

Quality Management System
for
Active pharmaceutical
Ingredients manufacturers

Integrating GMP into ISO 9001

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APIC *Active Pharmaceutical
Ingredients Committee*

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- EFPIA/CEFIC Good Manufacturing Practices for Active Ingredient Manufacturers published in August 1996, and
- EN ISO 9001 Quality Systems: Model for Quality Assurance in Design, Development, Production, Installation and Servicing published in July 1994.

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B. Introduction

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 is intended that these Guidelines are applicable to all APIs. However, in the case of a sterile API , the Guidelines should be applied at least to the point at which the API enters a sterilising process.

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 which supports the effective management of quality to an internationally recognised 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 must 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 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 (International Inspection Convention) 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.

For the purpose of this guidance document, the original EN-ISO 9001 subclauses have been addressed in twenty distinct chapters supplemented by four annexes in recognition of the importance of issues concerning hygiene; facilities and utilities; validation; and change control, to the API industry. Each chapter and each of the four annexes are structured in a way which summarises the appropriate QMS principle and philosophy as a preface to the main text which integrates relevant GMP requirements and QMS principles. The rationale/justification and business benefits of a combined QMS/GMP approach are considered in chapter 6. Chapter 7 addresses the importance of lower level and higher level performance measures for continued success, and as a solid foundation for those wishing to progress to European Quality Award/World Class status.

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

In this Guide the term “should” indicates requirements that are expected to apply unless shown to be inapplicable or replaced by an alternative demonstrated to provide at least an equivalent level of quality assurance.

C. Glossary

Principle

This glossary covers the meaning of the words used in this guide.

Active Pharmaceutical Ingredient (API)

Any pharmaceutically active material from organic, inorganic, microbiological, animal or plant origin, including that produced by recombinant DNA methods, intended for use in the manufacture of a medicinal product for human and or veterinary use.

Audit

Systematic and independent examination to determine whether quality activities and related results comply with quality policy and if this policy has been implemented effectively.

Batch (or lot)

A defined quantity of a 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 the batch (or lot) may be defined by a fixed quantity or time.

Batch number (or lot number)

A distinctive combination of numbers and/or letters which specifically identifies a batch or lot and from which the production history can be determined.

Calibration

Comparison of measuring instrument performance against an approved standard leading, if appropriate, to correction of performance of the instrument.

Change

Any deliberately introduced modification to existing documents, processes, equipment, systems or testing methods.

Change control

Formal system to evaluate effects of any change.

Computer system

A system including the input of data, electronic processing and the output of information to be used either for reporting or automatic control.

Computerised system

A system including computer system, all sensors, transmitters, actuators and wiring needed to control the process.

Conditional status

Status given to a material waiting to be fully tested and formally released.

Conformity

Fulfilment of specified requirements.

Contamination

The unintended, non-process related, introduction of impurities of a chemical or microbiological nature, or of foreign matter, into or onto a material during production, sampling, packaging or repackaging, storage or transport.

Continuous production

A process in which a material is continuously produced in a step or series of steps. In a continuous process the batches of raw materials and the process parameters can be statistically, but not necessarily, correlated to the material produced in a given window of time.

Contract review

Systematic activities carried out by the supplier before signing the contract to ensure that requirements are adequately defined, free from ambiguity, documented and achievable.

Corrective action

Action taken to rectify an identified nonconformity, defect or other undesirable situation and to prevent recurrence.

Cross contamination

A particular form of contamination in which material from one product contaminates another product.

Customer

Recipient of a product or service provided by the supplier.

Design review

Documented, comprehensive and systematic examination of a design to evaluate its capability to fulfil agreed requirements for quality. It will identify problems, if any, and propose the development of solutions.

Expiry 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.

Final intermediate

The last compound from which the API is produced. In the case of organic compounds this means a change in at least one covalent bond, whilst for inorganic compounds this may mean a change in an ionic bond. The final intermediate is thus a starting material for the process step which produces the finished API.

Impurity

Any component present in the API other than the substance defined as the API.

In-process control

Checks performed during production in order to monitor and, if necessary, to adjust the process, including repeating a process step, to ensure that the process performs as expected. The monitoring of the environment or utilities may also be regarded as part of the in-process control.

Inspection

Activity such as measuring, examining, testing or gauging one or more characteristics of an entity and comparing the results with specified requirements in order to establish whether conformity is achieved for each characteristic.

Intermediate

Partly processed material which must undergo further processing before it becomes an API.

Manufacture

All operations from purchase of materials and products, through production, quality control, release and storage, to distribution of API's, and the related controls.

Materials

A general term for raw materials, process aids, intermediates, API and packaging materials.

Nonconformity

Nonfulfillment of specified requirement.

Packaging materials

Any material used to protect an API during storage and transport, but excluding labels.

Preventive Action

Action taken to eliminate the causes of a potential nonconformity, defect, or other undesirable situation in order to prevent occurrence.

Procedure

Description of the operation(s) to be carried out, the precautions to be taken, and measures to be applied directly or indirectly, related to the manufacture of an API.

Process

Set of inter-related resources and activities which transform inputs into outputs.

Process aids

Materials used as an aid in the manufacture of an API which themselves do not participate in a chemical or biological reaction.

Production

All operations involved in obtaining an API commencing with the receipt and storage of raw materials, and continuing through processing to packaging, labelling and storage.

Qualification (equipment)

The action of proving that any equipment is properly installed, works correctly, and consistently produces the expected results according to the specified requirements. Qualification is part of, but not limited to, the validation of a process.

Quality

Totality of features and characteristics of a product or service and its ability to satisfy stated or implied needs. That is, meeting agreed requirements in a cost effective manner.

Quality assurance

The sum total of the organised arrangements made with the object of ensuring that API quality requirements are met.

Quality attribute

Any product characteristic which may reflect quality, or may affect safety or purity of the product during its expected shelf life.

Quality control

Quality Control is one or more organisational unit(s) with defined responsibilities for controlling, through checking or testing, that specifications are met.

Quality critical

A material (e.g. raw material, packaging material, process aid, intermediate), process step or process condition, test requirement or any other relevant parameter is considered to be critical when non-compliance with predetermined criteria directly influences the quality attributes of the API in a detrimental manner.

Quality function

Sum total of activities from Quality Assurance and Quality Control.

Quality manual

Key document stating the quality policy and briefly describing the quality system of an organisation.

Quality plan

Document setting out the specific quality practices, resources, responsibilities and sequence of activities relevant to a particular product, project or contract.

Quality system

Organisational structure, procedures, processes and resources needed to implement quality management.

Quarantine

The status of materials isolated physically or by other effective means while awaiting a decision on their subsequent use.

Raw material

Any ingredient intended for use in the production of API.

Record

Documented evidence of activities performed or results achieved.

Recovery

Any treatment of materials by a process intended to make them suitable for further use.

Reprocessing

The treatment of any batch or sub-batch of materials by repeating the same process steps from a defined stage of production.

Retest date

The date after which samples of the API should be re-examined to ensure that material is still suitable for use.

Reworking

The treatment of a batch or sub-batch of materials of unacceptable quality, by using a process other than that used to produce the original material, so that its quality may be made acceptable.

Supplier

Organisation that provides a product or service to the customer.

Standard Operating Procedure (SOP)

Documented instruction to support correct and consistent performance of activities.

Validation

Establishing documented evidence which provides a high degree of assurance that a specific process, method or system will consistently produce a result meeting pre-determined specifications and quality attributes.

D. Quality System

Chapter 1: Management responsibility

Principle

The API manufacturer should define a quality policy which has to be implemented throughout the whole organisation. The quality policy should be documented, together with responsibilities and lines of authority, for all levels of the organisation. It should aim to prevent occurrence of nonconformities, but when they do occur, it should allow for implementation of corrective measures. The API manufacturer should provide the necessary resources and trained personnel to meet quality needs. A representative of management should be appointed to oversee the establishment of a quality system and to assess its ongoing performance.

1.1 Quality policy

1.1.1 The API manufacturer should document a quality policy which gives direction to the achievement of corporate quality objectives through a commitment to GMP, and to ISO QMS principles.

1.1.2 The quality policy should emphasise the importance of planning to avoid quality failures. The need for continuous improvement should be emphasised by use of specific performance measures (see Part G).

1.1.3 Management should ensure that the quality policy is fully understood and implemented by all members of staff.

1.1.4 Management should clearly demonstrate their continuing support for the quality policy (e.g. by regular quality briefings).

1.2 Organisation

1.2.1 The organisation should be documented.

1.2.2 Responsibilities should be reflected in organisation charts and job descriptions. Lateral and horizontal quality critical interfaces should also be identified. The Quality Function should be independent of production.

1.2.3 All staff whose activities influence quality should be appropriately qualified, through education, training, experience or any combination thereof to perform their assigned responsibilities.

