Center for Biologics Evaluation and Research
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For information regarding animal feeds and animal drugs:
U.S. Food and Drug Administration
Center for Veterinary Medicine
HFV-200, 7500 Standish Place
Rockville, MD 20855
Ph. # (301) 827-6652; Fax # (301) 827-1484
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For consultation on issues related to human food:
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Center for Food Safety and Applied Nutrition
HFS-013, 5100 Paint Branch Parkway
College Park, MD 20740-3835
Ph # (301) 436-1715; Fax # (301) 436-2637
www.cfsan.fda.gov

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5600 Fishers Lane
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For information regarding medical devices:
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European Medicines Agency
Evaluation of Medicines for Human Use

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CHMP/BWP
(COMMITTEE ABBREVIATION)

GUIDELINE ON THE QUALITY OF BIOLOGICAL ACTIVE SUBSTANCES PRODUCED BY STABLE TRANSGENE EXPRESSION IN HIGHER PLANTS

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GUIDELINE ON THE QUALITY OF BIOLOGICAL ACTIVE SUBSTANCES PRODUCED BY STABLE TRANSGENE EXPRESSION IN HIGHER PLANTS

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EXECUTIVE SUMMARY

Transgenic plant technology has emerged as a possible complement to the longer-established range of prokaryotic, yeast and mammalian cell-based recombinant protein production systems. In this document guidance is provided on the approaches which should be employed in order to achieve satisfactory quality for biological active substances proposed to be produced using the new technology.

1. INTRODUCTION

The principal aim of this guideline is to adapt aspects of the quality guidance already in place for other production systems to the special case of transgenic higher plant-based systems.

As is the case with other biotechnologically produced active substances, both the production process and its control play important roles in defining the quality profile of transgenic plant produced active substances. An additional consideration for transgenic plants-based production is that, since experience with the technology is limited, applicants are advised to be appropriately vigilant when conducting the development studies.

Methods used to stably transform transgenic plant genomes include micro-particle bombardment, micro-injection, *Agrobacterium sp.* mediation (for nuclear genome transformations), and *Chlamydomonas sp.* mediation (for chloroplast genome transformations). Typical distinguishing features of plants include growth on soil or aqueous substrates, the presence of tough cell walls, and protein processing patterns (including glycosylation patterns) which differ from those of other eukaryotic species. These features obviously have potential to impact on the quality, safety and efficacy profiles of the active substances produced.

2. SCOPE

The quality issues (including adventitious agent safety evaluation considerations) affecting biological active substances[1] produced by the expression of one or more transgenes stably located in the nuclear or plastid genomes of higher plants (meaning those belonging to the Spermatophytae (Gymnospermae and Angiospermae) taxonomic group constitute the scope of this guideline. Production using transiently transfected plants and production using plant cell culture fall outside the scope.

The guidance offered applies primarily to active substances intended for parenteral administration. For substances intended for non-parenteral administration, although all aspects of the guidance offered may not be applicable, applicants for Marketing Authorisation are reminded that the same general principles apply.

3. LEGAL BASIS AND CONSIDERATIONS

This guideline should be read in conjunction with the introduction and general principles (4) and part I, module 3 of the Annex I to Directive 2001/83/EC as amended, and with all relevant EMEA Committee on Human Medicinal Products (CHMP) guidelines. Aspects of certain EMEA Herbal Medicinal Products Committee (HMPC) guidelines, although addressing a different a usage of plant species, may also find applicability.

Medicinal products containing biological active substances manufactured using transgenic higher plants fall within the scope of the Annex to Regulation (EC) No 726/2004[2] and may normally only be

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[1] As defined in Directive 2001/83/EC, as amended. The biological substances produced in transgenic plants are typically recombinant proteins or peptides.

[2] 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

placed on the market within the European Union if a marketing authorisation is granted in accordance with the Centralised Procedure as defined in this Regulation.

