		X	
9.46																			X	X
10 Storage and Distribution																				
10.1 Warehousing Procedures																				
10.10										X									X	
10.11						X				X										
10.2 Distribution Procedures																				
10.20							X													X
10.21																			X	
10.22	X																			
10.23						X	X													
10.24	X					X	X													X

Chapter 11 of ICH Q7a (Laboratory Controls)

ISO PROCESSES: 4 (QMS), 5 (Management), 6 (Resources), 7 (Product realization), 8 (MAI)

	4		5					6					7					8					
	4.1	4.2	5.1	5.2	5.3	5.4	5.5	5.6	6.1	6.2	6.3	6.4	7.1	7.2	7.3	7.4	7.5	7.6	8.1	8.2	8.3	8.4	8.5
11 Laboratory Controls																							
11.1 General Controls																							
11.10												X											
11.11	X																	X					
11.12	X						X								X								
11.13															X								
11.14	X																						
11.15	X																					X	
11.16	X																	X					
11.17	X																		X				
11.18	X														X				X				
11.19	X																		X				
11.2 Testing of Intermediates and APIs																							
11.20																		X					X
11.21																		X					X
11.22	X																						X
11.23																		X					
11.3 Validation of Analytical Procedures - see Section 12																							
11.4 Certificates of Analysis																							
11.40	X																						
11.41	X																						
11.42	X																						
11.43	X							X															
11.44	X																						
11.5 Stability Monitoring of APIs																							

14.5	Returns																				
14.50																				X	
14.51																				X	
14.52	X																			X	

Chapter 15 of ICH Q7a (Complaints and Recalls)

ISO PROCESSES; 4 (QMS), 5 (Management), 6 (Resources), 7 (Product realization), 8 (MAI)

	4		5					6					7					8					
	4.1	4.2	5.1	5.2	5.3	5.4	5.5	5.6	6.1	6.2	6.3	6.4	7.1	7.2	7.3	7.4	7.5	7.6	8.1	8.2	8.3	8.4	8.5
15	Complaints and Recalls																						
15.10		X					X							X								X	
15.11		X																					
15.12		X																				X	X
15.13		X					X															X	
15.14							X																
15.15							X															X	

Chapter 16 of ICH Q7a (Contract manufacturers, including Laboratories)

ISO PROCESSES; 4 (QMS), 5 (Management), 6 (Resources), 7 (Product realization), 8 (MAI)

	4		5					6					7					8					
	4.1	4.2	5.1	5.2	5.3	5.4	5.5	5.6	6.1	6.2	6.3	6.4	7.1	7.2	7.3	7.4	7.5	7.6	8.1	8.2	8.3	8.4	8.5
16	Contract Manufacturers (including Laboratories)																						
16.10							X						X			X	X						
16.11							X																
16.12		X					X						X										
16.13		X					X										X						
16.14							X									X							
16.15		X																					
16.16							X																

Chapter 17 of ICH Q7a (Agents, Brokers, Traders, Distributors, Repackers and Relabellers)

ISO PROCESSES; 4 (QMS), 5 (Management), 6 (Resources), 7 (Product realization), 8 (MAI)

	4		5					6					7					8					
	4.1	4.2	5.1	5.2	5.3	5.4	5.5	5.6	6.1	6.2	6.3	6.4	7.1	7.2	7.3	7.4	7.5	7.6	8.1	8.2	8.3	8.4	8.5
17	Agents, Brokers, Traders, Distributors, Repackers and Relabellers																						
17.1	Applicability																						
17.10																							
17.11							X						X			X							
17.2	Traceability of Distributed APIs and Intermediates																						
17.20																	X						
17.3	Quality Management																						
17.30	X																						
17.4	Repacking, Relabelling and Holding of APIs and Intermediates																						

V. Glossary

Acceptance Criteria

Numerical limits, ranges, or other suitable measures for acceptance of test results.