- 1.2.4 Management should provide suitably equipped facilities, trained personnel and adequate financial resources to perform operations in compliance with relevant quality requirements.

1.3 Quality management

1.3.1 Quality system manager (management representative)

A senior member of management should be appointed as quality system manager with freedom to operate across the organisation, and authority to co-ordinate development, implementation and maintenance of an effective quality system.

1.3.2 Quality Function

The Quality Function has responsibility for ensuring that all activities associated with design/development and manufacturing (purchase, storage, production, quality control, release and distribution) of API's are carried out in a systematic and approved manner in compliance with regulatory and GMP requirements. This may include commercial activities and customer support.

The Quality Function is also responsible for confirming, through testing, that approved specifications are met throughout the claimed shelf-life of the product.

The Quality Function encompasses Quality Assurance and Quality Control activities.

- 1.3.3 These functions can be assigned to a single person, or different persons according to the company's local organisation.

1.4 Management review

- 1.4.1 At defined intervals (recommendation: at least once a year) executive management should review 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.

- 1.4.2 The review should be based upon information gathered from the internal quality audit programme, audits by external inspectors, product reviews, trend analyses, investigations of deviations, customer complaints, and any other source of relevant information. Management review should initiate actions to improve the performance of the quality system.

- 1.4.3 Records of management reviews should be maintained for a specified period of time.

Chapter 2: Quality system

Principle

The Quality system - in the form of organisational structure, procedures, processes and resources needed to implement the quality policy - should be described in a quality manual. The quality manual should cover relevant EN ISO 9001 and GMP requirements, describe the documentation hierarchy and indicate how the quality system is managed.

The need for quality planning is an important feature of the QMS. It requires that adequate consideration is given to an activity before implementation, thereby reducing the risk and cost of failure.

2.1 Quality manual

2.1.1 The quality manual is the master quality document and, as such, should provide an outline of, and directory to, the quality system. It should cover relevant ISO 9001 and GMP quality management requirements

2.1.2 The quality manual should be positioned at the head of the documentation hierarchy, and be supported by other document groups such as policies, Guidelines, procedures (such as Standard Operating Procedures) etc.

2.1.3 The quality manual should be used as a basis for auditing the performance of the QMS.

2.1.4 The quality manual should be written in a clear, concise and user-friendly style since it will be read, and needs to be understood, by all grades of staff. It should also be open to inspection by external auditors and (possibly) by customers.

2.2 Quality system procedures

2.2.1 The quality system should ensure that all quality related activities are documented and carried out in a systematic and approved manner.

2.2.2 Duplication of content between documented procedures (e.g. operating procedures versus training modules) should be avoided in order to minimise the risk of documentation overload.

2.2.3 Procedures should, where appropriate, address control of the horizontal (cross-functional) communication interfaces as well as vertical communication in the organisation.

2.3 Quality planning

Activities related to quality should be systematically planned, and the plan documented. This will help to ensure consistency of performance and provide greater confidence that the outcome will be satisfactory. The quality manual is the overall plan for the QMS. Each policy, procedure etc. within the QMS is a form of quality plan supporting the achievement of short and long term objectives.

Some examples of activities whose implementation should be preceded by a quality plan are as follows:

- * Development/improvement projects
- * Technology transfer
- * Qualification/validation activities
- * Manufacturing operations
- * Inspection and testing
- * Sampling/cleaning/training/auditing
- * Controlling change
- * Complaint handling
- * Product recall

Chapter 3: Contract review

Principle

The API manufacturer should establish and maintain procedures, involving clear lines of communication, to ensure that customer requirements are understood, documented and agreed. This should include confirmation that the API manufacturer has the capability to meet the customer's requirements. Subsequent changes to the agreed contract should be adequately controlled.

3.1 Contract

3.1.1 In this context the term 'contract' usually applies to the agreement between the API manufacturer and the (downstream) customer.

3.1.2 The API manufacturer should establish a written contract containing all the customer order requirements.

3.1.3 Any differences of understanding between the API manufacturer and the customer should be resolved before the contract is signed.

3.1.4 The contract should take into consideration current regulatory and legislative requirements relevant to both the country of manufacture and the country (or countries) of intended use. It should also indicate to what degree manufacture and/or testing is to be subcontracted.

3.1.5 Some examples of items which should be considered in a contract are listed below:

- * Right of inspections
- * Materials purchasing
- * Testing and release of materials
- * In-process control (IPC)
- * Calibration, qualification and validation activities
- * Process Changes
- * Storage of samples
- * Quality Function responsibilities
- * Packaging, labelling, transport and storage
- * Handling of complaints and recalls
- * Archiving of records and documentation
- * Subcontracting

3.2 Contract review

- 3.2.1 The contract should be reviewed by all interested parties to ensure that its content is comprehensive, clearly documented, unambiguous, and fully understood.
- 3.2.2 All the relevant functions within the API manufacturer should be consulted to ensure that the capability (e.g. skills, capacity, equipment, standards, resources) exists to adequately fulfil the requirements of the contract.

3.3 Contract amendment

- 3.3.1 The API manufacturer should operate a change control procedure utilising clearly defined lines of communication if it becomes necessary to amend the agreed contract. This procedure should ensure that the customer is informed of relevant changes, and agreement reached before implementation of changes to allow the customer to take appropriate action (which may involve changes to registration documents).
- 3.3.2 The change control procedure should also ensure that, when changes are requested by the customer, all the relevant functions within the API manufacturer's organisation are informed in a timely manner.

3.4 Records

- 3.4.1 A record of the contract, its review, subsequent contract amendments, and relevant related communications - internal and external - from receipt of the initial customer enquiry should be archived and available.
- 3.4.2 Customer enquiries and orders received verbally should be documented.

Chapter 4: Design and development control

Principle

The design and development process should be controlled to ensure that the resulting product (or service) meets the agreed specification. To achieve this the API manufacturer should establish and maintain documented procedures to control and verify the design and development of the product. A plan should be prepared for each design and development activity showing responsibilities and organisational interfaces with relevant communication routes and resources for each phase. The plan should include regular meetings to compare design input requirements with output results in terms of agreed acceptance criteria, i.e. design verification. Once complete, verification should be followed by design validation. Design and development (excluding research) changes should be formally controlled. The output of all reviews, verification and validation activities should be recorded. Stability testing is part of the development phase of the API as it generates evidence to support shelf-life claims.

4.1 Planning

- 4.1.1 The API manufacturer should prepare plans which describe or make reference to each design and development activity. These plans should clearly indicate responsibilities, organisational and technical interfaces and establish channels for clear and timely communication of relevant information.
- 4.1.2 Planning activities should be assigned to qualified, trained and experienced personnel equipped with adequate resources.
- 4.1.3 Plans should be updated as the design and development stage evolves.

4.2 Input

- 4.2.1 Design and development input should incorporate all relevant information, including contract review findings and applicable statutory and regulatory requirements.
- 4.2.2 The design input plan should include a requirement for GMP compliance from the point at which the final API quality is likely to be affected, and at stages likely to be specified in the registration documentation. Less rigorous application of GMP principles may be appropriate, if justifiable, at earlier stages.
- 4.2.3 Design input should be documented and reviewed at appropriate stages (milestones)
- 4.2.4 Ambiguous or conflicting design requirements should be resolved with those responsible for imposing such requirements.

4.3 Output

- 4.3.1 Output (the results of processed inputs) should be recorded to facilitate subsequent verification against design input, and validation against customer requirements (acceptance criteria).
- 4.3.2 Quality critical parameters should be identified and acceptance criteria established.
- 4.3.3 Output should be reviewed prior to formal acceptance. This review should be recorded.

4.4 Review

- 4.4.1 At appropriate stages (milestones) in the design and development process a formal planned and documented review of progress with, and results from, the design plan should be conducted and recorded.
- 4.4.2 Representatives of all functions, including the Quality Function, concerned with the design stage being reviewed, and relevant specialists, should participate in design reviews.
- 4.4.3 Actions arising from design reviews (e.g. changes to the design plan) should be agreed, and recorded prior to implementation.
- 4.4.4 Records of design reviews should be archived for a specified period of time.

4.5 Verification

Design verification is concerned with ensuring that design output satisfies design input requirements, bearing in mind that quality critical features need to comply with agreed acceptance criteria.

4.6 Validation

- 4.6.1 Validation is concerned with ensuring that the product can be reproducibly manufactured in a way that consistently satisfies defined customer needs, predetermined specifications, and quality attributes.

4.6.2 Validation of an API manufacturing process generally starts during the development phase when the quality critical issues are identified and suitable process parameter ranges initially evaluated. Information obtained during scale-up activities should be used to confirm and refine this evaluation. Manufacture of production scale batches usually provides evidence that the process is reproducible (see Annex C).