Containment/confinement measures applied to transgenic plant production systems are likely to function in the respective realms of medicinal product quality assurance (by protecting transgenic material from the environment) and environmental protection (by protecting the environment from transgenic plant material). Manufacturers responsible for cultivating or handling transgene-bearing plant tissue in the European Union need to comply with relevant Community Genetically Modified Organism and other environmental legislation, and in particular with Directive 2001/18/EC[3]. The measures in place should include those intended to prevent deliberate or accidental ingestion of transgenic plant parts by animals or human beings, either via direct consumption, or through inadvertent release into food or feed supply chains.

4. MAIN GUIDELINE TEXT

4.1 Development genetics

4.1.1 The host plant

Applicants should document the rationale for the choice of host plant for the genetic manipulation, taking into account attributes such as phenotype/genotype variation and stability, suitability for routine cultivation in manageable environments, susceptibility/resistance to infection with extraneous agents (for example, plant viruses/viroids, and fungi), and post-translational patterns for proteins.

The chosen host plant should be defined in terms of family name, genus, species, sub-species, cultivar/breeding line and common name, quoting the classifying authority. The host plant may itself be engineered to express specific traits and characteristics, such as modification of the plant glycosylation process, growth performance, or resistant features. In such cases, the development of the engineered host plant should be described in detail, and the chosen strategy should be explained.

Appropriate purification strategies should be developed, and a risk assessment should be presented, if the host plant is known to produce constituents potentially harmful to humans such as secondary metabolites (for example, pharmacologically-active alkaloids or glycosides).

4.1.2 The transgene and expression construct

The manufacturer should describe the origin of the nucleotide sequence coding for the protein. All subsequent modifications of the DNA sequence should be identified and described.

The method of transformation used to generate the initial transformant should be justified, and the assembly of the expression construct should be described in detail. When using micro-organism-mediated transformation, for example using *Agrobacterium sp.*, full documentation on the origin, history, and biological characteristics of the system should be provided. The description of the expression construct should include the source and function of the component parts, for example, origins of replication, selection marker or reporter genes, promoters, enhancers, and leader/targeting sequences. A detailed component map and a complete annotated sequence of the plasmid should be given, indicating those regions that have been sequenced during the construction and those taken from the literature. The nucleotide sequence of the coding region of the gene of interest and associated flanking regions that are inserted into the vector, up to and including the junctions of insertion, should be determined. Other expressed proteins encoded by the plasmid should be indicated. Genetic material other than the gene of interest that are introduced or altered to regulate or modify a specific trait of the host plant (for example, factors affecting expression or inhibition of glycosyltransferase, factors affecting dissemination) should be documented and explained.

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[3] 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

4.1.3 Generation of the primay transformant

The description of procedures and materials employed for the transformation event should be presented. The status of the genetic material incorporated, or modified, should be documented for the primary and/or final transformant, as appropriate. This documentation should include at least information on the desired sequences, number of loci and inserts, tandem repeat, inverted repeat, sequence of insert, flanking regions, junctions of insertions, residues of process materials remaining from the transformation process (for example, the fate of *Agrobacterium* infection).

4.1.4 Generation of the final transformants

Primary transformants produced by the transformation event are typically bred through a series of generations to produce final or production transformants. In the Marketing Authorisation Application these may be designated T0 (for primary transformant), T1, T2, T3 etc for successive generations, and Tp for the production transformant, or an alternative system of nomenclature may be used if the circumstances warrant it. The operations involved should be described in detail, including information on all manipulations, reagents and media used.

If an elite plant line is employed in the process, a justification should be provided, and complete details as for the main transgenic line should be provided. The crossing events should be described in detail, and the impact of the crossing event on the properties of the generated plant line determined and described.

4.1.5 Transgenic banking system

Where possible and unless otherwise justified, a banking system should be included in the batch-to-batch consistency assurance strategy. Depending on the production strategy, there may be a need to bank both the production strain and an elite line. The fundamental principles underlying banking systems for substrates and materials used in the production of biological medicinal products are outlined in CHMP guidelines, and should be taken into account by manufacturers of transgenic plant-derived active substances when designing their systems.

