The ability of the purification process to remove impurities and contaminants should be demonstrated and the overall reduction factors for impurities as well as reduction factors for each stage of purification should be established. Where necessary, concentrations of impurities/contaminants higher then expected during normal production (i.e. spiking) should be used to study the robustness of the process for clearing these impurities/contaminants. In addition, quantitative estimations of residual levels of impurities/contaminants per dose should be performed using realistic conditions as well as worst-case scenarios.

4.3 Control of the active substance

4.3.1 Characterisation

The characterisation of an active substance derived from transgenic plants should be performed by appropriate techniques, taking into account relevant guideline (in particular the ICH Q6B guideline on specifications), pharmacopoeial, and other requirements. Characterisation studies should include a comparison of the active substance with its natural counterpart, when feasible and relevant. The potential impact of the differences observed should be carefully considered, and thoroughly discussed with regards to safety and efficacy.

A comprehensive quality profile of the active substance should be established using appropriate analytical techniques, which should include at least the determination of physicochemical properties, biological activity, immunochemical properties, purity and impurities. If there is an inherent degree of structural heterogeneity, for example due to the presence of post-translationally modified forms, the applicant should define the pattern of heterogeneity. In addition, the impact of cultivation, harvest, post-harvesting processing and storage on the pattern of heterogeneity of the active substance should be appropriately defined in order to establish a basis for establishing an appropriate set of controls and specifications which in turn should assure batch-to-batch consistency.

A comprehensive characterisation of the plant protein processing, including glycosylation patterns, both qualitatively and quantitatively, should be provided. This analysis should include the determination of the overall monosaccharide composition, the analysis of oligosaccharides released from the protein (e.g. determination of antennary structures, mapping) and oligosaccharides attached to the protein (e.g. glycosylation per site, glycoform distribution). Characterisation studies should also include analysis of post-translational modifications other than glycosylation (for example, acetylation, phosphorylation, addition of lectins, lipids, polyphenols). Particular attention should be paid to moieties or patterns that are not known to be present in natural human proteins. Where such moieties or patterns are observed, they should be highlighted, and the strategy employed to monitor them or to remove them should be fully documented.

Plants production system may give rise to secondary metabolites as well as host cell proteins, which should be removed by the purification process.

Appropriate methods should be used to characterise product- and process-related impurities. The following parameters should be considered for impurities from the host plant: (i) plant proteins other than the transgene-expressed protein (for example, lectins), (ii) proteases, (iii) plant DNA, (iv) secondary plant metabolites such as alkaloids or glycosides secreted by the production plants. The following parameters should be considered for impurities from the process itself: (i) materials employed in production and purification (including soil, fertilisers, pesticides, solvents, chromatographic materials leached from columns...), and (ii) materials (chemical, biochemical, microbial and/or biological) potentially introduced adventitiously during production and purification (including endotoxins, aflatoxins and other mycotoxins, toxic metals).

4.3.2 Specifications

Applicants for Marketing Authorisation are reminded that, taking into account the specificities inherent in transgenic plant-based production, the overall strategy aimed at routinely controlling the quality of each batch of active substance produced, and at ensuring batch-to-batch consistency, should embrace the control of starting materials, reagents, and materials used during cultivation and

processing, adherence to good production practice, and the application of appropriate in-process controls.

The selection of tests to be included in the specifications should be defined as described in ICH Q6B: *Specifications: Test Procedures and Acceptance Criteria for Biotechnological/Biological Products*. Selection of tests to be included in the specifications is product specific. The rationale used to establish the acceptable range of acceptance criteria should be described. Each acceptance criterion should be established and justified based on characterisation data, data obtained from lots used in non-clinical and/or clinical studies, and by data from lots used for the demonstration of manufacturing consistency, data from stability studies, and relevant development data.

4.4 Freedom from contamination with adventitious agents

4.4.1 Non-viral adventitious agents

Mycoplasmas, bacteria and fungi constitute the usual range of cellular organisms that need to be controlled and tested for during the course of the production of biological medicinal products. Where botanical materials are involved, however, applicants may also need to control the potential for infestation of harvest- and in-process level-plant tissue with unicellular and metazoan organisms which are possible contaminants of the material.

For materials and products intended to be sterile, the sterilisation process should be validated with reference to the worst-case contamination levels which may apply to the input material.

