

**This document can be downloaded from the Internet:**

**<http://www.rikilt.wageningen-ur.nl/nutraceuticals>**

# **Exploitation and regulation of plants genetically modified to express nutraceuticals and pharmaceuticals**

Gijs A. Kleter<sup>1</sup>, Wim M. van der Krieken<sup>2</sup>, Esther J. Kok<sup>1</sup> and Luud J.W.J. Gilissen<sup>2</sup>

<sup>1</sup> State Institute for Quality Control of Agricultural Products (RIKILT)  
Bornsesteeg 45, Wageningen, The Netherlands  
P.O.Box 230, NL- 6700 AE Wageningen, The Netherlands

<sup>2</sup> Plant Research International  
Droevendaalsesteeg 1, Wageningen, The Netherlands  
P.O.Box 16, NL-6700 AA Wageningen, The Netherlands

Exploitation and regulation of plants genetically modified to express nutraceuticals and pharmaceuticals

<http://www.rikilt.wageningen-ur.nl/nutraceuticals>

Copyright 2001, Wageningen University and Research Centre (Wageningen-UR)  
Reproduction or utilisation of (parts of) this report is permitted only with clear reference to this report.

Sound-board Committee:

Wilco J.R.M. Jordi (project co-ordinator) – Plant Research International

Dirk (H.) J. Bosch – Plant Research International

Ivo J.T.M. Claassen – ID-Lelystad

Hoc L. Oei – ID-Lelystad

First edition, September 2001 (Plant Research International, note 124)

Revised edition, December 2001

### **DISCLAIMER**

This document merely represents the interpretation by its authors of the current legislation and opportunities for products derived from plant biotechnology. It merely serves the purpose of information. No rights or damage can therefore be claimed related to this document.

## Contents

<i>Item</i>	<i>Page</i>
Executive Summary	7
1. Introduction	9
1.1. Pharmaceuticals and nutraceuticals: current developments	9
1.2. About the report	9
2. Definitions and descriptions	11
2.1. General	11
2.2. Nutraceuticals, functional foods and functional food crops	11
2.2.1. Definitions	11
2.2.2. Production	13
2.2.3. Health claims	14
2.3. Pharmaceuticals and medicinal plants	14
2.3.1. Definitions	14
2.3.2. Production	14
3. Regulations and Registrations	17
3.1. General	17
3.2. Cultivation and import of genetically modified crops and –crop products	18
3.2.1. Field trials	18
3.2.2. Commercial cultivation	19
3.2.3. Import of genetically modified crops or crop products	19
3.2.4. Contained use	21
3.3. Food uses	21
3.3.1. Food, food ingredients, and food additives	21
3.3.2. Food for special uses	24
3.3.3. Food supplements	25
3.3.4. Health claims	26
3.4. Feed uses	30
3.4.1. Feed and feed ingredients	30
3.4.2. Feed additives	31
3.4.3. Feed for special uses	31
3.5. Medicinal uses	31
3.5.1. Human medicines	31
3.5.2. Veterinary medicines	34
3.5.3. Health economics	35
3.6. Production Chain (GMP and similar conditions)	36
3.6.1. Foods and food ingredients	36
3.6.2. Food supplements	36
3.6.3. Animal feeds	37
3.6.4. Human and veterinary medicines	37
3.7. Patentability of the new product	38
3.7.1. Patenting GM plants	39