Active Pharmaceutical Ingredient (API) (or Drug Substance)

Any substance or mixture of substances intended to be used in the manufacture of a drug (medicinal) product and that, when used in the production of a drug, becomes an active ingredient of the drug product. Such substances are intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease or to affect the structure and function of the body.

Audit

A systematic, independent and documented process for obtaining evidence and determining the extent to which given requirements are fulfilled.

Batch (or Lot)

A specific quantity of material produced in a process or series of processes so that it is expected to be homogeneous within specified limits. In the case of continuous production, a batch may correspond to a defined fraction of the production. The batch size can be defined either by a fixed quantity or by the amount produced in a fixed time interval.

In a batch process, this is the quantity of finished chemical produced at one time. In a continuous or semi-continuous process, it is not possible to define a batch in the above sense, and consequently is usual to talk in terms of a lot.

Batch Number (or Lot Number)

A unique combination of numbers, letters, and/or symbols that identifies a batch (or lot) and from which the production and distribution history can be determined.

Bioburden

The level and type (e.g. objectionable or not) of micro-organisms that can be present in raw materials, API starting materials, intermediates or APIs. Bioburden should not be considered contamination unless the levels have been exceeded or defined objectionable organisms have been detected.

Calibration

The demonstration that a particular instrument or device produces results within specified limits by comparison with those produced by a reference or traceable standard over an appropriate range of measurements. *Good Manufacturing Practice Guide for Active Pharmaceutical Ingredients*

All the operations establishing, in specified conditions, the relation between the values given by an instrument and the corresponding known measured reference if available. In practice, the result of a calibration allows for establishing the value of deviations of an instrument indication against the national or international references. It also allows, by using systematic corrections, for the reduction of the measurement uncertainty.

Certificate of analysis

A document giving the specifications and results of testing of a representative sample drawn from the material to be delivered. In this case it incorporates test results, as agreed between customer and organization.

Certificate of conformity

A document of conformity to a specification. The provision of a certificate of conformity is not a requirement of the standard although customers may request organizations to provide this document. See the guidance notes to sections 7.2 and 7.4. A certificate of conformity does not imply that the actual material delivered has been tested, but that all the material from which the delivery have been made up, has, at some stage, been inspected and tested according to the requirements of the established Quality Management System, and found to conform to specification.

Certified reference material

A reference material of which one or several property values are certified by a technically valid procedure and having a certificate, or other documentation associated with it, provided by a certification body. This material is used for calibrating instruments.

Computer System

A group of hardware components and associated software, designed and assembled to perform a specific function or group of functions.

Computerized System

A process or operation integrated with a computer system.

Continual Improvement

Recurring activity to increase the ability to fulfil requirements.

Contamination

The undesired introduction of impurities of a chemical or microbiological nature, or of foreign matter, into or onto a raw material, intermediate, or API during production, sampling, packaging or repackaging, storage or transport.

Contract

Any type of agreement either written or in any form or type of medium between the organization and the customer (see 7.2).

Contract Manufacturer

A manufacturer performing some aspect of manufacturing on behalf of the original manufacturer.

Corrective Action

Action to eliminate the cause of a detected non-conformity.

Critical

Describes a process step, process condition, test requirement, or other relevant parameter or item that must be controlled within predetermined criteria to ensure that the API meets its specification.

Cross-Contamination

Contamination of a material or product with another material or product.

Customer

Organization or person that receives a product or service. This can be a company internal customer (different department / site) and/or external customer outside of the company.

Deviation

Departure from an approved instruction or established standard.

Distributor

A company which is formally appointed by a organization to buy, stock and resell all or part of the organization's product range, e.g. within defined geographical areas, use sectors, and load size

limitation for delivery. The distributor may be a manufacturer, may supply in part, purchase for resale and may also have his own direct sales organization with whom a close liaison will exist. A distributor takes ownership of the product in contrast to an agent who does not.

Drug (Medicinal) Product

A pharmaceutical product (e.g. tablet, capsule, solution, cream) containing ingredients such as an API or a combination of APIs and, if needed, excipients presented for diagnosis, treatment or preventing disease in human beings or animals.