4.4.2 Virus and viroid adventitious agents

There is a wide range of naturally occurring plant viruses and viroids. The species involved are generally plant and tissue specific, much in the way that mammalian viruses are. Long experience of regular exposure of humans to plant tissues and fluids, principally via the oral and topical routes but also in some cases by inadvertent parenteral inoculation, has not produced any evidence that these agents are pathogenic to humans or other vertebrates. Furthermore, attempts at propagating plant viruses in mammalian cells and at propagating mammalian viruses in plant cells have been unsuccessful.

Of more concern is the unintentional contamination of process material and/or equipment with extraneous material such as insect, bird and animal excreta, carcases or parts thereof, organic fertiliser residues, and/or production personnel-shed material, any of which might result in contamination of the material with viruses capable of causing disease in humans. For example, the Hantaviruses, which can be distributed in rodent excreta, are found worldwide and are responsible for a number of fatal diseases in humans. The range of potential contaminating viruses is, however, considerable and includes other viruses derived from excreta such as Minute Virus of Mice (MVM), avian influenza virus and Hepatitis A virus (HAV). Overall, the likelihood of viruses contaminating starting or in-process materials is likely to be dependent on the extent and nature of the operations involved, including the environments in which they are performed, the containment measures applied, the quality and good practice systems in place, and the personnel involved.

Potential viral contamination via the intentional introduction during manufacture of biologically derived material such as reagents, chromatographic materials, growth promoters, and growth media needs to be controlled using well-established approaches.

A programme to monitor for plant disease should be in place. Disease may not only result in high levels of plant viruses in the harvested material, which would be a general contaminant, but may also affect the expression and structure of the medicinal product. In designing the monitoring programme, it needs to be taken into account that infectious diseases of plants are not always overt.

Depending on the circumstances, production processes might amplify, eliminate, or concentrate contaminating viruses and viroids. However, in the event of contamination of the starting material or the manufacturing process with a mammalian virus of concern, it should be borne in mind that the virus would not be amplified, as it might be for example in a bioreactor containing mammalian cells.

Taking each of the above considerations into account, applicants should present a risk analysis of the potential for contamination of the active substance with adventitious viral agents. On the basis of this analysis, which should be quantitative insofar as this is possible, the applicant should propose an integrated step-wise strategy that reliably ensures the virus safety of each batch of medicinal product.

Effective strategies are likely to involve some or all of the following measures:

- Controls and tests on starting materials, raw materials, reagents and excipients.
- Barriers (containment) applied at the level of agricultural steps (cultivation, harvest, post-harvest processing) aimed at preventing the adventitious entry of extraneous materials and agents.
- *In vitro* and *in vivo* tests for the absence of adventitious agents at critical production stages, such as appropriate unprocessed bulk and/or processed bulk levels.
- Validated virus/viroid inactivation/removal procedures.

4.4.3 Transmissible Spongiform Encephalopathy (TSE) issues

Any materials introduced during production which fall within the scope of the European guideline on minimising the risk of animal TSE transmission should be identified, and compliance with the requirements of the guideline demonstrated.

DEFINITIONS

Definitions are provided for the purpose of this document.

Higher plant: plant belonging to the taxonomic group Spermatophytae (Gymnospermae and Angiospermae).

Expression construct: expression vector containing the sequences coding for a recombinant protein and for the elements necessary for the expression of the protein.

Transgene: heterologous DNA segment inserted into the genome of an organism and capable of expressing or inducing the expression of a polypeptide sequence in that organism. Most transgenes of medicinal interest are typically obtained from viral, bacterial or mammalian sources.

Transgenic organism: organism into which one or more transgenes have been introduced.

Initial transformant. A generation of plants homozygous for a particular transgene produced by a single transformational event.

Final or production transformant: normally a genetically homogenous group of plants with the characteristics of all production crop lots intended for routine consistent production of harvests possessing the desired characteristics and from which a master (and working) bank can be established.

Transgenic bank: a master or working bank of starting transgene plant material, capable of long-term storage and of providing sufficient starting material for a large number of production runs.

Elite plant line: an elite plant line is a plant line selected for its agricultural performance. Elite plant lines are typically non-transformed plants derived from the same species as the final transformant.

Production plant: a plant with defined quality cultivated and harvested to yield crude active substance.

REFERENCES (scientific and / or legal)

The pharmaceutical legislation (Eudralex) is available on the European Commission website (http://pharmacos.eudra.org/F2/eudralex/index.htm):

- Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use, as amended.
- Regulation (EC) No 726/2004 of the European Parliament and of the Council of 31 March 2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency.