4. Biosafety considerations of transgenic medicinal plants and functional food crops	41
4.1. Case-by-case	41
4.2. Crop type	41
4.3. Transgene and transgene product	41
4.4. Handling during culture and harvest	42
4.5. Residues	42
5. Blueprint of a greenhouse	43
5.1. General	43
5.2. Legislation for production in greenhouses	43
5.2.1. Legislation in the EU	43
5.2.2. Legislation in the USA	44
5.2.3. Legislation in The Netherlands	44
5.3. Greenhouse requirements and GAP	44
5.3.1. Seeds and propagation material	45
5.3.2. Cultivation	45
5.3.3. Harvest	45
5.3.4. Primary processing	45
5.3.5. Packaging	46
5.3.6. Storage and transport	46
5.3.7. Equipment	46
5.3.8. Personnel and facilities	46
5.3.9. Documentation	46
5.3.10. Education	47
5.3.11. Quality assurance	47
5.4. Implementation of the Dutch regulations on greenhouse requirements	47
5.4.1. PK-I greenhouse	48
5.4.2. PK-II greenhouse	48
5.4.3. PK-III greenhouse	48
5.5. Conclusions for greenhouse facilities	49
6. Case: Crop plants producing rFSH	51
6.1. Purposes	51
6.2. Cultivation	52
6.3. Application for medicinal use	52
7. General conclusions	55
7.1. Definitions	55
7.2. Biosafety considerations	55
7.3. Regulatory options	55
7.4. Options for contained culture	57
7.5. Conclusions on the case: Crop producing recombinant FSH	57
References	61

**Tables**

Table 1	Applications envisioned for a functional food, nutraceutical, or pharmaceutical in the EU and the USA	18
Table 2	Facilities related to different levels of containment.	50
Table 3	Recombinant FSH and gonadotropin approved for medicinal use	53
Table 4	Approvals for the use of non recombinant FSH and gonadotropin as human and veterinary medicine	53

**Figures**

Figure 1	Procedure for market approval of a genetically modified crop under EU Directive 90/220	20
Figure 2	Procedure for market approval of Novel Food under EU Regulation 258/97	23

Exploitation and regulation of plants genetically modified to express nutraceuticals and pharmaceuticals  
<http://www.rikilt.wageningen-ur.nl/nutraceuticals>

## Executive summary

Plants may serve as new hosts for the production of recombinant nutraceuticals and pharmaceuticals. Nutraceuticals and pharmaceuticals can be distinguished at best on the basis of their aim.

Nutraceuticals on the one hand aim to maintain the health situation of principally healthy humans or animals. They are single compounds that are naturally present in, or (purified) added to foods for daily consumption. Such foods are called 'functional foods' (and in the case of animal application: 'functional feed'). They can be supplied with a health claim.

Pharmaceuticals on the other hand aim to cure (human, animal) patients, to mitigate, or to serve in diagnostics. They are purified, well defined medicinal and/or therapeutic preparations that have passed the clinical tests and that are supplied with a medicinal claim.

Plants, transgenically producing nutraceuticals or pharmaceuticals, should meet the general requirements for genetically modified organisms, and, additionally, the specific requirements related to the production of the specific medicinal or health compounds. To guarantee safety, to properly regulate the production processes, and for the sake of consumers trust, in the EU and USA, an extensive variety of (often region-specific) guidelines and regulations encircle both categories of activities, the GM technology, and the production of health foods and medicinal articles:

- ?? For the cultivation, import, marketing and animal feeding of a genetically modified crop approval must be sought from the EU. A distinction is made by Dutch legislation between the in-doors- and out-doors- cultivation of genetically modified plants. The in-doors cultivation, will require a less elaborate risk assessment than the out-doors cultivation.
- ?? Production of pharmaceuticals and nutraceuticals in GMOs in greenhouses is bound by special rules related to the transgenic status of the plants and should occur according to the guidelines for "good agricultural practice" (GAP). GAP guidelines apply to the production of all plant materials used in the food, feed, medicinal, flavoring and perfume industries. GAP conditions must also be met concerning processing of the harvested transgenic plant material. The type of greenhouse (PK-I, PK-II or PK-III) that needs to be used depends on the specific case and is related to the characteristics of the inserted gene, the biological and agronomic characteristics, and the treatments of the crop plant involved.
- ?? Food applications include whole foods and food ingredients on one side and food additives on the other side. Both categories are differently regulated. In the EU, genetically modified organisms are regulated as a specific category for use as novel foods or novel-food ingredients but not for use as food additives, colourants, or flavourings.