Manufacturers should therefore establish a master and working transgenic bank of plant material derived from the final transformant, capable of long-term storage and of providing consistent and sufficient starting material for a number of production runs which is sufficiently large to ensure long-term continuation of supply.

The generation, establishment and maintenance of both the master and the working transgenic banks should be defined and clearly described. The approach applied to characterising and testing the master transgenic bank and the working transgenic bank should take into account the guidance outlined in CHMP guidelines, with adaptation to the particular transgenic plant production system in question. The plant material used to establish the master transgenic bank should be thoroughly characterised genotypically and phenotypically. The characterisation of the material used to form the master transgenic bank should include a comparison of its botanical, horticultural, agricultural and phytochemical characteristics with its natural counterpart, with a view to identifying any emerging characteristics which might have significance for the production crop, such as gene silencing activity or pleiotropic effects resulting from the presence of the transgene, which might have consequences for the quality, and safety of the active substance.

This study should include an analysis of the transgene (for example, sequence(s), integrity, site(s) of insertion, copy number, and fates of marker sequences), its expression (tissue/organ specific, regulation, and expression level), plant gene silencing effects, over-expression of other proteins, ploidy, and karyology).

The stability behaviour of the banked material should be investigated and on the basis of the results the following should be defined:

- Specifications for container and closure systems.
- Storage conditions.

- Shelf-life.

4.1.6 Genetic stability

The genetic stability should be determined for the production system, from the primary transformant stage through to the crop at time of harvest. Data from successive crops should be included in the determination. A limit of plant age for the intended culture conditions should be defined. Genetic stability studies should be complemented with supportive data obtained from in-process controls during cultivation, and the results of control testing of the batches of the active substance. It is important to inter-relate these issues in Marketing Authorisation Applications.

4.2 Manufacturing issues

4.2.1 General manufacturing strategy

For all biological active substances, the production system and its control is one of the factors determining both the consistency of production and the quality of the material produced. In the case of production of active substances using transgenic higher plant technology, a clear strategy for implementing this principle should be proposed, and illustrated by means of a flow diagram.

Good production practice

The Master Transgenic Bank and the Working Transgenic Bank should normally be established and maintained under GMP conditions.

The production process of each batch of active substance should be considered to start with an aliquot taken from the working transgenic bank and to conclude with the testing and release of the batch.

Production processes employing transgenic plants can normally be divided into two distinct phases.

The first production phase is specific to transgenic plant technology and includes the cultivation, harvest and primary processing (for example screening, cleaning, sorting, macerating, transporting and/or storing) of the harvested material. Where classical GMP principles prove impractical to apply to elements of this phase, a suitable Quality System should be developed and put in place.

The heading used to describe the Quality System should include at least personnel, including qualifications and training, documentation including traceability, arrangements for audits and inspections, and information on whether the system is certificated by any official organisation. The development of the System may use as a starting point the basic principles outlined in the HMPC "Guideline on Good Agricultural and Collection Practice (GACP) for Starting Materials of Herbal Origin", though confirmation of compliance with the GACP Guideline, which is aimed at a different usage of plants, is not alone considered adequate for controlling transgenic plant-based production.

Ultimately, whether performed in accordance with GMP or with a defined quality system, the early steps of the manufacturing process should be well controlled by the application of suitable in-process controls, provide a well-defined starting material suitable for subsequent processing under GMP, and be well documented. The operations and the documentation should be available for inspection.

Production operations for the active substance downstream of primary processing (the second production phase) should normally be conducted according to GMP. The second phase, encompassing product isolation, purification, formulation, etc., is common to all biotechnology-derived products and the general requirements are documented in the relevant CHMP and GMP guidelines.

4.2.2 First production phase

Description of the site

- Geographical location, with boundaries exactly defined.