- Directive 2001/18/EC of the European Parliament and of the Council of 12 March 2001 on the deliberate release into the environment of genetically modified organisms and repealing Council Directive 90/220/EEC.
- Eudralex Volume 4 - Good Manufacturing Practice – Part II Basic Requirements for Active Substances used as Starting Materials

Available on EMEA website (www.emea.eu.int):

- Guideline on Good Agricultural and Collection Practice (GACP) for starting materials of herbal origin (EMEA/HMPC/246816/2005).
- Note for Guidance on minimising the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products (2004/C 24/03)

WHO guidelines on good agricultural and collection practices (GACP) for medicinal plants (2003 - published by WHO).

ICH Q5A: Viral safety evaluation of biotechnology products derived from cell lines of human or animal origin

ICH Q6B Specifications: Test Procedures and Acceptance Criteria for Biotechnological/Biological Products.

Guidelines are available on EMEA (www.emea.europa.eu) and ICH websites (www.ich.org).

ICH Q10 PHARMACEUTICAL QUALITY SYSTEM

ICH Harmonised Tripartite Guideline

TABLE OF CONTENTS

PHARMACEUTICAL QUALITY SYSTEM

1. PHARMACEUTICAL QUALITY SYSTEM

1.1 Introduction

This document establishes a new ICH tripartite guideline describing a model for an effective *quality* management system for the pharmaceutical industry, referred to as the *Pharmaceutical Quality System*. Throughout this guideline, the term "pharmaceutical quality system" refers to the ICH Q10 model.

ICH Q10 describes one comprehensive model for an effective pharmaceutical quality system that is based on International Standards Organisation (ISO) quality concepts, includes applicable Good Manufacturing Practice (GMP) regulations and complements ICH Q8 "Pharmaceutical Development" and ICH Q9 "Quality Risk Management". ICH Q10 is a model for a pharmaceutical quality system that can be implemented throughout the different stages of a product lifecycle. Much of the content of ICH Q10 applicable to manufacturing sites is currently specified by regional GMP requirements. ICH Q10 is not intended to create any new expectations beyond current regulatory requirements. Consequently, the content of ICH Q10 that is additional to current regional GMP requirements is optional.

ICH Q10 demonstrates industry and regulatory authorities' support of an effective pharmaceutical quality system to enhance the quality and availability of medicines around the world in the interest of public health. Implementation of ICH Q10 throughout the product lifecycle should facilitate *innovation* and *continual improvement* and strengthen the link between pharmaceutical development and manufacturing activities.

1.2 Scope

This guideline applies to the systems supporting the development and manufacture of pharmaceutical drug substances (i.e., API) and drug products, including biotechnology and biological products, throughout the product lifecycle.

The elements of ICH Q10 should be applied in a manner that is appropriate and proportionate to each of the product lifecycle stages, recognising the differences among, and the different goals of each stage (see Section 3).

For the purposes of this guideline, the product lifecycle includes the following technical activities for new and existing products:

- Pharmaceutical Development
  - Drug substance development;
  - Formulation development (including container/closure system);
  - Manufacture of investigational products;
  - Delivery system development (where relevant);
  - Manufacturing process development and scale-up;
  - Analytical method development.

- Technology Transfer
  - New product transfers during Development through Manufacturing;
  - Transfers within or between manufacturing and testing sites for marketed products.

- Commercial Manufacturing
  - Acquisition and control of materials;
  - Provision of facilities, utilities, and equipment;
  - Production (including packaging and labelling);
  - Quality control and assurance;
  - Release;
  - Storage;
  - Distribution (excluding wholesaler activities).

- Product Discontinuation
  - Retention of documentation;
  - Sample retention;
  - Continued product assessment and reporting.

1.3 Relationship of ICH Q10 to Regional GMP Requirements, ISO Standards and ICH Q7

Regional GMP requirements, the ICH Q7 Guideline, "Good Manufacturing Practice Guide for Active Pharmaceutical Ingredients", and ISO quality management system guidelines form the foundation for ICH Q10. To meet the objectives described below, ICH Q10 augments GMPs by describing specific quality system elements and management responsibilities. ICH Q10 provides a harmonised model for a pharmaceutical quality system throughout the lifecycle of a product and is intended to be used together with regional GMP requirements.

The regional GMPs do not explicitly address all stages of the product lifecycle (e.g., Development). The quality system elements and management responsibilities described in this guideline are intended to encourage the use of science and risk based approaches at each lifecycle stage, thereby promoting continual improvement across the entire product lifecycle.