- ?? Foods that are considered safe can eventually be accommodated into foods for special dietary uses. Both in the EU and USA, these dietary foods are specifically regulated.
- ?? With regard to food supplements, the EU limits its scope to vitamins, minerals, and herbal extracts, whereas the scope of the American legislation is less narrow.
- ?? Different national regulations exist in the EU on the use of food-related health claims, as no EU-harmonisation has been reached yet. In The Netherlands, where health claims are voluntarily verified, three institutions are active in this field. In the USA, regulations on health claims are somewhat different for foods and food supplements.
- ?? Both for food-, feed-, and pharmaceutical- production, requirements have been formulated for “good manufacturing practices” (GMP) in The Netherlands and abroad.
- ?? With regard to the patenting of genetically modified plants, there are some restrictions, such as the exclusion of plant varieties from patentability.
- ?? Marketing approval of human and veterinary medicines will require a prior pre-clinical and clinical testing of the pharmaceutical to demonstrate its effectiveness and safety. In general, a “short-cut” approval procedure can be followed if a medicine is equivalent to a previously approved medicine. In the EU, however, biotechnology-derived pharmaceuticals will always have to go through the full procedure, contrary to the shorter procedures for some “bio-equivalent” medicines in the USA. Medicines are available either on prescription or “over the counter”.

A hypothetical case is discussed that serves as a model for crops that are enhanced with components of pharmaceutical interest, namely a crop expressing recombinant “follicle stimulating hormone” (FSH). Preparations containing FSH for human and veterinary use that are currently in the market are produced either from body fluids or from genetically modified hamster cells.

## **1. Introduction**

### **1.1 Nutraceuticals and pharmaceuticals: current developments**

During the last decade, many millions of hectares have been planted worldwide with transgenic crops. Over 90% of these crops provide transgenically the agronomic properties of herbicide and pest tolerance. Currently, a new phase in genetic modification is beginning. This phase can be considered the engineering of plants, not for the improvement of their agronomic properties, but to make new or improved products. This development enables farmers to produce higher-value products, for food and feed, for medical and for industrial objectives, and is expected to have a high economic impact. In this report we focus on the exploitation and regulatory aspects of the transgenic production of health foods and feeds, and pharmaceutical products.

Genetic modification of plants has provoked lots of discussions on safety. This has resulted in national and international regulations on field releases and market introductions. The production and marketing of medically related products has already been encircled by requirements and regulations for a longer time. Entering the new phase of engineering plants for health and medical purposes, there is a need for the evaluation and attunement of regulations and requirements from the GMO and the medical/health side along the entire production chain.

### **1.2. About the report**

Initially, there were discussions within the project group about the borders between health food and medicines. A grey area seemed to exist between the two fields of production and products, where both deal with the production of compounds that are physiologically active in human or animals. From these discussions it has been concluded to prepare in the report a separate chapter (Chapter 2) that is introductory to the next chapters. In this chapter definitions and descriptions are given of the terms 'pharmaceutical', 'nutraceutical', 'functional food', etc.

The regulatory aspects involved in the production of nutraceuticals and pharmaceuticals form the essential and most substantial part of the present report (Chapter 3). The current state has been elaborated and extensive comparisons have been presented about the relevant regulations in the EU and USA on GMOs on the one hand, and on pharmaceuticals for human and veterinary use, nutraceuticals and functional foods on the other hand. Where relevant, the specific Dutch situation is indicated. Further attention has been given to the manufacturing practice conditions throughout the production chain. Also the requirements for the use of health claims have been dealt with, and the issue of patentability has been treated. The hypothetical example of the production of recombinant FSH, given in Chapter 6, clearly indicates the regulatory issues that have to be considered.

Chapter 4 summarises biosafety considerations of transgenic plants producing functional foods, nutraceuticals, and pharmaceuticals.

Chapter 5 gives the details on the legal requirements for a greenhouse to be used for the production of pharmaceuticals, nutraceuticals and functional foods, including

Exploitation and regulation of plants genetically modified to express nutraceuticals and pharmaceuticals

<http://www.rikilt.wageningen-ur.nl/nutraceuticals>

guidelines for "good agricultural practice" and "good manufacturing practice" (GAP and GMP, respectively) and the required degrees of physical containments in different greenhouse applications.

