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

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Comments received on the 'Points to Consider on quality aspects on medicinal products containing active substances produced by stable transgene expression in Higher Plants (CPMP/BWP/764/02)' released for consultation on April 2002 have been taken into account in the preparation of this guideline, which replaces the Points to Consider document.

Comments should be provided using this template to alexis.nolte@emea.europa.eu (Fax +44 20 7418 8545)

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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 new route to producing pharmacologically active proteins. The special characteristics of higher plants and of transgenic higher plant-based production are identified in this document, and guidance is provided on the approaches which should be employed in order to achieve satisfactory quality for the active substances produced. The emphasis is on guidance specific to the transgenic plants field.

Since the technology is an emerging one, there has not been much experience with its application, and detailed guidance is difficult to produce in certain areas, including in particular the following:

- Standardisation of the special terms which should be used.
- Transgenic banking system.
- In-process monitoring and controls applicable to the cultivation and primary processing phase of production.
- Quality and good practice systems applicable to the cultivation and primary processing phase of production.

As a result these areas are identified as boxed text in this draft as issues on which comment is especially invited.

1. INTRODUCTION

As an approach to producing recombinant proteins, the use of transgenic plants has emerged as a possible complement to the longer-established range of prokaryotic, yeast and mammalian cell-based systems. However, certain transgenic plant-specific considerations need to be taken into account. For example, protein-processing patterns in plants, including glycosylation mechanisms, differ in certain significant respects from those found in other eukaryotic systems, and may lead to differences in the quality attributes of the product, which in turn may impact on the safety and efficacy profile, including the immnnogenicity of the active substance produced. For instance, plant N-linked glycans do not have terminal sialic acid residues, plants do not phosphorylate high-mannose glycans, and many complex plant glycans contain either fucose or xylose residues with linkages that do not occur in humans.

As is the case with all biotechnologically produced active substances, both the production process and its control are critical in defining the quality profile of transgenic-plant produced active substances. In addition, since experience with transgenic plant production is limited, applicants are advised to be appropriately vigilant when performing the development studies.

2. SCOPE

The quality issues, including biological safety, affecting biological active substances[5] produced by the expression of one or more transgenes stably located in the genomes of higher plants constitute the scope of this guideline. For the purpose of this document, a higher plant is one which belongs to the taxonomic group Spermatophytae (Gymnospermae and Angiospermae). Production using transiently transfected plants and production using plant cell culture fall outside the scope of this guideline.

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

The guideline applies primarily to transgenic plant-derived substances intended for parenteral administration. For substances intended for non-parenteral administration, although all aspects of the guidance may not be applicable, the same fundamental principles apply.

Applicants should consider this guideline in conjunction with other relevant guidelines, including in particular guidelines addressing biotechnological medicinal products.

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.

Medicinal products containing biological active substances manufactured using transgenic higher plants fall within the scope of the Annex to Regulation (EC) No 726/2004[6] and may only be 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 measures applied to transgenic plant production systems are likely to function in the respective realms of medicinal product quality maintenance (by protecting transgenic material from the environment) and environmental protection (by protecting the environment from transgenic material). Manufacturers responsible for cultivating or handling transgene-bearing plant tissue in the European Union need to comply with relevant Community GMO and other environmental legislation, an in particular with Directive 2001/18/EC[7]. 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

In view of the diversity in manufacturing strategies, interested parties are encouraged to comment on special plant biology terms used in this guideline in order to standardise the plant propagation-specific terminology used.

4.1.1 The host plant

Applicants should document the rationale for the choice of host plant for the genetic manipulation, taking into account issues such as phenotype/genotype variation and stability, suitability for routine cultivation in manageable environments, susceptibility to infection with extraneous agents (e.g. plant viruses/viroids, fungi), protein processing patterns and any others of relevance.

The chosen 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.

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[6] 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

[7] 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

A risk assessment should be presented if the host plant is known to produce constituents potentially harmful to humans such as secondary metabolites (e.g. certain 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. This should include the identification and source of the cell from which the nucleotide sequence was originally obtained. All subsequent modifications/optimisations of the DNA sequence should be identified and described. Methods used to prepare the DNA coding for the protein should be described.

The suitability of the vector system should be established, and the assembly of the expression construct into the vector should be described in detail. For biological vectors (e.g. *Agrobacterium* spp. or viral vectors) full documentation on the origin, history, and biological characteristics should be provided. The description of the expression construct should include the source and function of the component parts, e.g. origins of replication, selection marker or reporter genes, promoters, enhancers, 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 (e.g. factors affecting expression or inhibition of glycosyltransferase, factors affecting dissemination) should be documented and explained.