4.7 Changes

Design changes (including minor modifications) should be identified to all relevant functions, documented, reviewed, and approved by a suitable level of authority prior to implementation (see Annex D).

4.8 Stability testing, retest and expiry date

The date after which an API should be retested should be based on the findings of well designed stability studies. The continuing validity of retest and expiry dates should be verified by monitoring current production. A company policy regarding the relationship between retest and expiry date should be established. The protocol for conducting stability studies should be based on internationally accepted concepts such as the ICH (International Conference on Harmonisation) Harmonised Tripartite Guideline "Stability Testing of New Drug Substances and Products".

With regard to existing products described in the pharmacopoeia (including degradation products) produced according to well established processes, an expiry and/or retest date could be determined on the basis of historical data and/or published literature.

4.8.1 Storage Conditions, retest and expiry date

4.8.1.1 The conditions under which API are stored should be based on results of stability studies, which take into account the potential effects of storage time, temperature and relative humidity.

4.8.1.2 Based on the results of stability studies, a date should be established after which an analytical retest of the API should be carried out before further use.

4.8.1.3 The assigned retest and expiry dates may differ for different climatic zones. This will depend on the differences observed or measured in the models used in the stability studies to reflect the potential climatic conditions under which the product may be stored.

4.8.1.4 The written specification which should be met at the retest and expiry date may be different from the (more stringent) specification applicable at the time of release.

4.8.2 Stability testing

- 4.8.2.1 Test methods should be stability indicating and be validated.
- 4.8.2.2 The samples to be analysed in the stability programme should be stored in containers simulating the physical and, if necessary, chemical properties of those in which the product will be marketed.
- 4.8.2.3 Once the initial retest and expiry date has been established, it should be monitored by adding at least one batch a year, if appropriate, to the stability programme.
- 4.8.2.4 When the same API is produced at several sites, at least one batch a year from each site should be added to the stability programme.
- 4.8.2.5 The potential effects of quality critical process changes upon established retest and expiry periods should be monitored by adding samples made by the modified process to the stability programme.
- 4.8.2.6 Data collected during stability testing should be evaluated after each test point to determine if there is a significant change to the previously established retest and expiry date(s).
- 4.8.2.7 Records of stability testing should be archived for a specified period of time (see chapter 16).

Chapter 5: Document control

Principle

There should be a written procedure for the systematic control of all quality related documents such as quality manual, cross-functional procedures, organisation charts, standard operating procedures (SOP's), and formats for repetitive processes. This also applies to any document received from external sources (i.e. regulatory authorities or customers).

5.1 Document issue

- 5.1.1 The procedure should include the design, identification, review, approval and distribution of documents. Obsolete documents should be under control and archived.
- 5.1.2 All quality related documents should be designed by persons with practical knowledge of the process described.
- 5.1.3 Documents should be reviewed, coded, signed and approved by competent and authorised persons. The status of the documents should be indicated (issue date and version/revision) and verifiable by reference to the master document or a master list.
- 5.1.4 The procedure should insure that current documents are correctly distributed and available when and where needed.
- 5.1.5 When entries need to be made in documents, sufficient space should be available for the entry. The type of entry, date, units used and the person making the entry should be indicated and identifiable.
- 5.1.6 The procedure for controlling documentation should insure that obsolete documents are promptly removed. A list identifying the current version of all the documents should be readily available.
- 5.1.7 Original versions of obsolete documents should be retained for legal / historical / knowledge preservation purposes. Obsolete documents should be clearly identified to prevent unintended use.

5.2 Document changes

- 5.2.1 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.
- 5.2.2 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.
- 5.2.3 Relevant changes in documents previously submitted to regulatory authorities and/or customers should also be notified.

Chapter 6: Purchasing

Principle

Purchased product and service should conform to clear and concise specified requirements. There should be mechanisms in place for evaluating sub-contractors, agreeing purchasing data, and verifying the quality of purchased product.

6.1 Evaluation of suppliers

- 6.1.1 There should be a system in place for qualification of suppliers.
- 6.1.2 Suppliers may be approved on the basis of one or more factors such as historical experience, quality audit, third party certification etc., bearing in mind the nature of the purchase and its likely impact on final product quality.
- 6.1.3 A list of approved suppliers should be supported by appropriate records reflecting performance in terms of quality, delivery, cost-benefit etc. of each supplier.

6.2 Purchasing data

- 6.2.1 There should be a written and approved contract between supplier and API manufacturer, which clearly states the responsibilities of each party. The scope of, and level of details within, the contract may be dependent upon the significance of the purchase in relation to the quality of the final API.
- 6.2.2 Purchasing documents should contain data clearly describing the product ordered, including where applicable:
 - product identification, including grade or special requirements.
 - the applicable specifications as well as any additional quality system document or SOP that would apply to the goods when received
 - changes planned by the supplier of purchased goods
- 6.2.3 Purchasing documents should be reviewed and approved for accuracy of specified requirements prior to use.

6.3 Verification of purchased product

- 6.3.1 The mechanism by which the quality of purchases are verified should be documented, understood, and agreed by the API manufacturer and the supplier of the purchased material. This may involve inspection and testing at the supplier site prior to despatch and/or by the API manufacturer upon receipt, and/or acceptance on the basis of a Certificate of Analysis/Conformance.

- 6.3.2 There should be a mechanism for resolving quality issues which may arise from time to time.

Chapter 7: Control of customer supplied product

Principle

Customer supplied product is raw material, intermediate, product component etc. owned by the customer, for which the API manufacturer is temporarily responsible by virtue of performing a processing activity. Management control over the quality of customer supplied product should be included in the scope of the API manufacturers quality system. In particular, instances of damage, or otherwise adverse findings, should be recorded and reported to the customer without delay.

- 7.1 There should be a written and approved contract between the contract giver and the contract acceptor, which lays down the responsibilities of each party.
- 7.2 Items provided by the customer should be clearly identifiable.
- 7.3 Items provided by the customer should have their quality verified by inspection and/or testing, and subsequently handled in such a way as to prevent deterioration, damage or loss.
- 7.4 Items provided by the customer should be stored under appropriate conditions to avoid deterioration or damage.
- 7.5 Damage to, or otherwise adverse findings associated with, customer supplied product should be notified to the customer without delay.

Chapter 8: Product and equipment identification and traceability

Principle

It should be possible to identify and trace any material from receipt through production and delivery to the customer. All quality critical equipment should also be identified and its use be traceable.

8.1 Materials and equipment identification

8.1.1 Raw materials, auxiliaries, packaging materials, intermediates and API should be assigned a unique code which allows the traceability of materials. Where appropriate, this code should be included on the label of each container upon receipt or isolation.

8.1.2 Each item of equipment influencing product quality should be clearly identified.

8.2 Batch (or lot) identification

Any batch (or lot), received or produced should be assigned a unique code to allow for the traceability of all materials and equipment used in its manufacture.

8.3 Labelling

8.3.1 There should be a written procedure describing the system for labelling materials and equipment.

8.3.2 Each container should be identified by an appropriate label, showing at least the product identification and the assigned batch code, or any other easily understandable combination of both. Other data, such as weight, storage conditions, safety or transport instructions can also be included on the label.

8.3.3 Control should be exercised over labels used during the manufacture and filling of API, including label reconciliation, to absolutely minimise the risk of label mix-ups or the use of incorrect or out-of-date labels.

8.3.4 Containers for external distribution may require additional labels. These should be adequately controlled and contain relevant information to meet user requirements as well as compliance with applicable safety and transport regulations. If the API requires special transport or storage conditions, this should be stated on the label and complied with.

- 8.3.5 If containers are reused a check should be performed to ensure that the previous labels have been removed or adequately defaced.
- 8.3.6 Quality critical equipment should be clearly and uniquely identified, together with an indication of status (e.g. clean; awaiting cleaning; in use; out of order). When in use the content of each item of equipment should be identifiable.
- 8.3.7 Material, product, equipment and status information should be recorded to facilitate subsequent traceability.

Chapter 9: Manufacturing process control

Principle

Production, installation and servicing processes that affect quality should be identified, planned, documented and performed under control.

This chapter should be considered in conjunction with Annexes A, B, C and D.

9.1 Documentation

9.1.1 Written procedures should exist for all activities related to product quality. These procedures should be available at or near the point of use.

9.1.2 There should be a written manufacturing instruction (e.g. master formula, master production record) including, where appropriate, details of:

- raw materials
- reactions
- process steps
- in-process controls
- intermediates
- isolation of crude and pure API
- drying
- sieving
- milling
- filling and packaging

This list may not be considered as complete.