- The quality and nature of the growth substrate (typically soil, aqueous solution, or aqueous suspension), water supply and other raw materials (including fertilisers and pesticides) should be defined, and specifications should be set, where appropriate.
- The prevailing meteorological conditions, with seasonality and general variability should be documented. Extreme conditions for the locality should also be mentioned.
- Supervision of the site.
- Local flora and fauna.
- Cultivation of other genetically modified plants in the vicinity.
- The quality and/or good practice system in operation at the site.

Procedures for cultivation

- Propagation steps and techniques. Depending on the cultivation strategy, the number of generations should be clearly defined for each step with reference to the documented genetic stability of the process.
- Procedures for the detection and removal of undesirable plants and ingress of foreign genetic material, including pollen.
- Procedures for the detection and removal of pests.
- Procedures for monitoring the status of plant health, plus actions to be taken in case of disease.
- In-process monitoring of production consistency. The critical parameters for cultivation should be defined and justified, and are likely to include:
- Planting technique and location, taking into account environmental conditions including seasonality and nature of neighbouring flora.
- The nature of the soil substrate (including potential radioactivity).
- Plant hormone and fertiliser application.
- Pesticide application, including the use of chemical and biological agents.
- Potential for genotype proliferation arising from sexual reproductive techniques.

Harvesting and primary processing

- Criteria for initiation of harvesting.
- Harvesting technique including techniques to prevent contamination with rodents, birds and carcasses.
- Procedures and validation of the immediate manipulation of biomass once harvested, including transport and storage arrangements, and mechanical, physical, chemical and biological treatments applied.
- Conditions and duration of storage of isolated primary-processed material

The definition of a batch of post-harvesting material, active substance and final product should be provided, and the arrangements for the traceability of each batch back to the original unit of the Working Transgenic Bank should be described. Provisions for pooling of harvest or any other intermediate should be defined, and where appropriate, specifications should be set.

4.2.3 Second production phase (downstream processing)

As is the case with biotechnology-derived medicinal products generally, the methods used to purify the product and their in-process controls including their specifications should be described in detail, justified and validated. Considering the specificities inherent to plant cultivation, particular attention should be placed on the demonstration of the robustness of the production processes.

Potential impurities or contaminants derived from the plant and the production process (for example, host-cell proteins, DNA, plant metabolites, herbicide, fertiliser, and mycotoxins) should be evaluated. Care should be taken to document host proteins homologous to the required product, contaminants which may co-purify with the desired material, and any elements with potential to raise safety concerns (including hypersensitivity reactions).

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 Draft
Supporting documentation

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Subject: **Questions and Answers - Vol 1**

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Table of Contents

1 Introduction

This Questions and Answers document (Q&A) refers to the current working procedure of the ICH Q-IWG on implementing the guidelines of Q8, Q9 and Q10 which have been approved by the ICH Steering committee.

References

ICH Q8	Pharmaceutical Development	approved Nov. 10 2006
ICH Q8(R1)	Pharmaceutical Development - Annex	approved Nov. 13 2008
ICH Q9	Quality Risk Management	approved Nov. 09 2006
ICH Q10	Pharmaceutical Quality Systems	approved Jun. 04 2008

2 Knowledge Management

Q01: How has the implementation of ICH Q8, Q9, and Q10 changed the significance and use of knowledge management?

Q10 defines knowledge management as: 'Systematic approach to acquiring, analyzing, storing, and disseminating information related to products, manufacturing processes and components'.

Knowledge Management is not a new concept. It is always important regardless of the development approach. Q10 highlights knowledge management because it is expected that more complex information (e.g. QbD, real time data generation and monitoring systems) will need to be better captured, managed and shared.

In conjunction with Quality Risk Management, Knowledge Management can facilitate the use of concepts such as prior knowledge, development of design space, control strategy, technology transfer, and continual improvement across the product life cycle.

Q02: Does Q10 suggest an ideal way to manage knowledge?

No. Q10 does not explain how to implement knowledge management. Each company decides how to implement knowledge management, including the depth and extent of information assessment.