4.1.3 Generation of the initial transformant

The description of procedures and materials employed for the transformation should be presented. The status of the genetic material incorporated or modified should be documented for the initial 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 (e.g. the fate of *Agrobacterium sp.* infection).

4.1.4 Stabilisation of the final transformants

The initial transformant is the cell or the plant derived from the manipulation which inserted the gene of interest. Intial transformants are typically subject to a series of operations such as screenings and selections to yield the final transformant. These operations need to be described in detail, including information on all manipulations, reagents and media used. Some manufacturing strategies may involve crossing with an elite plant line to obtain the final transformant. Elite plant lines may be non-transformed or transformed plant lines. They are selected for their agricultural performance and are crossed with the transgenic plant to obtain the final transformant. When elite plant lines are used in the manufacturing strategy, the choice of the plant line should be justified, and complete documentation including botanical, horticultural, agricultural and phytochemical characteristics of the elite plant line should be included in the application.

The final transformant is normally a distinct, homogenous and stable group of plants possessing the desired characteristics required for routine culture and harvest.

4.1.5 Transgenic banking system

The establishment of an appropriate transgenic banking system is critical for ensuring consistent production using transgenic plants. However, in view of the diversity of plant tissue and organ types,

and of plant-based production systems, it was considered that it is difficult to provide more specific guidance in this area at the present time. Interested parties are encouraged to comment on this section and to describe adequate banking systems so as to establish the current state-of-the-art.

Manufacture should begin with a well-characterised homogeneous and stable transgenic plant material from which consistent production of the harvest and active substance can be demonstrated. Consequently, manufacturers should 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 large number of production runs. The generation of both the master and the working transgenic banks should be defined and clearly described.

The approach applied to characterising and resting the master transgenic bank and the working transgenic bank should take into account the principles defined in CHMP-adopted guidelines, including ICH Q6B, with adaptation to the transgenic plant situation. 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 pleotropic 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 (e.g. sequence(s), integrity, site(s) of insertion, copy number, fates of marker sequences), its expression (tissue/organ specific, regulation, expression level), plant gene silencing effects, over-expression of other proteins, ploidy, 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.

Some manufacturing strategies may employ crossing of the transgenic plant with a plant line to establish production plant material directly or via intermediate generations. In such situation, this plant line should be well characterised, appropriate controls and specifications should be established, and it should be maintained using an appropriate banking system, similar to the system used for the transgenic plant.

4.1.6 Genetic stability

The design of the genetic stability studies should follow a global strategy, which takes into account relevant parameters characterising the expression construct and the plant, with genotypic and phenotypic markers being monitored at different levels from establishment of the expression construct up to, or beyond, the limit of normal production conditions. In this respect, the parameters controlling the end of production should be specified, and a limit of plant age for the intended culture conditions should be defined. Genetic stability studies may be complemented with supportive data obtained from in-process controls during culture, and controls of the active substance.

4.2 Manufacturing issues

4.2.1 General manufacturing strategy

The manufacturing process of each batch of active substance starts with the working transgenic bank and concludes with the testing and release of the batch. The process can be divided into two distinct phases.

The first production phase is specific to transgenic technologies and includes the cultivation, harvest and primary processing (for example screening, cleaning, sorting, transporting and storing) of the harvested material. The second phase, encompassing product isolation, purification, formulation, etc., is common to all biotechnology-derived products and the general requirements are well documented in the relevant guidelines.

For the first phase of the production process, a justified a quality system and/or good practice system should be defined and fully described. The recommendations of the respective WHO and HMPC guidelines on Good Agricultural and Collection Practices (GACP)[8] should be taken into account when defining the system, though it needs to be borne in mind that neither of these guidelines constitutes a quality system. However, the establishment, control and maintenance of the transgenic bank(s) should normally be conducted under GMP conditions.

Ultimately, whether performed to GMP or an alternative Quality system, the early steps of the manufacturing process should be well controlled and provide a well-defined starting material suitable for subsequent processing under GMP. Additional product specific controls during growth, harvesting and primary processing should also be considered in addition to the proposed Quality system.

Details on both the Quality system and product specific controls should be included in the Marketing Authorisation Application, along with a description of the growth, harvesting and primary processing of the plant material, and a clear set of specifications of the plant raw material and its extract, if appropriate. All operations involved, and the quality system, need to be available for regular pharmaceutical inspection.