9.1.3 Batch records should be available for each batch of each product and should, if appropriate, include details of:

- the name of the material to be produced and the batch number or equivalent
- the dates between which the batch was made
- identification and signature of operators
- the names, batch numbers and quantities of raw materials to be used
- the equipment used

- process steps and conditions, including permitted ranges and special precautions together with the actual process conditions used
- the results of in-process tests
- the yield obtained
- a record of all deviations from the process instructions and all unusual occurrences

This list may not be considered as complete.

9.1.4 Written instructions for the packaging operations involving the pure or finished API should be available and should detail:

- specifications for the labels and for those packaging components that have direct contact with the API
- a list of other packaging materials
- any appropriate special precautions

9.1.5 Written instructions for cleaning, calibration and maintenance of equipment should be available.

9.2 Prevention of product contamination

9.2.1 Measures to avoid contamination should be designed into the manufacturing process, because the control of potential contaminants in the product itself is extremely difficult.

9.2.2 Care should be taken to prevent contamination. This should be considered for all stages, but is essential after the final purification stage. Appropriate measures include:

- the use and location of equipment should be designed to minimise contamination
- the avoidance of contamination due to the use of inadequately cleaned or maintained equipment, corrosion or bearing leakage
- the use of adequately purified solvents
- the prevention of contamination by materials or utilities that have direct contact with the pure or final API

9.2.3 Special care needs to be taken during processing steps involving API such as isolation, drying and milling. Such precautions should include:

- isolation, drying, milling and homogenisation should be performed in closed systems or controlled environments

- special care should be taken to avoid contamination of other equipment, other products, or the environment
- if local dust extraction alone is used, a subsequent clean up should be performed to minimise contamination or cross contamination

9.2.4 Where highly toxic or highly active API are being processed, isolation, drying and blending should be performed in a closed system or a separate dedicated area.

9.2.5 Filling and packaging operations should be performed in facilities which prevent cross contamination either of the material being handled or of other materials by that material.

9.3 Specific requirements

9.3.1 The process should be controlled in compliance with quality plans, manufacturing instructions and Good Manufacturing Practice principles.

9.3.2 Suitable monitoring and control parameters should be chosen to ensure that the process is performing as intended by the process design.

9.3.3 Monitoring of appropriate in-process controls and parameters will be required to give the necessary level of confidence in the quality of the finished product.

9.3.4 If materials are recovered for re-use in future manufacturing processes, there should be written evidence that the use of these materials will result in a product that meets specification.

9.3.5 Solvents may be recovered and should be monitored for suitability of use.

9.3.6 If the working up of mother liquors or similar materials to obtain further materials or an API is performed, the action should be specifically described in writing and recorded.

9.3.7 The practice of blending out-of-specification API with material that meets specification, in order to disguise the defects and create a composite that meets specification, is not acceptable.

9.4 Criteria of workmanship

There should be documentation available that describes in clear detail the standard of workmanship required. For training purposes, the use of diagrams, illustrations, reference standards and / or pictures showing the expected results are recommended.

9.5 Maintenance

There should be a maintenance policy established to ensure that equipment is maintained to a standard sufficient to ensure that it is capable of performing its intended function (see Annex B).

Chapter 10: Inspection and testing

Principle

Inspection and testing activities before, during and after manufacture that verify that the product meets specification should be supported by written procedures. The inspection and testing required, together with the records thereof, should be documented in the quality plan and approved by the Quality Function.

10.1 General

- 10.1.1 The responsibilities of the Quality Function should be described in writing and should include as a minimum:
- approving specifications
 - validation and approval of test procedures
 - sampling
 - controlling reference standards
 - analytical investigations and evaluation of results
 - testing materials
 - providing analytical reports
 - approving or rejecting raw materials, packaging materials, intermediates, in-process controls and API
 - stability studies
- 10.1.2 Specifications and methods should be established for the inspection and testing of raw materials, intermediates, API and packaging materials. They may also be required for process aids, e.g. filters, gaskets or other items which are used in production and could have a critical impact on product quality.
- 10.1.3 Written, validated, approved and dated test procedures should be available for checking if the specifications are met. They should be clearly understandable and sufficiently detailed to enable a trained operator to follow them.
- 10.1.4 In case of 'Out of Specification' (OOS) results, re-analysis should be in accordance with a written procedure.

10.2 Receiving inspection and testing

- 10.2.1 Incoming material should not be used until it has been inspected and verified as conforming to the specified requirements. This verification should be in accordance with the requirements of the quality plan or other documented procedures. This verification should include a check that:
- the labels indicate that it is the item ordered
 - the containers are not damaged and all seals are intact
 - materials and packaging components received do correspond to the items ordered
 - there is no evidence of tampering and that the delivery generally appears to be in good condition and suitable for use
- 10.2.2 The procedures should detail the action to be taken if these conditions are not met. There should be a procedure that defines the number of samples to be taken in relationship to the size of the delivery; and whether individual or composite samples are required. Sampling plans should also be available for primary packaging components.
- 10.2.3 The amount and nature of the incoming goods inspection may be modified depending on the amount of control exercised by the supplier of the incoming material during its manufacture. Consideration should be given to the quality history of previous deliveries and to the evidence of conformance to specification of previously supplied material. The identification of each batch of raw material is a minimum requirement.
- 10.2.4 In normal circumstances materials should not be issued for use until testing has been completed and results have been evaluated by the Quality Function. However in cases of urgency, material may be issued for use on a conditional status. The material itself and batches in which it is used should be identified to indicate that the material is still awaiting approval. Procedures should exist to prevent API in which the unpassed material has been used being approved for sale or supply until the material in question has been passed as suitable for use.
- 10.2.5 While it is acknowledged that it may, from time to time, be necessary to release material under conditional status this should be an exceptional event and a justification should be documented. This principle also applies to In-process testing and inspection.
- 10.2.6 In the case of hazardous and sensitive materials it may be advisable not to open a container for sampling purposes. In these circumstances, it is essential that other methods or evidence are available to ensure that the material is fit for use. A Certificate of Analysis from an approved supplier might be relied upon in such circumstances.

10.3 In-process testing and inspection

10.3.1 The product should be tested according to the requirements detailed in the quality plan or the documented procedures; intermediate lots should be held in quarantine until the inspection and testing has been completed or the relevant reports have been received and verified (for exceptions see 10.2.4).

10.3.2 Designated persons within the Quality Function should approve:

- the in-process controls
- the warning and/or action control limits
- the points in the process where samples are to be taken for in-process testing
- the test procedures

All these matters should be defined in written procedures issued by the Quality Function.

10.3.3 In-process test procedures should be validated where the result is critical to the quality of the product. Test results should be recorded in writing and these records should become part of the batch record.

10.4 Final inspection and testing

10.4.1 All final inspection and testing should be performed as described in the quality plan (i.e. written procedures; methods and specifications; etc.) to ensure the completeness of the evidence that the API meets specified requirements.

10.4.2 All relevant batch-related information, including inspection findings, analytical results for raw materials/intermediates/finished API, production conditions and related deviations from defined procedures, should be collated or referenced into the batch manufacturing records. This document should be reviewed for completeness by an authorised representative of the production function and for conformance with the quality plan and compliance with approved standards by an authorised member of the Quality Function.

10.4.3 Batches of finished API should only be released for use when all relevant information has been reviewed and found to be satisfactory by an authorised member of the Quality Function.

10.4.4 Finished API should not be despatched to the customer until formally released by an authorised member of the Quality Function.

10.5 Inspection and test records

10.5.1 Records should be established and maintained that demonstrate that each batch of product has been inspected and tested according to the pre-defined criteria. The records should clearly show whether the batch passed or failed the inspections and tests. In cases where a batch fails there should be established procedures for controlling non-conforming product and these should be applied as outlined in chapter 13.

10.5.2 Records of tests should include:

- the name and batch number of the material being tested
- a reference to the relevant specification and the test procedure being used
- an identification of the standard, if used
- results of all weighings, measurements and readings taken
- all observations and calculations and the results obtained therefrom, which should be dated and signed by the person conducting the test
- analytical equipment identification

These records should be checked for accuracy independently. Quality critical records should be countersigned where they contain manual calculations. Inspection and test records should be retained for a specified period of time, (see chapter 16).

10.6 Retained samples

10.6.1 Relevant samples should be retained for a prescribed period and under defined conditions, so that investigation of quality status may be performed, if necessary, at a later date. As retained samples are a form of quality record, the reader is also referred to chapter 16.

10.6.2 Samples should be stored in a container (the same as, or equivalent to, that used for bulk storage or market packaging) and under conditions (consistent with the product label) which prevent loss, damage or deterioration.

10.6.3 Samples should be retained in quantities sufficient to allow at least two full analyses to be performed.

10.6.4 Samples of raw material and intermediate should be retained for at least 12 months following release of the batch(es) of API to which they relate.