1.4 Relationship of ICH Q10 to Regulatory Approaches

Regulatory approaches for a specific product or manufacturing facility should be commensurate with the level of product and process understanding, the results of *quality risk management*, and the effectiveness of the pharmaceutical quality system. When implemented, the effectiveness of the pharmaceutical quality system can normally be evaluated during a regulatory inspection at the manufacturing site. Potential opportunities to enhance science and risk based regulatory approaches are identified in Annex 1. Regulatory processes will be determined by region.

1.5 ICH Q10 Objectives

Implementation of the Q10 model should result in achievement of three main objectives which complement or enhance regional GMP requirements.

1.5.1 Achieve *Product Realisation*

To establish, implement and maintain a system that allows the delivery of products with the

quality attributes appropriate to meet the needs of patients, health care professionals, regulatory authorities (including compliance with approved regulatory filings) and other internal and external customers.

1.5.2 Establish and Maintain a *State of Control*

To develop and use effective monitoring and control systems for process performance and product quality, thereby providing assurance of continued suitability and *capability of processes*. Quality risk management can be useful in identifying the monitoring and control systems.

1.5.3 Facilitate Continual Improvement

To identify and implement appropriate product quality improvements, process improvements, variability reduction, innovations and pharmaceutical quality system enhancements, thereby increasing the ability to fulfil quality needs consistently. Quality risk management can be useful for identifying and prioritising areas for continual improvement.

1.6 *Enablers*: Knowledge Management and Quality Risk Management

Use of *knowledge management* and quality risk management will enable a company to implement ICH Q10 effectively and successfully. These enablers will facilitate achievement of the objectives described in Section 1.5 above by providing the means for science and risk based decisions related to product quality.

1.6.1 Knowledge Management

Product and process knowledge should be managed from development through the commercial life of the product up to and including product discontinuation. For example, development activities using scientific approaches provide knowledge for product and process understanding. Knowledge management is a systematic approach to acquiring, analysing, storing and disseminating information related to products, manufacturing processes and components. Sources of knowledge include, but are not limited to prior knowledge (public domain or internally documented); pharmaceutical development studies; technology transfer activities; process validation studies over the product lifecycle; manufacturing experience; innovation; continual improvement; and *change management* activities.

1.6.2 Quality risk Management

Quality risk management is integral to an effective pharmaceutical quality system. It can provide a proactive approach to identifying, scientifically evaluating and controlling potential risks to quality. It facilitates continual improvement of process performance and product quality throughout the product lifecycle. ICH Q9 provides principles and examples of tools for quality risk management that can be applied to different aspects of pharmaceutical quality.

1.7 Design and Content Considerations

(a) The design, organisation and documentation of the pharmaceutical quality system should be well structured and clear to facilitate common understanding and consistent application.

(b) The elements of ICH Q10 should be applied in a manner that is appropriate and proportionate to each of the product lifecycle stages, recognising the different goals and knowledge available for each stage.

(c) The size and complexity of the company's activities should be taken into consideration when developing a new pharmaceutical quality system or modifying an existing one. The design of the pharmaceutical quality system should incorporate appropriate risk management principles. While some aspects of the pharmaceutical quality system can be company-wide and others site-specific, the effectiveness of the pharmaceutical quality system is normally demonstrated at the site level.

(d) The pharmaceutical quality system should include appropriate processes, resources and responsibilities to provide assurance of the quality of *outsourced activities* and purchased materials as described in Section 2.7.

(e) Management responsibilities, as described in Section 2, should be identified within the pharmaceutical quality system.

(f) The pharmaceutical quality system should include the following elements, as described in Section 3: process performance and product quality monitoring, *corrective* and *preventive action*, change management and management review.

(g) *Performance indicators*, as described in Section 4, should be identified and used to monitor the effectiveness of processes within the pharmaceutical quality system.

1.8 Quality Manual

A *Quality Manual* or equivalent documentation approach should be established and should contain the description of the pharmaceutical quality system. The description should include:

(a) The *quality policy* (see Section 2);

(b) The scope of the pharmaceutical quality system;

(c) Identification of the pharmaceutical quality system processes, as well as their sequences, linkages and interdependencies. Process maps and flow charts can be useful tools to facilitate depicting pharmaceutical quality system processes in a visual manner;

(d) Management responsibilities within the pharmaceutical quality system (see Section 2).

2. MANAGEMENT RESPONSIBILITY

Leadership is essential to establish and maintain a company-wide commitment to quality and for the performance of the pharmaceutical quality system.

2.1 Management Commitment

(a) *Senior management* has the ultimate responsibility to ensure an effective pharmaceutical quality system is in place to achieve the *quality objectives*, and that roles, responsibilities, and authorities are defined, communicated and implemented throughout the company.