Q03: What are potential sources of information for Knowledge Management?

Q10 includes some examples of knowledge sources [see ICH Q10, section 1.6.1]:

- Prior knowledge
- Pharmaceutical development studies
- Technology transfer activities
- Process validation studies
- Manufacturing experience
- Innovation
- Continual improvement
- Change management activities.

Additional examples of potential sources of knowledge are

- Stability reports
- Product Quality Reviews/Annual Product Reviews
- Complaint Reports
- Adverse event reports (Patient safety)
- Deviation Reports, Recall Information
- CAPA reports
- Suppliers and Contractors
- Product history of manufacturing history
- Ongoing manufacturing processes information (e.g. trends)

Information from the above can be shared across a site or company, between companies and suppliers /contractors, products and across different disciplines (e.g. development, manufacturing, engineering, quality units).

Q04: Is an IT system required for the implementation of knowledge management with respect to ICH Q8, Q9 and Q10?

No, but IT systems can be helpful in capturing, managing and sharing complex data and information.

Q05: Will regulatory agencies expect to see a formal knowledge management approach?

No. There is no GMP requirement for a formal knowledge management system. However inspectors will expect to see that knowledge from different processes and systems has been appropriately utilised.

3 Quality by Design topics

Q01: Is it always necessary to have a Design Space, RTR testing and CS to implement QbD?

Under Quality by Design, establishing a design space or using real time release testing is not necessarily expected [ICH Q8R, step 4]. However, a control strategy is always expected regardless of the development approach, minimal or enhanced. A control strategy needs to be based on product and process understanding together with risk assessment.

3.1 Design Space

Q01: Does a set of proven acceptable ranges alone constitute a design space?

No, a combination of proven acceptable ranges (PARs) does not constitute a design space [Q8(R1), chapter 2.4.5.]. Proven acceptable ranges continue to be acceptable from the regulatory perspective but are not considered a design space [see ICH Q8(R1) section 2.4.5]. The applicant may elect to use proven acceptable ranges or design space for different aspects of the manufacturing process.

Proven acceptable ranges may lack an understanding of interactions between the process parameters and/or material attributes. PARs are often determined by one variable at a time experimentation while keeping other parameters constant, which does not reveal relationships between parameters.

Q02: Is it necessary to study multivariate interactions of all parameters to develop a design space?

No, the applicant will need to justify the choice of parameters for multivariate experimentation based on risk assessment and desired operational flexibility.

Q03: Can a design space be applicable to scale-up?

Yes, [additional details see Q8(R1) section 2.4.4]. An example is provided in the EFPIA Mock P2 document [*EFPIA Mock P2 submission on "Exemplain"*: Chris Potter*, Rafael Beerbohm, Alastair Coupe, Fritz Erni, Gerd Fischer, Staffan Folestad, Gordon Muirhead, Stephan Roenninger, Alistair Swanson, **A guide to EFPIA's "Mock P.2" Document**, Pharm. Tech. (Europe), *18*, **December 2006**, 39-44].

Q04: Can a design space be applicable to a site change?

It is possible to justify a site independent design space based on a demonstrated understanding of the robustness of the process and an in depth consideration of site specific factors, e.g. utilities, manufacturing environment, and equipment. There are region specific regulatory requirements associated with site changes that need to be followed.

Q05: Can a design space be developed for single and/or multiple unit operations?

Yes, it is possible to develop a design space for single unit operations or across a series of unit operations [see Q8(R1) section 2.4.3].

Q06: Is there a regulatory expectation to develop a design space for an existing product?

No, development of design space for existing products is not necessary unless the applicant desires to achieve a higher degree of manufacturing flexibility.

Q07: Is it possible to develop a design space for existing products?

Yes, it is possible. Manufacturing data and process knowledge can be used to support a design space for existing products. Relevant information should be utilised from e.g. commercial scale manufacturing, process improvement, CAPA and existing development data.