- 10.6.5 Samples of API should be retained for at least 12 months after the assigned retest and expiry date of the batch, or 3 years after distribution of the batch. If the batch retest and expiry date is extended, then the sample retention period should be correspondingly extended.
- 10.6.6 Representative samples of API should be visually examined annually for evidence of deterioration (unless such examination would adversely affect the sample). Any evidence of deterioration should be investigated. The examination and its outcome should be recorded.
- 10.6.7 Samples of hazardous, gaseous, inflammable, environmentally dangerous or unstable raw material or intermediate need not be retained.

Note: Samples retained in this context are not intended for stability indicating or retest and expiry date use. For such information the reader is referred to chapter 4.8 and, particularly 4.8.2.2.

Chapter 11: Control of inspection, measuring and test equipment

Principle

While all equipment (including relevant software) should be properly controlled and suitably maintained, instruments used to make quality critical measurements should be regularly calibrated against a recognised, traceable standard.

- 11.1 Selection of equipment should be based upon a consideration of the type of measurement, the required accuracy, and the capability (accuracy and precision) of the available equipment.
- 11.2 Equipment and its calibration status should be clearly identifiable.
- 11.3 Equipment should be calibrated by a competent person against, and traceable to, a national or international standard whenever possible. When no such standard exists, the basis for calibration should be clearly documented.
- 11.4 Equipment should be recalibrated in accordance with a predetermined schedule, and using an approved documented procedure. The frequency of recalibration may vary from one piece of equipment to another. It should initially reflect the equipment manufacturer's recommendation but, as experience is gained, the extent and frequency of recalibration may need to be adjusted to ensure consistent optimum performance. Any changes in calibration frequency should be justified by previous calibration records.
- 11.5 Use, calibration, repairs, and maintenance of quality critical inspection, measuring and test equipment, should be recorded, and these records (including calibration certificates) maintained for a prescribed period of time.
- 11.6 Deviations from approved standards of equipment maintenance should be investigated to determine if they could have an impact upon product quality.
- 11.7 If equipment is found to be out of calibration it should be identified as such and, if possible, physically removed to prevent inadvertent use until it can be checked, recalibrated, and deemed suitable for use again. The validity of the equipment's use since it was last known to be performing satisfactorily (i.e. last calibrated) should also be investigated.

- 11.8 Equipment should only be used by fully trained, or appropriately supervised, staff in order to ensure correct use consistent with the required measurement capability, and to safeguard against the likelihood of unauthorised adjustments being made which could invalidate the calibration setting.
- 11.9 Equipment should only be calibrated, used, and stored in a suitable environment that will not lead to possible deterioration in performance.
- 11.10 The degree to which equipment needs to be calibrated should be given careful consideration, since overkill calibration (e.g. accurate to 3 decimal places when only one decimal place is sufficient) will prove unnecessarily costly.

Chapter 12: Inspection and test status

Principle

It should be possible to readily identify, at all stages from design through manufacture to delivery to the customer, if a product has 'pass' or 'fail' status, or if it is waiting to be tested.

- 12.1 The identification of material/intermediate/product quality status should be maintained throughout the various manufacturing, storage, delivery stages to ensure that only passed material (or material under conditional status) is used. Only satisfactory product should be supplied to the customer.
- 12.2 The means of identifying inspection and test status may vary depending on circumstances. For example, in stores and warehouses it may be possible to use labels, while in production environments colour-coded bins may provide the distinction between passed versus rejected material. Computer tracking can also be acceptable. Whichever approach is taken, it should be capable of quickly and clearly allowing identification of inspection and test status.
- 12.3 Inspection and test procedures should be written and approved by the Quality Function and should define who has responsibility for determining inspection and test status during processing stages and at final release.

Chapter 13: Control of nonconforming product

Principle

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

- 13.1 Responsibility for reviewing information relevant to, and authority to, decide the disposition of nonconforming product should be clearly documented.
- 13.2 Subsequent use of nonconforming material should be approved by the Quality Function.
- 13.3 The likely effect upon related batches of product should be assessed.
- 13.4 Any decision to reprocess returned nonconforming product should take into consideration the fact that the product has been outside the control of the manufacturing company.
- 13.5 Reworked product should be retested in accordance with documented procedures incorporating appropriate controls agreed between production and the Quality Function.
- 13.6 Reprocessing and rework should be documented and included in the batch records. A new batch number should be assigned following rework.
- 13.7 The nature of the nonconformity together with details of the associated investigation and justification for disposition of the nonconforming product should be recorded.
- 13.8 If reprocessing and/or reworking becomes a regular occurrence, the adequacy of the original manufacturing process should be investigated. (see chapter 14)

Chapter 14: Corrective and preventive action

Principle

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

14.1 Corrective action

- 14.1.1 Corrective action is intended to both rectify an existing nonconformance and avoid a recurrence. It is, therefore, necessary to identify the underlying cause of the problem.
- 14.1.2 Corrective action may arise from customer complaints, audit findings, management reviews and other situations where nonconformance is likely to be identified.
- 14.1.3 All customer complaints should be recorded, promptly investigated and reported in accordance with a written, approved procedure.
- 14.1.4 A carefully planned and timely investigation should take place to determine the reason(s) for the nonconformance and agree appropriate action.
- 14.1.5 Details of the nonconformance, the associated investigation and agreed actions should be recorded.
- 14.1.6 Progress with agreed actions resulting from the nonconformance investigation should be closely monitored until all are satisfactorily completed.
- 14.1.7 A written, approved procedure should clarify in what circumstances recall of an API should be considered. This document should also indicate responsibilities and actions in the event of a recall.
- 14.1.8 In the event of a serious and potentially life-threatening situation, (local and national) authorities should be informed and their advice sought.

14.2 Preventive action

- 14.2.1 Preventive action is intended to avoid the initial occurrence of a nonconformance.

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- 14.2.2 Preventive action may include analysis of trends in product, process, analytical data and quality system performance. Sources of information could include audit reports, annual (product) reviews, customer complaints and any other data likely to assist in identifying areas of potential nonconformance.

- 14.2.3 As with corrective action, preventive action should be authorised, carefully planned, implemented in a controlled manner and adequately monitored to ensure the desired outcome.

- 14.2.4 Information relevant to preventive (and corrective) actions should be regularly collated and presented for management review in support of maintaining and improving the effectiveness of the quality system.

Chapter 15: Handling, storage, packaging, preservation and delivery

Principle

Loss, damage or deterioration should be prevented during the handling, storage, packaging and preservation of material from receipt through manufacture, final release to despatch and, if appropriate, delivery to the customer. The application of relevant procedures should be adequately controlled and monitored.

15.1 Handling

- 15.1.1 Plant and handling procedures, including equipment maintenance and cleaning, should be properly identified, planned and designed for use by trained staff.
- 15.1.2 Incoming materials should not be mixed with existing stocks (e.g. solvents or stocks in silos) until they have been inspected and/or tested and released.
- 15.1.3 Sampling of API should be performed in an appropriate area and using procedures designed to prevent contamination. Containers should be opened carefully and subsequently resealed in an approved manner.
- 15.1.4 Weighing or subdivision of material prior to use should be performed in an appropriate area to minimise the risk of cross-contamination.
- 15.1.5 Pure and final API should be handled in an environment giving adequate protection against contamination.
- 15.1.6 Highly sensitising material such as penicillins and cephalosporins should be handled in separate production areas.
- 15.1.7 Highly active or toxic API (e.g. certain steroids, cytostatic substances) should be manufactured in a dedicated area and using dedicated equipment.

15.2 Storage

- 15.2.1 Secure storage facilities should be designated for use to prevent damage or deterioration of materials. These should be kept clean and tidy and subject to appropriate pest control measures. Environmental conditions should be recorded.

- 15.2.2 Receipt into and despatch from storage should be authorised and recorded and the principle of FIFO (first in, first out) or FEFO (first expired, first out) is recommended.
- 15.2.3 The condition of stored material should be assessed at appropriate intervals.
- 15.2.4 Storage conditions for API should be based upon stability studies taking into account time, temperature, humidity, light etc.
- 15.2.5 Materials requiring special storage conditions (temperature, humidity, light etc.) should be clearly labelled and held in a suitable environment.
- 15.2.6 Storage procedures should ensure physical (or an effective alternative) segregation of materials to avoid mix-ups occurring. Materials which have been rejected, recalled or returned should be physically segregated from other stock until their final disposition has been determined unless adequate control can be ensured by validated electronic systems.

15.3 Packaging

- 15.3.1 Labelling and packaging processes should be defined and controlled to ensure that correct packaging materials are used correctly and other specified requirements are met.
- 15.3.2 Printed labels should be securely stored to avoid mix-ups arising.
- 15.3.3 Marking and labelling should be legible and durable, provide sufficient information for accurate identification and indicate, if appropriate, required storage conditions, retest and/or expiry date.