(b) Management should:

(1) Participate in the design, implementation, monitoring and maintenance of an effective pharmaceutical quality system;
(2) Demonstrate strong and visible support for the pharmaceutical quality system and ensure its implementation throughout their organisation;
(3) Ensure a timely and effective communication and escalation process exists to raise quality issues to the appropriate levels of management;
(4) Define individual and collective roles, responsibilities, authorities and inter-relationships of all organisational units related to the pharmaceutical quality system. Ensure these interactions are communicated and understood at all levels of the organisation. An independent quality unit/structure with authority to fulfil certain pharmaceutical quality system responsibilities is required by regional regulations;
(5) Conduct management reviews of process performance and product quality and of the pharmaceutical quality system;
(6) Advocate continual improvement;
(7) Commit appropriate resources.

2.2 Quality Policy

(a) Senior management should establish a quality policy that describes the overall intentions and direction of the company related to quality.

(b) The quality policy should include an expectation to comply with applicable regulatory requirements and should facilitate continual improvement of the pharmaceutical quality system.

(c) The quality policy should be communicated to and understood by personnel at all levels in the company.

(d) The quality policy should be reviewed periodically for continuing effectiveness.

2.3 *Quality Planning*

(a) Senior management should ensure the quality objectives needed to implement the quality policy are defined and communicated.

(b) Quality objectives should be supported by all relevant levels of the company.

(c) Quality objectives should align with the company's strategies and be consistent with the quality policy.

(d) Management should provide the appropriate resources and training to achieve the quality objectives.

(e) Performance indicators that measure progress against quality objectives should be established, monitored, communicated regularly and acted upon as appropriate as described in Section 4.1 of this document.

2.4 Resource Management

(a) Management should determine and provide adequate and appropriate resources (human, financial, materials, facilities and equipment) to implement and maintain the

pharmaceutical quality system and continually improve its effectiveness.

(b) Management should ensure that resources are appropriately applied to a specific product, process or site.

2.5 Internal Communication

(a) Management should ensure appropriate communication processes are established and implemented within the organisation.

(b) Communications processes should ensure the flow of appropriate information between all levels of the company.

(c) Communication processes should ensure the appropriate and timely escalation of certain product quality and pharmaceutical quality system issues.

2.6 Management Review

(a) Senior management should be responsible for pharmaceutical quality system governance through management review to ensure its continuing suitability and effectiveness.

(b) Management should assess the conclusions of periodic reviews of process performance and product quality and of the pharmaceutical quality system, as described in Sections 3 and 4.

2.7 Management of Outsourced Activities and Purchased Materials

The pharmaceutical quality system, including the management responsibilities described in this section, extends to the control and review of any outsourced activities and quality of purchased materials. The pharmaceutical company is ultimately responsible to ensure processes are in place to assure the control of outsourced activities and quality of purchased materials. These processes should incorporate quality risk management and include:

(a) Assessing prior to outsourcing operations or selecting material suppliers, the suitability and competence of the other party to carry out the activity or provide the material using a defined supply chain (e.g., audits, material evaluations, qualification);

(b) Defining the responsibilities and communication processes for quality-related activities of the involved parties. For outsourced activities, this should be included in a written agreement between the contract giver and contract acceptor;

(c) Monitoring and review of the performance of the contract acceptor or the quality of the material from the provider, and the identification and implementation of any needed improvements;

(d) Monitoring incoming ingredients and materials to ensure they are from approved sources using the agreed supply chain.

2.8 Management of Change in Product Ownership

When product ownership changes, (e.g., through acquisitions) management should consider the complexity of this and ensure:

(a) The ongoing responsibilities are defined for each company involved;

(b) The necessary information is transferred.

3. CONTINUAL IMPROVEMENT OF PROCESS PERFORMANCE AND PRODUCT QUALITY

This section describes the lifecycle stage goals and the four specific pharmaceutical quality system elements that augment regional requirements to achieve the ICH Q10 objectives, as defined in Section 1.5. It does not restate all regional GMP requirements.

3.1 Lifecycle Stage Goals

The goals of each product lifecycle stage are described below.

3.1.1 Pharmaceutical Development

The goal of pharmaceutical development activities is to design a product and its manufacturing process to consistently deliver the intended performance and meet the needs of patients and healthcare professionals, and regulatory authorities and internal customers' requirements. Approaches to pharmaceutical development are described in ICH Q8. The results of exploratory and clinical development studies, while outside the scope of this guidance, are inputs to pharmaceutical development.