Concluding and summarizing remarks are made and regulatory options are given in Chapter 7. The case-by-case approach to biosafety, containment aspects, post-market surveillance in the case of out-doors cultivation, and options for contained culture have been given attention. Also the two cases have been shortly evaluated in this last chapter.

## **2. Definitions and Descriptions**

### **2.1. General**

In common literature, nutraceuticals and pharmaceuticals are often mentioned in one breath. The reason is that these products have physiological activity in human and animals, and all are related to health in its broadest sense. Irrespective of their exact definition, nutraceuticals and pharmaceuticals can be distinguished at best on the basis of their direct aim: is the product a food, or is the product a medicine. Nutraceuticals aim at maintenance of the health situation of healthy individuals. Nutraceuticals add health promotion to the regular function of a foodstuff being a source of building material and energy. Nutraceuticals are available over the counter, e.g. in a supermarket, and can be consumed as part of the daily diet. Pharmaceuticals are produced to cure human or animal individuals, for mitigation or for diagnostics and are generally available from a doctor or veterinary surgeon. Some pharmaceutical products, especially those for mitigation and self-diagnostic purposes, are freely available.

The aims and controlled availability make the position in daily life of pharmaceuticals clear, in contrast to the position of nutraceuticals. Pharmaceuticals are medicinal preparations. Their effects and side-effects in human and animals must be known exactly from medical and veterinary trials. Nutraceuticals have primarily to be proven safe-to-eat; of many nutraceuticals, the beneficial activity as such has not been demonstrated unambiguously. For the purpose of this report, more elaborate definitions and descriptions on production and application of the various types of products are given below.

### **2.2. Nutraceuticals, functional foods and functional food crops**

#### **2.2.1. Definitions**

##### *Confusing terminologies*

There is a lot of terminology around nutraceuticals which may raise considerable confusion as will be shown in this paragraph. Synonymous to, or belonging to the same field of terminology of 'nutraceuticals' are 'functional foods', 'designer foods', 'positive nutrition', 'foods with dietary supplements', 'foods with functional ingredients', 'health food', 'dietary food', 'functional food ingredient', etc. Nutraceuticals are colloquially understood as a product that can be a single well-defined food compounds with health promoting characteristics, but also as complex foods with such beneficial characteristics. Nutraceuticals may be briefly and meaningless defined as 'nutritionally or medicinally enhanced foods' (Brower, 1998), whereas other authors give more extended descriptions. Anyway, the term 'nutraceutical' originates from DeFilice (1979), founder of the Foundation for Innovation in Medicine. He defined nutraceutical as: 'food, or part of food, that provide medical or health benefits, including the prevention and treatment of disease' (quoted in Brower, 1998). The first part of this definition relates to a complete (complex) food product or a single compound. The latter part makes a nutraceutical similar to a pharmaceutical. On the other hand, Schaafsma (1994) defines 'nutraceutical' (written as nutriceutical)

in a narrower sense as the specific purified or extracted food supplement, that is also available separately (encapsulated) from a drug store or a reform shop (over the counter). Examples are vitamins, minerals, unsaturated fatty acids, milk proteins, etc. Further he defines foods supplemented with specific nutraceuticals to meet a particular objective as ‘designer foods’, whereas ‘functional foods’ include all health promoting foods with ‘designer foods’ among them (Schaafsma, 1994). Different definitions distinguish between nutraceuticals, as food products that function as (and therefore substitute) pharmaceuticals, and functional foods, as foods with human health enhancing qualities (Bijman, 1999). The problem is that these terminologies and definitions blur the border between foods and medicines. Such situation should be prevented.