15.4 Preservation

Precautions should be taken to maintain the quality of materials and APIs.

15.5 Delivery

- 15.5.1 If necessary the supplier should ensure that released material is transported under adequately controlled conditions such that quality is maintained upon delivery to the customer.

Controls should include, but may not be limited to, the following:

- Vehicles should be checked to ensure that they are clean and dry with no evidence of chemical contamination or infestation, and offer adequate protection from the weather.
- Materials should be clearly and securely identified, adequately segregated from other materials, protected from breakage and theft and subject to appropriate environmental controls.

15.5.2 Records of distribution should be maintained so that, if necessary, users can be readily contacted.

Chapter 16: Control of quality records

Principle

Quality records (including records from external sources) are documents in hard copy or electronic form and retained samples (see also chapter 10.6) which provide objective evidence for the effective operation of the quality system. It is important that records are correctly identified, suitably stored and available when required. Procedures for controlling quality records including an archiving policy should be documented.

- 16.1 Quality records should be legible, clearly identifiable and allow adequate traceability. Manual entries in documents should generally be made directly after performing the activity, be legible and indelible. Corrections to entries should be dated, initialled, and explained when necessary. The original entry should still be legible.
- 16.2 Quality records should be suitably indexed and available when required.
- 16.3 Quality records may include, but are not limited to, the following:
- Audit reports
 - Calibration certificates
 - Training records
 - Investigation reports
 - Batch and analytical records
 - Management reviews
 - Validation/qualification plans/reports
 - Complaints
- 16.4 Quality records should be retained for a specified period of time in compliance with appropriate regulatory requirements. After this period they should be either retained for a further specified period, or authorised for controlled destruction. This action should be recorded.
- 16.5 Quality records should be stored in a secure, restricted access, environment to prevent deterioration, damage or loss.
- 16.6 An archiving procedure should be available. It should indicate storage conditions and retention time. Consideration should be given to aspects such as:
- environmental conditions
 - assigned responsibility for archiving, and
 - a policy addressing the retention of duplicates for selected records (back-up).

Chapter 17: Internal quality audits

Principle

Internal quality audits, incorporating EN ISO 9001 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 continuous 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 regulatory requirements.

- 17.1 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.
- 17.2 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 organisation.
- 17.3 Internal quality system audit findings should be discussed with responsible management. Agreed, time-limited remedial actions should be recorded and followed up to completion and sign-off.
- 17.4 The follow-up activities should verify the effectiveness of the corrective action taken.
- 17.5 Output of the internal quality audit programme should be summarised and periodically submitted to senior management as an integral part of the management review process.
- 17.6 Further guidance for conducting quality system audits is provided in ISO 10011.

Chapter 18: Training

Principle

There should be an effective mechanism for identifying training needs and taking appropriate action to ensure that all personnel (including managers), are appropriately qualified and adequately trained.

- 18.1 Qualification and training needs should be identified, documented and regularly reviewed in order that additional (or repeat) training can be given in a timely manner. This is particularly important when new processes are being introduced. The use of documented training modules is recommended to ensure consistency of training. The effectiveness of training should be evaluated.
- 18.2 GMP awareness training should be repeated at prescribed intervals for all relevant personnel.
- 18.3 Training should be recorded and individuals training records should be retained for a specified period of time.
- 18.4 Tasks should be assigned on the basis of qualifications, training and experience.

Chapter 19: Servicing

This requirement is concerned with ‘after sales service’ (usually of equipment). Where servicing is a specified requirement, documented procedures should be established to show that servicing specifications are met.

This chapter should not normally apply to API manufacturers.

Chapter 20: Statistical techniques

Principle

Appropriate statistical techniques should be identified, documented and implemented to control quality critical processes.

20.1 Identification of need

20.1.1 The main activities for the application of statistical techniques are likely to be sampling plans, stability testing, validation, interpretation of analytical data, identifying process capability and trend analysis. A statistical perspective is essential when planning a complex investigation if maximum benefit is to be derived.

20.1.2 API manufacturers should identify and document the need for, and application of, appropriate statistical techniques.

20.2 Procedures

20.2.1 Documented procedures and adequate training should be used to control the application of statistical techniques.

20.2.2 Whenever possible recognised published statistical techniques should be selected for use. If alternatives are applied, their use should be justified through traceability to basic statistical theory.

Annex A: Hygiene

Principle

While not directly addressed under the specific heading in the EN ISO 9001 framework as applied to personnel and to facilities, principles relevant to hygiene are encompassed within the requirements of Process Control (chapter 9) and Training (chapter 18) in order to ensure the correct behaviour of those whose activities affect quality. This is exemplified through the need for qualified, trained personnel to comply with codes of practice, standards and procedures in a suitable working environment.

A.1 Personnel

- A.1.1 Direct contact with API should be avoided.
- A.1.2 Clothing designed to protect both product and personnel should be worn and changed when necessary.
- A.1.3 Personnel suffering from an infectious disease or having open lesions on the exposed surface of the body should avoid activities which could compromise the quality of API.
- A.1.4 Smoking, eating, drinking, chewing and storage of food should be restricted to designated areas separated from production or control areas.

A.2 Facilities and equipment

- A.2.1 Building and equipment should be of an appropriate design to facilitate cleaning and to avoid contamination.
- A.2.2 Changing, washing, toilet and refreshment rooms should be separate from production areas.
- A.2.3 Areas used to store, produce or control raw materials, intermediates, API and packaging materials should be kept clean and tidy.
- A.2.4 Premises should be cleaned in accordance with written procedures. Sanitation or disinfection agents and their usage should be specified.
- A.2.5 Product contact surfaces of equipment and connections between equipment should be easily cleanable.

- A.2.6 Procedures for cleaning equipment should be documented and their use and effectiveness recorded.

- A.2.7 Clean equipment should be protected from recontamination and checked for cleanliness before use.

Annex B: Facilities and cleaning, utilities and engineering

Principle

This Annex addresses in more detail some of the issues raised in Process Control (chapter 9), together with equipment cleaning and computerised systems. Buildings and equipment should be suited to, and properly maintained for, the production, storage, and testing of API. Only suitable areas for manufacture, storage, and testing of raw materials, intermediates, and final product should be used, and adequate utilities should be available.

Sufficient engineering expertise should be in place to support and maintain production and packaging processes in a GMP compliant manner.

B.1 Facilities and equipment

- B.1.1 The location, design, and construction of buildings should be suitable for the type and stage of manufacture involved, protecting the product from contamination (including cross-contamination) and protecting operators and the environment from the product.
- B.1.2 Separate buildings and/or areas and/or equipment should be used for sensitising agents, highly active or toxic drugs.
- B.1.3 Where ventilation systems are necessary, they should be designed, constructed and operated to protect both the operators and the API. Air intakes should be positioned away from potential sources of contamination (such as air exhaust points).
- B.1.4 Filters in ventilation systems should remove particulate contamination to a defined level determined as a result of filter validation, if appropriate. Recirculated air should not cause demonstrable cross-contamination.
- B.1.5 Facilities for sampling should protect against cross-contamination.
- B.1.6 The environment in which pure and/or final API is handled (e.g. filtered/filled, packed) should afford sufficient protection against cross-contamination.
- B.1.7 Laboratory areas for final product testing should be separated from production areas.
- B.1.8 Equipment should be designed, constructed, located, and used so as to minimise the risk of contamination or mix-ups arising during manufacture of API.

- B.1.9 Equipment surfaces in contact with materials used in API manufacture should be non-reactive.
- B.1.10 Equipment should be clearly and uniquely identifiable, as should be its status.
- B.1.11 Disposal of solid, liquid or gaseous by-products should comply with local environmental protection requirements.
- B.1.12 Plant security should be sufficient to prevent unauthorised persons from gaining access to API manufacturing facilities.

B.2 Computerised systems

- B.2.1 Quality critical configurable and specific computer software should be validated. This validation should include a full description of the programme and a chart relating the various main and sub-programmes. Well tried operating systems and software with demonstrated market performance require a different level of validation.
- B.2.2 The validation should concentrate on those aspects of the programme that affect or could affect product quality.
- B.2.3 Computer systems should be designed and operated to prevent unauthorised entries or changes to the programme.
- B.2.4 In the case of manual entry of quality critical data there should be a second independent check to verify accuracy of the initial entry.
- B.2.5 A back-up system should be provided of all quality critical data.
- B.2.6 There should be written operating procedures describing:
 - the operation of the system
 - the action to be taken in case of malfunction
 - the means of detecting, recording and correcting errors
 - the process for re-starting, and recovery of data
 - change control
 - the use of electronic signatures
- B.2.7 Incidents that could affect the quality of API or the reliability of records or test results should be recorded and investigated.