3.1.2 Technology Transfer

The goal of technology transfer activities is to transfer product and process knowledge between development and manufacturing, and within or between manufacturing sites to achieve product realisation. This knowledge forms the basis for the manufacturing process, *control strategy*, process validation approach and ongoing continual improvement.

3.1.3 Commercial Manufacturing

The goals of manufacturing activities include achieving product realisation, establishing and maintaining a state of control and facilitating continual improvement. The pharmaceutical quality system should assure that the desired product quality is routinely met, suitable process performance is achieved, the set of controls are appropriate, improvement opportunities are identified and evaluated, and the body of knowledge is continually expanded.

3.1.4 Product Discontinuation

The goal of product discontinuation activities is to manage the terminal stage of the product lifecycle effectively. For product discontinuation, a pre-defined approach should be used to manage activities such as retention of documentation and samples and continued product assessment (e.g., complaint handling and stability) and reporting in accordance with regulatory requirements.

3.2 Pharmaceutical Quality System Elements

The elements described below might be, required in part under regional GMP regulations. However, the Q10 model's intent is to enhance these elements in order to promote the lifecycle approach to product quality. These four elements are:

- Process performance and product quality monitoring system;
- *Corrective action* and *preventive action* (CAPA) system;
- Change management system;
- Management review of process performance and product quality.

These elements should be applied in a manner that is appropriate and proportionate to each of the product lifecycle stages, recognising the differences among, and the different goals of, each stage. Throughout the product lifecycle, companies are encouraged to evaluate opportunities for innovative approaches to improve product quality.

Each element is followed by a table of example applications of the element to the stages of the pharmaceutical lifecycle.

3.2.1 Process Performance and Product Quality Monitoring System

Pharmaceutical companies should plan and execute a system for the monitoring of process performance and product quality to ensure a state of control is maintained. An effective monitoring system provides assurance of the continued capability of processes and controls to produce a product of desired quality and to identify areas for continual improvement. The process performance and product quality monitoring system should:

(a) Use quality risk management to establish the control strategy. This can include parameters and attributes related to drug substance and drug product materials and components, facility and equipment operating conditions, in-process controls, finished product specifications, and the associated methods and frequency of monitoring and control. The control strategy should facilitate timely *feedback / feedforward* and appropriate corrective action and preventive action;

(b) Provide the tools for measurement and analysis of parameters and attributes identified in the control strategy (e.g., data management and statistical tools);

(c) Analyse parameters and attributes identified in the control strategy to verify continued operation within a state of control;

(d) Identify sources of variation affecting process performance and product quality for potential continual improvement activities to reduce or control variation;

(e) Include feedback on product quality from both internal and external sources, e.g., complaints, product rejections, non-conformances, recalls, deviations, audits and regulatory inspections and findings;

(f) Provide knowledge to enhance process understanding, enrich the *design space* (where established), and enable innovative approaches to process validation.

Table I: Application of Process Performance and Product Quality Monitoring System throughout the Product Lifecycle

Pharmaceutical Development	Technology Transfer	Commercial Manufacturing	Product Discontinuation
Process and product knowledge generated and process and product monitoring conducted throughout development can be used to establish a control strategy for manufacturing.	Monitoring during scale-up activities can provide a preliminary indication of process performance and the successful integration into manufacturing. Knowledge obtained during transfer and scale up activities can be useful in further developing the control strategy.	A well-defined system for process performance and product quality monitoring should be applied to assure performance within a state of control and to identify improvement areas.	Once manufacturing ceases, monitoring such as stability testing should continue to completion of the studies. Appropriate action on marketed product should continue to be executed according to regional regulations.

3.2.2 Corrective Action and Preventive Action (CAPA) System

The pharmaceutical company should have a system for implementing corrective actions and preventive actions resulting from the investigation of complaints, product rejections, non-conformances, recalls, deviations, audits, regulatory inspections and findings, and trends from process performance and product quality monitoring. A structured approach to the investigation process should be used with the objective of determining the root cause. The level of effort, formality, and documentation of the investigation should be commensurate with the level of risk, in line with ICH Q9. CAPA methodology should result in product and process improvements and enhanced product and process understanding.

Table II: Application of Corrective Action and Preventive Action System throughout the Product Lifecycle

Pharmaceutical Development	Technology Transfer	Commercial Manufacturing	Product Discontinuation
Product or process variability is explored. CAPA methodology is useful where corrective actions and preventive actions are incorporated into the iterative design and development process.	CAPA can be used as an effective system for feedback, feedforward and continual improvement.	CAPA should be used and the effectiveness of the actions should be evaluated.	CAPA should continue after the product is discontinued. The impact on product remaining on the market should be considered as well as other products which might be impacted.