Typically, manufacturing operations run under narrow operational ranges in fixed equipment. Consequently, an expanded region of operation and an understanding of multi-parameter interactions may not be achievable from existing manufacturing data alone.

3.2 Real Time Release Testing

Q01: What is the difference between "real time release" and real time release testing?

The definition of real time release testing in Q8R, step 4 is 'the ability to evaluate and ensure the acceptable quality of in-process and/or final product based on process data, which typically includes a valid combination of measured material attributes and process controls.'

"Real time release" encompasses real time release testing as described above plus the quality release decision, including GMP requirements

Q02: How is batch release affected by employing real time release testing?

Batch release is the final decision to release the product to the market regardless whether RTR testing or end product testing is employed. End product testing involves performance of specific analytical procedures on a defined sample size of the final product after completion of all processing for a given batch of that product. Batch release involves an independent review of batch conformance to predefined criteria through review of testing results and manufacturing records.

Q03: Does real time release testing mean elimination of end product testing?

Real time release testing does not necessarily eliminate end product testing. For example, an applicant may propose RTR testing for some attributes only and not all. If all CQA's are addressed by in-process monitoring of parameters and/or testing of materials, then end product testing might not be needed for batch release. In addition, some product testing will be expected for certain regulatory processes such as stability studies and/or importation testing.

Q04: Is a product specification still necessary in the case of RTR testing?

Yes, product specifications [see ICH Q6a and Q6b] still need to be established and met, if tested.

Q05: When using RTR testing, is there a need for additional stability test methods?

Analytical procedures for monitoring stability need to be developed, even where RTR testing is employed [see ICH Q1a and ICH Q5c].

Q06: What is the relationship between Control Strategy and RTR testing?

RTR testing, if utilized, is an element of the Control Strategy in which tests and/or monitoring can be performed on-line rather than on the end product.

Q07: Do traditional sampling approaches apply to RTR testing?

Traditionally sampling plans for in process and end product testing involve a discrete sample size that represents the minimal sampling expectations. Generally, the use of RTR testing will include more extensive on-line/in-line measurement and an adapted sampling approach should be developed and justified.

Q08: What approaches can be taken in the event of on-line testing or on-line monitoring equipment breakdown?

As in the case of a minimal drug development approach, equipment breakdown needs to be managed in the context of a deviation under GMP. The control strategy provided in the application should include a proposal for use of alternative testing approach in the case of testing equipment failure. The alternative approach could involve use of end product testing, while maintaining an acceptable level of quality assurance, until the equipment is brought back in operation.

Q09: If RTR testing results fail or trending toward failure can end product testing be used to release the batch?

No, in principle the RTR testing results should be routinely used for the batch release decisions and not be substituted by end product testing. Any failure should be investigated. However, batch release decisions will need to be made based on the results of the investigations. In the case of failure of the testing equipment please refer to the previous question.

3.3 Control Strategy

Refer to the definition of control strategy provided in the ICH Q10 glossary:

Q10 Control Strategy definition –
'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.'

Q01: What is the difference in a control strategy for products developed using the minimal approach vs. 'quality-by-design' approach?

Control strategies are expected irrespective of the development approach. Control strategy includes different types of control proposed by the applicant to assure compliance with specifications, such as in-process testing and end product testing. For products developed following the minimal approach, the control strategy is derived empirically and typically relies more on discrete sampling and end product testing. Under QbD, the control strategy is derived using a systematic science and risk-based approach. Testing, monitoring or controlling is often shifted earlier into the process and conducted on- or at-line. Some traditional tests may not be necessary based on demonstrated process knowledge, process control and robustness.

Q02: Are GMP requirements different for batch release under QbD?

No, The same GMP requirements apply for batch release under minimal and QbD approaches.

Q03: What is the relationship between a Design Space and a Control Strategy?

If a Design Space is developed and approved for a QbD approach, the control strategy (e.g. facility, operating condition and monitoring) also ensures that the manufacturing process is maintained within the boundaries described by the Design Space.