B.3 Cleaning

- B.3.1 Buildings should be maintained in a clean condition and cleaning procedures should be documented and readily available.

- B.3.2 Equipment should have product contact surfaces that are easily cleanable. Connections between various pieces of equipment should also be easily cleanable. Items that are difficult to clean in situ should be dismantled whenever there is a potential for contamination.

- B.3.3 There should be written procedures describing the cleaning of equipment including related equipment such as heat exchangers or connections. There should be a record that the cleaning activity has been completed and the cleanliness status of the equipment should be identifiable. Where appropriate, the cleaning procedures should be validated (see Annex C).

- B.3.4 Cleaned equipment should be protected from re-contamination. It should be checked for cleanliness before use and the result of this check should be recorded.

- B.3.5 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.

- B.3.6 Sampling tools and containers should be maintained in a clean condition so as to prevent contamination of both the sample taken and the material being sampled.

B.4 Utilities

- B.4.1 Quality critical utilities (e.g. water, steam, air, nitrogen) should be validated and frequently monitored. Action should be taken when defined warning levels are reached.

- B.4.2 Chemical and microbiological specifications should be established to control water quality (e.g. potable water; heated water; endotoxin-free water; steam). Water quality should be monitored during quality critical manufacturing steps.

- B.4.3 Pipework and valves should be designed to minimise 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.

B.5 Engineering

- B.5.1 The engineering function plays a major role in the application of GMP concerning design, installation, maintenance of, and any changes to, buildings, equipment, and utilities. Calibration, qualification of equipment and validation of processes also involve engineering expertise.

- B.5.2 Engineers should receive adequate training in GMP and its application in API manufacture.

Annex C: Validation

Principle

The August 1996 edition of the CEFIC/EFPIA Guidelines on Good Manufacturing Practices for Active Ingredients Manufacturers defines validation as the action of proving and documenting that any procedure, process, equipment, activity or system will, with a high degree of assurance, lead to expected results.

Validation is inherently relevant to many of the chapters of this document, and particularly to chapter 4 (Design and Development Control), chapter 9 (Manufacturing Process Control) and chapter 10 (Inspection and Testing). Because the concept and practice of validation is of such predominant importance to the API industry, it is considered in more detail in this Annex.

C.1 Identification of need for validation

- C.1.1 While all processes used in the production of API should be well controlled, quality critical steps which have a direct impact on the quality of the API, particularly from the final intermediate onward, should be validated.
- C.1.2 The development and introduction of new quality critical activities such as manufacturing processes, equipment, analytical methods, etc. should activate the validation process.
- C.1.3 Changes to existing quality critical activities should only be introduced once validation is completed, documented and approved.

C.2 Chronological aspects of validation

- C.2.1 Retrospective validation should review and analyse on the basis of historical evidence in the form of accumulated production, testing, and control data.
- C.2.2 Concurrent validation should generate the necessary evidence during actual implementation. During this phase, batches of product will be released on the basis of more extensive testing than when the validation programme is fully completed.
- C.2.3 Prospective validation should apply to all relevant new or modified processes, and should commence during the development stage. It is usually the result of a risk analysis performed on the proposed new or modified production process.

C.3 Qualification of equipment

- C.3.1 Design qualification should confirm and document the proposed design of facilities, equipment, systems etc., as suitable for the intended purpose.
- C.3.2 Installation qualification should confirm and document that facilities, equipment, systems, etc., once installed or modified, comply with the approved design and the manufacturer's recommendations.
- C.3.3 Operational qualification should confirm and document that facilities, equipment, systems etc., as installed or modified, perform as intended throughout the anticipated operating ranges.
- C.3.4 Performance qualification should confirm and document that performance is as intended when manufacturing the API.

C.4 Validation documentation

- C.4.1 There should be a written validation policy clarifying the circumstances under which validation needs are to be identified; who is responsible for managing the validation programme; and outlining how validation should be conducted and documented.
- C.4.2 Before commencing work, a validation plan should be drawn up defining validation objectives; the process to be validated; the facilities, equipment, utilities, and systems to be used; acceptance criteria; the persons responsible for conducting the work; those responsible for reviewing and approving the plan and reviewing the results. The validation plan should be approved by managers with appropriate authority in production and Quality Functions respectively.
- C.4.3 Upon completion of the validation work, a validation report should be prepared summarising findings, commenting on any relevant deviations, and drawing justifiable conclusions. This report should be approved by assigned responsible staff. If the report concludes that validation has not been achieved, then it should propose changes in order to achieve the validation purposes.
- C.4.4 Validation records should be archived for a prescribed period of time, and be available if required.

C.5 Validation of computerised systems

C.5.1 A computerised system should offer at least the same level of security as a manual system.

C.5.2 The extent of validation required will depend largely upon the use of the computerised system, but will also be influenced by the type of the required validation (prospective or retrospective) and whether or not novel features are incorporated.

C.5.3 Prospective validation should be undertaken for all new computerised systems and for systems experiencing major upgrades. Existing computerised systems which were not validated at the time of installation may be more appropriate for retrospective validation.

C.5.4 Only configurable or specific application software should be considered as needing validation. Software with demonstrated market performance (operating and executive software) is normally not subject to validation.

C.5.5 Documentation supporting the validation of computerised systems should include:

- user requirements
- technical specifications
- functional specifications
- risk assessment on functionality
- validation plan, protocol and report
- change control

C.5.6 Although general validation principles still hold good, validation of computerised systems is considered something of a specialist activity. Suppliers of computerised systems should be required to follow the principles laid down in

- Quality Management and Quality Assurance Standards; Part 3: Guidelines for the application of ISO 9001 to the Development, Supply and Maintenance of Software (ISO 9000-3)
- Good Automated Manufacturing Practice (GAMP) - Supplier Guide for Validation of Automated Systems in Pharmaceutical Manufacture.

C.6 Cleaning validation

C.6.1 A guideline is presently being developed by CEFIC.

C.7 Re-validation

C.7.1 Validated processes (including computerised systems) should be monitored and/or periodically evaluated, and previous changes assessed, to determine the need for re-validation.

Annex D: Change control

Principle

A continuous 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.

D.1 Change control procedures

D.1.1 Evaluation and approval of proposed changes to specifications, test procedures, production processes, production equipment, etc., should be controlled by written procedures.

D.1.2 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.

D.1.3 Proposed changes should be reviewed and approved by the relevant departments and the Quality Function.

D.2 Implementation of changes

D.2.1 All documents affected by the change should be identified and revised accordingly.

D.2.2 Any operator training needed should be satisfactorily completed (and recorded).

D.2.3 Several batches of API produced following implementation of the change should be extensively evaluated.

E. Rationale and benefits

There is a very good reason why the EN-ISO 9000 series is the world's best selling quality standard. If applied correctly, and sensibly, the common sense contained within its pages has the potential to generate significant and sustainable business benefits through improved performance, reduced failure costs, and increased competitiveness.

From a business perspective the potential benefits to all stakeholders of an effective QMS may be grouped as follows.

Customer Focus

A clear understanding of each customer's current needs is essential to ensure that quality requirements are met. It is important, therefore, to have in place a robust communications network with effective interfaces between not only Marketing/Sales and the customer but also between Marketing/Sales and other relevant departments within the Organisation in order to achieve full and effective contract review.

The changing needs of customers present a constant challenge to any company whose objective is to remain the supplier of choice. In today's increasingly competitive marketplace delay in launching a new product and/or a major development overspend can significantly reduce the lifetime profits of a new product. To meet this challenge the design and development process must be carefully planned and controlled by a system which must be both flexible enough to cope with the changes inherent in any development process, yet robust enough to ensure that stringent time and budget targets are achieved.

Continuous Improvement Focus

If the QMS is designed and implemented to emphasise continuous 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 basic cause of quality problems, and in so doing provides an important improvement opportunity.

A comprehensive internal quality audit system is a vital healthcheck 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.

Quality Management System - integrating GMP into ISO

A well trained workforce is likely to be better motivated, more efficient, and less likely to make expensive mistakes. As competency requirements change and evolve, an efficient training system is an invaluable contribution to any company's competitive edge and overall success.

Experience in a variety of industries has confirmed the value of an EN-ISO 9001 based QMS as a firm foundation for progressing to world class status as exemplified by achievement of the European Quality Award and equivalent. It also provides a suitable springboard for developing an Integrated Management System incorporating quality, safety and environment.

Regulatory Compliance and (Continuous) Inspection Readiness

It is common for a company to commit a vast number of costly man-hours, and expose staff to the associated stress and disruption, in preparing for inspection by a regulatory authority. Because such inspections look for evidence of GMP compliance, the ability to demonstrate effective control through a documented QMS will help demonstrate to the inspecting authority that all relevant aspects of product quality have been addressed.