### *Defining nutraceuticals, functional foods, and pharmaceuticals*

For the purpose of clarity in the present report, we would suggest to limit the terminology to the following used by Health Canada as working definitions (Health Canada, 1998):

⚡⚡ A functional food is similar in appearance to, or may be, a conventional food, is consumed as part of a usual diet, and is demonstrated to have physiological benefits and/or reduce the risk of chronic disease beyond basic nutritional functions (Health Canada working definition)

⚡⚡ A nutraceutical is a product isolated or purified from foods that is generally sold in medicinal forms not usually associated with food and demonstrated to have a physiological benefit or provide protection against chronic disease (Health Canada working definition)

The definition for a functional food is very similar to that formulated by the EU funded Concerted Action on Functional Food Sciences in Europe (FUFOSE), namely “foods that have been satisfactorily demonstrated to affect beneficially one or more target functions of the body, beyond adequate nutritional effects, in a way which is relevant to either an improved state of health and well-being, or reduction of the risk to diseases”. The “adequate nutritional effects” are basic needs defined by the recommended daily intakes, e.g. for vitamins (Diplock et al., 1999; ILSI, 1998).

In addition to the definition for a functional food, “functional feed” and “functional crop” are used with similar meanings.

The Canadian working definition for a nutraceutical is similar to that of Schaafsma (1994). In this report, the definition for nutraceutical is used also for purified substances that are added to foods. The inclusion of a nutraceutical in a food may render it a functional food based on the health-beneficial properties of the nutraceutical.

These definitions will be used as “working definitions” throughout this report. It should be noted that they are not *legal* definitions themselves, and the products defined by these working definitions may fall under various legal definitions, depending on the scope of their application (see section 3.1).

### 2.2.2. Production

#### *Approaches*

A food can be made a functional food by using different approaches (FUFOSE, 1999):

- ?? to eliminate a component known to cause deleterious effects to the consumer (e.g. an allergenic protein),
- ?? to increase the concentration of a natural component in food,
- ?? to add a component which is not normally present in most foods, but for which beneficial effects have been demonstrated (e.g. non-vitamin anti-oxidants, or fructans),
- ?? to replace a component, usually a macronutrient, the intake of which is usually excessive (e.g. fats) by a component which has beneficial effects (e.g. oligosaccharides), and
- ?? to improve the bioavailability of, or to modify, food components for which beneficial effects have been demonstrated

#### *Role of genetic modification*

For several of the approaches given above, genetic modification can be used to improve a food crop directly into a functional food crop:

- ?? antisense technique for elimination of health-impairing proteins;
- ?? overexpression to increase the concentration of specific functional ingredients;
- ?? introduction of a new metabolic pathway or side chain;
- ?? blocking of a metabolic pathway.

#### *Interesting opportunities for nutraceuticals*

Compounds with health promoting properties that can be considered for inclusion into a nutraceutical or a functional food are, for example, flavonoids, carotenoids, unsaturated fatty acids, oligosaccharides, fibres, and minerals. Flavonoids may inhibit the development of cancer and arteriosclerosis. Carotenoids can scavenge toxic oxygen radicals and function as provitamins. Multiple unsaturated fatty acids may prevent heart and vascular diseases. Oligosaccharides and fibres can bind toxic compounds and may serve as food for, and this way improve the quantity and quality of, the intestinal flora. Oligosaccharides and fibres are poorly digestible and are therefore helpful in keeping the dietary energy low. In addition, health effects have been attributed to minerals, including the minerals calcium (bone development), selenium (as an anti-oxidant) and iron (to prevent anaemia) (Helsper, 1998). Increasingly, transgenic research in plants is directed to engineer the relevant metabolic pathways (Dixon & Arntzen, 1997; Hammond et al., 1999; Ohlrogge, 1999; Willmitzer, 1999; Schmidt-Dannert et al., 2000).

#### *The market*

Functional foods and nutraceuticals are becoming more and more popular with consumers who desire to influence their own health and well-being through their diet. On the other side, there are the food producing industries that experience new market niches for their products when they are upgraded to a functional food. The scientific

basis for the application of functional foods is much less clear than that of (recombinant) pharmaceuticals and (genetically modified) medicinal (food) plants. At present, for most existing functional foods adequate scientific bases for their health benefits are lacking.