The establishment of an appropriate in-house Quality system for the first phase of the process when GMP cannot be applied is critical for ensuring consistent production using transgenic plants. It was considered that it is difficult to provide more specific guidance in this area at the present time. Interested parties are encouraged to comment on this section so as to establish the current state-of-the-art.

4.2.2 Cultivation, harvest and primary processing

The choice of adequate cultivation, harvest and primary processing procedures as well as adequate in-process monitoring control measures is critical for ensuring consistent production using transgenic plants. It is considered that more specific guidance would be helpful in this area. In view of the non-pharmaceutical nature of these steps in the manufacturing process, interested parties are encouraged to comment on this section of the guideline so as to establish the current state-of-the-art.

The production process for the active substance starts with the expansion/propagation of an aliquot of the working transgenic bank. With reference to a flow diagram for the manufacturing process, the operations for cultivation, harvesting and immediate post-harvesting primary processing should be

[8] Public Statement on Good Agricultural and Collection Practice for starting materials of Herbal Origin (EMEA/HMPC/246816/05) and WHO guidelines on good agricultural and collection practices (GACP) for medicinal plants.

described in detail. The descriptions, and validation where appropriate, should reflect the essentially pharmaceutical nature of operations and address at least the following process variables.

Site(s) of cultivation and quality of raw materials

- 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 at the site.
- Local flora and fauna.
- Cultivation of other genetically modified plants in the vicinity.
- Equipment used.
- Qualifications of, and training for, personnel involved in crop monitoring, cultivation, and control.

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: (i) planting technique and location, taking into account environmental conditions including seasonality and nature of neighbouring flora, (ii) soil type and radioactivity, (iii) plant hormone and fertiliser application, (iv) pesticide application, including the use of chemical and biological agents, (v) potential for genotype proliferation arising from sexual reproductive techniques.

Harvesting, primary post-harvesting processing and storage

- 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 Downstream processing

As for all biotechnology-derived products, the methods used to purify the product and their in-process controls including their specification limits 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 process in relation to an appropriately defined quality of materials entering into the purification process.

Potential impurities or contaminants derived from the plant and the production process (e.g. host-cell proteins, DNA, plant metabolites, herbicide, fertiliser, 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 element that may raise safety concerns (including hypersensitivity). It is acknowledged that it may not be possible to identify and control all impurities/contaminants individually. Nevertheless, appropriate quality indicators should be selected and their choice should be justified.

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 guidelines (i.e. ICH Q6B Specifications) and relevant technical publications. Characterisation studies should include a comparison of the product 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 the determination of physicochemical properties, biological activity, immunochemical properties, purity and impurities. If there is an inherent degree of structural heterogeneity, in part due to post-translationally modified forms, the applicant should define the pattern of heterogeneity of the active substance. 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 glycosylation pattern, 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 (e.g. 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 motifs 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 process related impurities and contaminants coming from the host plant, the process itself or the environment. The following parameters should be considered for impurities from the host plant: (i) plant proteins other than the transgene-expressed protein (e.g. 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

As for any biotechnology-derived product, 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 criteria should be established and justified based on 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.

The setting of specifications is part of an overall control strategy which includes control of raw materials and excipients, in-process testing, process evaluation or validation, adherence to Good Manufacturing Practices, stability testing, and testing for consistency of lots. In addition, considering the specificities of plant-based production, this control strategy also comprises control of materials used during culture, control of culture environment, testing before and after harvesting, adherence to appropriate culturing practice. When combined in total, these elements provide assurance that the appropriate quality of the product will be maintained. Since specifications are chosen to confirm the quality rather than to characterize the product, the manufacturer should provide the rationale and justification for including and/or excluding testing for specific quality attributes.

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 ensure the absence of infestation of plant tissue with various unicellular and metazoan organisms which are potential 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 dependendent 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 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 CHMP animal TSE guideline on minimising the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products[9] should be identified, and compliance with the requirements of the guideline should be demonstrated.

[9] EMEA/410/01

DEFINITIONS

Definitions are provided for the purpose of this document.

Higher plant: plant which belongs 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 obtained from viral, bacterial or mammalian sources.

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

Final 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):

- Public Statement on Good Agricultural and Collection Practice for starting materials of Herbal Origin (EMEA/HMPC/246816/05).

- 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).