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 continuous inspection readiness.

Recognised Best Practice

Compliance with this internationally recognised business standard for managing quality, whether through third party certification or a less formal in-house approach, will provide visible evidence to regulatory authorities, customers, and staff alike that a company's processes are under control. The strong emphasis on forward planning will minimise expensive quality failures. A realistic practical balance between the level of documented procedures, training, qualifications, and experience will ensure a minimum of bureaucracy. The level of documentation should not exceed that required to maintain the desired level of quality.

Reduced Stress

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.

F. Quality system performance measurement

The API industry is constantly changing. It is driven by the influence of technological advances and constrained by regulatory requirements, global market forces and local market pricing considerations. Setting and achieving medium and long term objectives is, therefore, not easy. When failures occur the true underlying cause(s) must be established if learning points are to be identified and appropriate corrective measures applied.

The EN-ISO 9001 QMS approach requires the adoption of a corporate philosophy of continuous improvement leading to greater efficiency and increased customer satisfaction. Although the implementation of an effective QMS is complex, if done correctly and successfully, it provides a sound basis for progression towards excellence. Experience has shown that once a QMS has been introduced there is a risk that the pace of ongoing improvement generated by the introduction of the QMS may falter and lose momentum. It is for this reason that an objective evaluation of improving performance is essential. A number of possibilities exist.

At the strategic level, the corporate goal may be to achieve recognition through formal ISO certification as a stepping stone leading on to gaining the European Quality Award or the US-based Malcolm Baldrige Award. Each involve detailed evaluation of systems performance which, in itself, allows Management to redefine processes which fail to meet performance objectives.

At the tactical level, an integral part of successfully implementing an effective QMS is the need to identify, agree and use realistic criteria for routinely monitoring performance trends. Some general examples are provided below. The nature and emphasis of performance measures will, inevitably, vary from one company to another:

- 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)
- Laboratory retest rate
- Process deviation frequency
- Staff training status
- Equipment breakdowns per month

G. Matrix: cross referencing the EFPIA / CEFIC August 1996 GMP guideline to ISO-based chapters in this document

ISO Chapters	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	A	B	C	D
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3. Organisation, Personnel and Training																									
3.1 Organisation																									
3.1.1	X																								
3.1.2	X																	X							
3.2 General Personnel and Training																									
3.2.1	X																								
3.2.2																		X							
3.3 Hygiene																									
3.3.1																						X			
3.3.2																						X			
3.3.3																						X			

4. Facilities and Utilities																									
4.1 Buildings																									
4.1.1																								X	
4.1.2																								X	
4.1.3																								X	
4.1.4																								X	
4.1.5															X									X	
4.1.6																								X	
4.1.7																								X	
4.1.8																								X	
4.2 Ventilation																									
4.2.1																								X	
4.2.2																								X	
4.2.3																								X	
4.2.4																								X	

ISO Chapters	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	A	B	C	D
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4.3 Utilities and Services																									
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4.3.2																									X
4.3.3																									X
4.3.3.1																									X
4.3.3.2																									X
4.3.3.3																									X
4.3.3.4																									X
4.3.4																									X
4.3.5																									X
4.4 Pipework																									
4.4.1																									X
4.4.2																									X
4.5 Waste Disposal																									
4.5.1																									X
4.5.2																									X
4.6 Security																									
4.6																									X
4.7 Storage Facilities																									
4.7.1																X									
4.7.2																X									
4.7.3													X												
4.8 Cleanliness and Hygiene																									
4.8.1															X										X
4.8.2																									X
4.8.3																									X

5. Equipment and Production																									
5.1 Equipment																									
5.1.1																									X
5.1.2																									X
5.1.3																									X
5.1.4																									X
5.1.5																									X

ISO Chapters	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	A	B	C	D
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5.2 Cleanliness of Equipment																									
5.2.1																									X
5.2.2																									X
5.2.3																									X
5.2.4										X															X
5.2.5																									X
5.3 Control of Product Contamination																									
5.3.1										X															
5.3.1.1										X															
5.3.1.2										X															
5.3.2										X															
5.3.2.1										X															
5.3.2.2										X															
5.3.2.3										X															
5.4 Control, Monitoring and Testing Equipment																									
5.4.1											X														
5.4.2											X														

6. Computerised Systems																									
6.1 Validation																									
6.1.1																									X
6.1.2																									X
6.1.3																									X
6.2 Software																									
6.2																									X
6.3 Changes																									
6.3.1																									X
6.3.2																									X
6.4 Testing																									
6.4																									X

ISO Chapters	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	A	B	C	D
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6.5 Security																									
6.5.1																									X
6.5.2																									X
6.5.3																									X
6.6 Documentation																									
6.6																									X X
6.7 Ancillary Aspects																									
6.7																									X

7. Documentation																									
7.1 General Considerations																									
7.1.1					X																				
7.1.2					X																				
7.1.3					X																				
7.1.4					X																				
7.1.5					X																				
7.2 Specifications and Test Procedures																									
7.2.1										X															
7.2.2										X															
7.2.3										X															X
7.3 Test Records																									
7.3.1										X															
7.3.2										X															
7.3.3																	X								
7.4 Production Documentation																									
7.4.1										X															
7.4.2										X															
7.4.3										X															
7.4.4										X															
7.4.5										X															
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7.4.10										X															

ISO Chapters	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	A	B	C	D
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8. Validation																								
8.1 Validation Policy																								
8.1																								X
8.2 Preliminary Considerations																								
8.2.1				X																				
8.2.2				X																				
8.3 Qualification																								
8.3.1																								X
8.3.2																								X
8.4 Process Validation																								
8.4.1																								X
8.4.1.1																								X
8.4.1.2																								X
8.4.2																								X
8.4.3																								X
8.5 Scope																								
8.5.1																								X
8.5.2																								X
8.5.3																								X
8.5.4																								X
8.6 Validation Documentation																								
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8.6.3.1																								X
8.6.3.2																								X
8.6.4																								X
8.6.5																								X
8.7 Revalidation																								
8.7.1																								X
8.7.2																								X

ISO Chapters	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	A	B	C	D
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9. Change Control																								
9.1 Change Control Procedures																								
9.1.1																								X
9.1.2																								X
9.1.3																								X
9.2 Implementation of Changes																								
9.2.1																								X
9.2.2																								X

10. Contract Manufacture or Analysis																								
10.1 Contract																								
10.1.1			X																					
10.1.2			X																					

11. Materials Management																								
11.1 Purchasing and Control																								
11.1.1						X																		
11.1.2						X																		
11.1.3						X																		
11.1.4																								X
11.2 Receipt and Quarantine of Materials																								
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11.2.9												X	X		X									
11.3 Issuing or Distribution of Materials																								
11.3.1									X															
11.3.2									X															
11.3.3								X																
ISO Chapters	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	A	B	C	D

ISO Chapters	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	A	B	C	D
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11.4 Specific Management of API.																									
11.4.1																									
11.4.2										X															
11.4.3																									

12. Sampling																									
12.1 Facilities for Sampling																									
12.1.1																									
12.1.2																									
12.2 Sampling Procedures																									
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13. Filling and Labelling of API																									
13.1 Packaging Materials																									
13.1.2																									
13.2 Filling/Packaging																									
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13.3 Labels and Labelling																									
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ISO Chapters	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	A	B	C	D
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14. Engineering																									
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14.2																									X
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15. Quality Management																									
15.1 Quality Assurance																									
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15.1.6																	X								
15.2 Quality Control																									
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15.2.3		X								X															
15.2.4					X																				
15.2.5			X																						
15.3 In-Process Control (IPC)																									
15.3.1										X															
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15.3.4										X															
15.3.5											X														
15.3.6										X															

16. Rejection, Recovery, Reprocessing and Returns																									
16.1 Rejection of Materials																									
16.1.1														X											
16.1.2														X											
16.1.3														X											
16.1.4														X	X										

ISO Chapters	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	A	B	C	D
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16.2 Recovery of Materials and Solvents																								
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16.2.3																								
16.3 Reprocessing or Reworking of Materials																								
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16.3.5																								
16.4 Returned Materials																								
16.4.1																								
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17. Stability Testing and Retest Date																								
17.1 Storage Conditions and Retest Date																								
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17.1.4																								
17.2 Stability Testing																								
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18. Complaint and Recall Procedures																								
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ISO Chapters	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	A	B	C	D
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18.2 Recall Procedures																																				
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18.2.2																									X	X										
18.2.3																									X	X										

19. Self-Inspections																																					
19.1																																					X
19.2																																					X
19.3																																					X

I. Appendix: Retention Periods																																					
1. Documentation																																					
1.1																																					X
1.2																																					X
1.3																																					X
2. Samples																																					
2.1																																					X
2.2																																					X
2.3																																					X
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H. References

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