Drug Substance

See Active Pharmaceutical Ingredient

Effectiveness

Extend to which planned activities are realized and planned results achieved.

Efficiency

Relationship between the result achieved and the resources used.

Expiry Date (or Expiration Date)

The date placed on the container/labels of an API designating the time during which the API is expected to remain within established shelf life specifications if stored under defined conditions, and after which it should not be used.

Impurity

Any component present in the intermediate or API that is not the desired entity.

Impurity Profile

A description of the identified and unidentified impurities present in an API.

In-Process Control (or Process Control)

Checks performed during production in order to monitor and, if appropriate, to adjust the process and/or to ensure that the intermediate or API conforms to its specifications. *Good Manufacturing Practice Guide for Active Pharmaceutical Ingredients 42*

Intermediate

A material produced during steps of the processing of an API that undergoes further molecular change or purification before it becomes an API. Intermediates may or may not be isolated. (Note: this Guide only addresses those intermediates produced after the point that the company has defined as the point at which the production of the API begins.)

Lot

See Batch

The quantity of chemical, from which a representative sample is available, for example, a quantity of chemical drummed off or packed out from bulk tank or silo storage.

Lot Number

See Batch Number

Management

Coordinated activities to direct and control an organization.

Manufacture

All operations of receipt of materials, production, packaging, repackaging, labelling, re-labelling, quality control, release, storage, and distribution of APIs and related controls.

Measurement process

Set of operations to determine the value of a quantity.

Organization

A group of people and facilities with an arrangement of responsibilities, authorities and relationships.

Outsourcing

The transfer of an activity, service or product manufacture to a third party.

Preventive Action

Action to eliminate the root cause of a non-conformity.

Procedure

A documented description of the operations to be performed, the precautions to be taken and measures to be applied directly or indirectly related to the manufacture of an intermediate or API.

Process

A set of interrelated or interacting activities which transforms inputs into outputs.

Process Control

See In-Process Control

Production

All operations involved in the preparation of an API from receipt of materials through processing and packaging of the API.

Qualification

Action of proving and documenting that equipment or ancillary systems are properly installed, work correctly, and actually lead to the expected results. Qualification is part *Good Manufacturing Practice Guide for Active Pharmaceutical Ingredients* 43 of validation, but the individual qualification steps alone do not constitute process validation.

Quality

Degree to which a set of inherent properties of a product, system or process fulfils requirements.

Quality Assurance (QA)

The sum total of the organized arrangements made with the object of ensuring that all APIs are of the quality required for their intended use and that quality systems are maintained.

Quality Control (QC)

Checking or testing that specifications are met.

Quality Management

Coordinated activities to direct and control an organization throughout all areas and processes with regard to quality.

Quality Management System

System needed to implement Quality Management.

Quality Manual

Document specifying the Quality Management System.

Quality Unit(s)

An organizational unit independent of production which fulfills both Quality Assurance and Quality Control responsibilities. This can be in the form of separate QA and QC units or a single individual or group, depending upon the size and structure of the organization.

Reprocessing

Introducing an intermediate or API, including one that does not conform to standards or specifications, back into the process and repeating a crystallization step or other appropriate chemical or physical manipulation steps (e.g., distillation, filtration, chromatography, milling) that are part of the established manufacturing process. Continuation of a process step after an in-process control test has shown that the step is incomplete is considered to be part of the normal process, and not reprocessing.

Retest Date

The date when a product should be re-examined to ensure that it is still suitable for use. *Good Manufacturing Practice Guide for Active Pharmaceutical Ingredients 44*

Reworking

Subjecting an intermediate or API that does not conform to standards or specifications to one or more processing steps that are different from the established manufacturing process to obtain acceptable quality intermediate or API (e.g., re-crystallizing with a different solvent).

Signature (signed)

See definition for signed

Signed (signature)

The record of the individual who performed a particular action or review. This record can be initials, full handwritten signature, personal seal, or authenticated and secure electronic signature.