3.2.3 Change Management System

Innovation, continual improvement, the outputs of process performance and product quality monitoring and CAPA drive change. In order to evaluate, approve and implement these changes properly, a company should have an effective change management system. There is generally a difference in formality of change management processes prior to the initial regulatory submission and after submission, where changes to the regulatory filing might be required under regional requirements.

The change management system ensures continual improvement is undertaken in a timely and effective manner. It should provide a high degree of assurance there are no unintended consequences of the change.

The change management system should include the following, as appropriate for the stage of the lifecycle:

(a) Quality risk management should be utilised to evaluate proposed changes. The level of effort and formality of the evaluation should be commensurate with the level of risk;

(b) Proposed changes should be evaluated relative to the marketing authorisation, including design space, where established, and/or current product and process understanding. There should be an assessment to determine whether a change to the regulatory filing is required under regional requirements. As stated in ICH Q8, working within the design space is not considered a change (from a regulatory filing perspective). However, from a pharmaceutical quality system standpoint, all changes should be evaluated by a company's change management system;

(c) Proposed changes should be evaluated by expert teams contributing the appropriate expertise and knowledge from relevant areas (e.g., Pharmaceutical Development, Manufacturing, Quality, Regulatory Affairs and Medical), to ensure the change is technically justified. Prospective evaluation criteria for a proposed change should be set;

(d) After implementation, an evaluation of the change should be undertaken to confirm the change objectives were achieved and that there was no deleterious impact on product quality.

Table III: Application of Change Management System throughout the Product Lifecycle

Pharmaceutical Development	Technology Transfer	Commercial Manufacturing	Product Discontinuation
Change is an inherent part of the development process and should be documented; the formality of the change management process should be consistent with the stage of pharmaceutical development.	The change management system should provide management and documentation of adjustments made to the process during technology transfer activities.	A formal change management system should be in place for commercial manufacturing. Oversight by the quality unit should provide assurance of appropriate science and risk based assessments.	Any changes after product discontinuation should go through an appropriate change management system.

3.2.4 Management Review of Process Performance and Product Quality

Management review should provide assurance that process performance and product quality are managed over the lifecycle. Depending on the size and complexity of the company, management review can be a series of reviews at various levels of management and should include a timely and effective communication and escalation process to raise appropriate quality issues to senior levels of management for review.

(a) The management review system should include:

(1) The results of regulatory inspections and findings, audits and other assessments, and commitments made to regulatory authorities;
(2) Periodic quality reviews, that can include:
(i) Measures of customer satisfaction such as product quality complaints and recalls;
(ii) Conclusions of process performance and product quality monitoring;
(iii) The effectiveness of process and product changes including those arising from corrective action and preventive actions.
(3) Any follow-up actions from previous management reviews.

(b) The management review system should identify appropriate actions, such as:

(1) Improvements to manufacturing processes and products;
(2) Provision, training and/or realignment of resources;
(3) Capture and dissemination of knowledge.

Table IV: Application of Management Review of Process Performance and Product Quality throughout the Product Lifecycle

Pharmaceutical Development	Technology Transfer	Commercial Manufacturing	Product Discontinuation
Aspects of management review can be performed to ensure adequacy of the product and process design.	Aspects of management review should be performed to ensure the developed product and process can be manufactured at commercial scale.	Management review should be a structured system, as described above, and should support continual improvement.	Management review should include such items as product stability and product quality complaints.

4. CONTINUAL IMPROVEMENT OF THE PHARMACEUTICAL QUALITY SYSTEM

This section describes activities that should be conducted to manage and continually improve the pharmaceutical quality system.

4.1 Management Review of the Pharmaceutical Quality System

Management should have a formal process for reviewing the pharmaceutical quality system on a periodic basis. The review should include:

(a) Measurement of achievement of pharmaceutical quality system objectives;

(b) Assessment of performance indicators that can be used to monitor the effectiveness of processes within the pharmaceutical quality system, such as:

(1) Complaint, deviation, CAPA and change management processes;
(2) Feedback on outsourced activities;
(3) Self-assessment processes including risk assessments, trending, and audits;
(4) External assessments such as regulatory inspections and findings and customer audits.

4.2 Monitoring of Internal and External Factors Impacting the Pharmaceutical Quality System

Factors monitored by management can include:

(a) Emerging regulations, guidance and quality issues that can impact the Pharmaceutical Quality System;

(b) Innovations that might enhance the pharmaceutical quality system;

(c) Changes in business environment and objectives;

(d) Changes in product ownership.