### 2.2.3. Health claims

Nutraceuticals and functional foods both have, by definition, positive effects on consumers' health. The issue of health claims that are attached to these products is therefore important. The specific requirements for health claims are detailed in Section 3.3.4. In short, there is no law in The Netherlands on the use of health claims, but voluntary procedures have been installed by three institutions that are active in this field. Important in this respect is the weight of scientific evidence that can be provided in support of the health claim (Diplock et al., 1999).

In the EU, the concerted action FUF0SE has been established to assess critically the scientific base required

- ?? to provide evidence that specific nutrients positively affect target functions in the body;
- ?? to examine the available sciences from a function driven point of view rather than a product-driven one; and
- ?? to reach consensus on targeted modifications of food and food constituents, and options for their applications.

## 2.3. **Pharmaceuticals and medicinal plants**

### 2.3.1. Definitions

Pharmaceuticals are single, well-defined medicinal and therapeutic compounds that are administered with the purpose to cure, mitigate, or diagnose disease. Similar compounds for veterinary application are also categorized to pharmaceuticals. Medicinal plants are plants that produce pharmaceuticals naturally.

### 2.3.2. Production

Pharmaceuticals can be produced chemically, or biologically by micro-organisms, animal cell cultures, and plants. In these biological systems, the pharmaceutical can be a natural product, or can result from genetic modification. Plants are one of the new hosts that can serve for the production of recombinant pharmaceuticals. Biologically produced pharmaceuticals are often indicated as biopharmaceuticals (Miele, 1997). In this report we will use the term pharmaceuticals, referring only to the function of the compound and not to the (biological) way of production.

#### *Recombinant pharmaceuticals in crop plants*

Currently, the production of recombinant pharmaceuticals in crop plants includes especially proteinaceous compounds such as hormones, antibodies, plasma proteins, enzymes and vaccines. The production of oral vaccines with transgenic crop plants offers the advantage that the crop needs not be purified to be consumed as a vaccine, such as raw tomatoes and bananas. Such specialty crops enable to combine

experiences from the production of pharmaceuticals in microbial and animal cell production systems with experiences on the genetics and agricultural characteristics of the crop involved, including the typical biological and production characteristics. As for other genetically modified crops (such as those producing nutraceuticals), human and environmental safety during production must be assessed before such plants can be approved as specialty crops in agriculture (greenhouse or open field). Such assessment will show which concerns have practical relevance, and enables to set up strategies to deal with these concerns. Risk assessments on genetically modified crops in general, including pharmaceutical-producing plants, always need a case-by-case approach (see Chapter 4) using sound scientific and clinical judgement. For the large-scale agricultural production of recombinant pharmaceuticals, the choice of plant species, geographic location of test plots and production fields, the choice for production under contained greenhouse conditions, and monitoring protocols are essential to prevent adverse consequences (Miele, 1997; Hammond et al. 1999). The legal requirements that regulate such choice are given in the next chapter.

### *Purification*

With a qualified harvest of plant material (e.g. seeds), the challenge is to convert an agronomical commodity into a pharmaceutical, that is essentially identical to the same product from any other production system. This requires every step in the production process to be described as good manufacturing practice (GMP) (Section 3.6.4 and Chapter 5).

### *Recombinant nutraceuticals and pharmaceuticals*

Comparing recombinant nutraceuticals and pharmaceuticals produced in plants, the nutraceuticals are often products from the primary or secondary metabolism of the plant cell whereas pharmaceuticals may also consist of proteinaceous compounds directly resulting from an introduced single transgene. Metabolic pathway engineering in plants will in future enable to produce exotic and rare compounds at increased scales.

### *Medicinal plants*

Medicinal plants are known from a long history. Many plant species have been named according to some medical application such as 'Hepaticae' (liver mosses) as old medicine against liver diseases. And a common species name of many plants is 'officinalis' which refers to medical application. About one-third of medicines used today are derived from plants, with aspirin, morphine, artemisin and taxol as well-known examples.