Specification

A list of tests, references to analytical procedures, and appropriate acceptance criteria that are numerical limits, ranges, or other criteria for the test described. It establishes the set of criteria to which a material should conform to be considered acceptable for its intended use. "Conformance to specification" means that the material, when tested according to the listed analytical procedures, will meet the listed acceptance criteria.

Supplier

An organization or person that provides a product or service.

System

A set of interrelated or interacting activities and/or techniques united to form an organized whole.

Top Management

Person or group of people who directs and controls an organization at the highest level.

Validation

A documented program that provides a high degree of assurance that a specific process, method, or system will consistently produce a result meeting pre-determined acceptance criteria.

VI. Abbreviations

API	Active Pharmaceutical Ingredients
APIC	Active Pharmaceutical Ingredients Committee of CEFIC
CAPA	Corrective Action - Preventive Action
CEFIC	European Chemical Industry Council
CEP	Certificate of Suitability
CFR	Code of Federal Regulation
CTD	Common Technical Document
CIP	Cleaning in Place
DCS	Distribution Control System
DQ	Design Qualification
(E)DMF	(European) Drug Master File
EFPIA	European Federation of Pharmaceutical Industries and Associations
EFQM	European Foundation of Quality Management
FDA	Food and Drug Administration
FEFO	First Expired - First Out
FIFO	First In - First Out
GMP	Good Manufacturing Practices
GXP	Good (X = e.g. C(linical), L(aboratory), S(torage), E(ngineering), etc) Practices
HACCP	Hazard Analysis Critical Control Point
HVAC	Heat Ventilation Air Conditioning
ICH	International Conference on Harmonization
ISO (EN ISO)	International Organization for Standardization
IQ	Installation Qualification
IT	Information Technology
KPI	Key Performance Indicators
LIMS	Labor Information Management System
MAI	Measurement, Analysis, Improvement
OOS	Out of Specification
OQ	Operational Qualification
PAR	Proven Acceptable Ranges
PIC/S	Pharmaceutical Inspection Cooperation Scheme
P & ID	Piping & Instrumentation Documentation
PAT	Process Analytical Technology
PDCA	Plan-Do-Check-Act
PQ	Performance Qualification
QA	Quality Assurance
QC	Quality Control
QMS	Quality Management System
QSIT	Quality System Inspection Technique
QU	Quality Unit
SAP	System Analyse und Programmentwicklung
SHE	Safety, Health, Environment
SIP	Sterile in Place
SMART	Specific, measurable, achievable, relevant, time framed
SOP	Standard Operating Procedure
SPS	Statistical Process System
VAT	Value added time analysis

VII. References

1. ICH Q7a: "Good Manufacturing Practice (GMP) Guide for Active Pharmaceutical Ingredients (APIs)", published November 2000
2. EN ISO 9001: 2000 "Quality Management Systems - Requirements", published December 2000
3. EN ISO 9004: 2000 "Quality Management Systems - Guidelines for performance improvements", published December 2000
4. EN ISO 9000: 2000 "Quality Management Systems - Fundamentals and vocabulary", published December 2000
5. ISO 9000: "Introduction and support package; Guidance on the concept and use of the process approach for management systems" - document: ISO/TC 176/SC 2/N544R2, published 13 May 2004
6. CEFIC: "ISO 9001: 2000 CEFIC Guidelines for use by the chemical industry", published March 2001
7. APIC/CEFIC: "How to do - an interpretation of ICH Q7a", published 2002
8. APIC/CEFIC: Quality Management System for Active Pharmaceutical Ingredients Manufacturers - integrating GMP into ISO 9001: 1994, published 1998

VIII. Acknowledgements

The Active Pharmaceutical Ingredients Committee (APIC), a sector group of CEFIC acknowledges the following documents which have been used as basis for the establishment of the present guideline:

- International Conference on Harmonization ICH
 - Q7a: Good Manufacturing Practice (GMP) for Active Pharmaceutical Ingredients (API), published November 2000
- EN ISO 9001: 2000 Quality Management Systems - Requirements published in December 2000.

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