4.3 Outcomes of Management Review and Monitoring

The outcome of management review of the pharmaceutical quality system and monitoring of internal and external factors can include:

(a) Improvements to the pharmaceutical quality system and related processes;

(b) Allocation or reallocation of resources and/or personnel training;

(c) Revisions to quality policy and quality objectives;

(d) Documentation and timely and effective communication of the results of the management review and actions, including escalation of appropriate issues to senior management.

5. GLOSSARY

ICH and ISO definitions are used in ICH Q10 where they exist. For the purpose of ICH Q10, where the words "requirement", "requirements" or "necessary" appear in an ISO definition, they do not necessarily reflect a regulatory requirement. The source of the definition is identified in parentheses after the definition. Where no appropriate ICH or ISO definition was available, an ICH Q10 definition was developed.

Capability of a Process:

Ability of a process to realise a product that will fulfil the requirements of that product. The concept of process capability can also be defined in statistical terms. (ISO 9000:2005)

Change Management:

A systematic approach to proposing, evaluating, approving, implementing and reviewing changes. (ICH Q10)

Continual Improvement:

Recurring activity to increase the ability to fulfil requirements. (ISO 9000:2005)

Control Strategy:

A planned set of controls, derived from current product and process understanding, that assures process performance and product quality. The controls can include parameters and attributes related to drug substance and drug product materials and components, facility and equipment operating conditions, in-process controls, finished product specifications, and the associated methods and frequency of monitoring and control. (ICH Q10)

Corrective Action:

Action to eliminate the cause of a detected non-conformity or other undesirable situation. NOTE: Corrective action is taken to prevent recurrence whereas preventive action is taken to prevent occurrence. (ISO 9000:2005)

Design Space:

The multidimensional combination and interaction of input variables (e.g., material attributes) and process parameters that have been demonstrated to provide assurance of quality. (ICH Q8)

Enabler:

A tool or process which provides the means to achieve an objective. (ICH Q10)

Feedback / Feedforward:

Feedback: The modification or control of a process or system by its results or effects.

Feedforward: The modification or control of a process using its anticipated results or effects. (Oxford Dictionary of English by Oxford University Press, 2003)

Feedback/ feedforward can be applied technically in process control strategies and conceptually in quality management. (ICH Q10)

Innovation:

The introduction of new technologies or methodologies. (ICH Q10)

Knowledge Management:

Systematic approach to acquiring, analysing, storing, and disseminating information related to products, manufacturing processes and components. (ICH Q10)

Outsourced Activities:

Activities conducted by a contract acceptor under a written agreement with a contract giver. (ICH Q10)

Performance Indicators:

Measurable values used to quantify quality objectives to reflect the performance of an organisation, process or system, also known as "performance metrics" in some regions. (ICH Q10)

Pharmaceutical Quality System (PQS):

Management system to direct and control a pharmaceutical company with regard to quality. (ICH Q10 based upon ISO 9000:2005)

Preventive Action:

Action to eliminate the cause of a potential non-conformity or other undesirable potential situation. NOTE: Preventive action is taken to prevent occurrence whereas corrective action is taken to prevent recurrence. (ISO 9000:2005)

Product Realisation:

Achievement of a product with the quality attributes appropriate to meet the needs of patients, health care professionals, and regulatory authorities (including compliance with marketing authorisation) and internal customers requirements. (ICH Q10)

Quality:

The degree to which a set of inherent properties of a product, system or process fulfils requirements. (ICH Q9)

Quality Manual:

Document specifying the quality management system of an organisation. (ISO 9000:2005)

Quality Objectives:

A means to translate the quality policy and strategies into measurable activities. (ICH Q10)

Quality Planning:

Part of quality management focused on setting quality objectives and specifying necessary operational processes and related resources to fulfil the quality objectives. (ISO 9000:2005)

Quality Policy:

Overall intentions and direction of an organisation related to quality as formally expressed by senior management. (ISO 9000:2005)

Quality Risk Management:

A systematic process for the assessment, control, communication and review of risks to the quality of the drug (medicinal) product across the product lifecycle. (ICH Q9)

Senior Management:

Person(s) who direct and control a company or site at the highest levels with the authority and responsibility to mobilise resources within the company or site. (ICH Q10 based in part on ISO 9000:2005)

State of Control:

A condition in which the set of controls consistently provides assurance of continued process performance and product quality. (ICH Q10)