Exploitation and regulation of plants genetically modified to express nutraceuticals and pharmaceuticals  
<http://www.rikilt.wageningen-ur.nl/nutraceuticals>

### 3. Regulations and Registrations

#### 3.1. General

The scope of this report covers the production of physiologically active compounds by genetically modified plants. Three possibilities are considered here for the novel product derived from genetically modified plants:

1. The product is a “functional food / feed / crop plant”; the product is used for food purposes (food, food ingredient, a dietary food) or animal feed purposes (feed, feed ingredient).
2. The product is a “nutraceutical”; the product is used for food purposes (food ingredient, food additive, food supplement) or animal feed purposes (feed ingredient, feed additive).
3. The product is a pharmaceutical and is used as a medicinal preparation.

For the various shapes that the novel product from a genetically modified plant may take within any of these possibilities, different regulations apply both in the EU and the USA. These regulations, which are detailed below, determine how dossiers should be prepared with regard to, for example, safety tests on- and manufacturing conditions of- the product. These dossiers are submitted to the competent authorities for review. Table 1 summarises the product opportunities that we describe for a functional food / feed / crop plant, nutraceutical, or pharmaceutical in the EU and the USA.

Throughout the text, references are made to EU-, Dutch-, and American- legislation. Most of these references can be retrieved through the Internet:

?? EU: [http://europa.eu.int/eur-lex/en/search\\_lif\\_simple.html](http://europa.eu.int/eur-lex/en/search_lif_simple.html).

?? Netherlands: <http://www.minvrom.nl/minvrom/pagina.html?id=1&goto=1489>.

?? USA: <http://www.fda.gov/opacom/laws/lawtoc.htm> and

<http://www.epa.gov/epahome/lawreg.htm>.

The Dutch legislation is discussed as far as there are relevant differences from EU legislation that would affect the envisioned applications of a novel product derived from a genetically modified plant.

The applications of functional foods, functional feed, and purified nutraceuticals that are possible within the EU-, and American- regulatory framework are summarised in Table 1.

**Table 1 Applications envisioned for a functional food, nutraceutical, or pharmaceutical in the EU and the USA**

	functional food / feed / crop plant		(purified) nutraceutical		pharmaceutical	
<i>Food uses</i>						
Food, whole	EU	USA				
Food ingredient	EU	USA	EU	USA		
Food additive <sup>1</sup>		USA	EU	USA		
Food supplement		USA	EU	USA		
Food for special uses	EU	USA				
<i>Feed uses</i>						
Feed & feed ingredient	EU	USA	EU	USA		
Feed additive <sup>1</sup>		USA	EU	USA		
<i>Medicinal uses</i>						
Medicine, human					EU	USA
Medicine, veterinary					EU	USA

<sup>1</sup> “additive” is defined differently in the EU and the USA

### 3.2. Cultivation and import of genetically modified crops and –crop products

Only cultivation in the EU is considered here.

#### 3.2.1. Field trials

##### *EU*

Permission shall be sought for field trials, for which a dossier will be forwarded to the national authority. Such a dossier contains, among others, data on environmental- and human-health- risks of the GM plant. This dossier is reviewed by the national authority, which keeps the European Commission informed about the application, as specified under Part B of EU Directive 90/220 on the environmental release of GMOs. EU Directives have to be implemented by EU Member States, including The Netherlands, but leaves room for national adaptations of these Directives.

##### *Netherlands*

The notifier of an application for the large-scale-experimental release of a genetically modified plant is required to compile a more elaborate dossier on its molecular characteristics and its safety to the environment and, if applicable, animals and/or humans similar to that under part C of EU Directive 90/220 (See section 3.2.2).

### 3.2.2. Commercial cultivation

For the commercial release of a genetically modified crop, permission at an EU level should be sought. The notifier is therefore required to supply details, among others, on the DNA insert, expression levels of transgenic proteins, composition of the transgenic plant, and safety of the transgene product, including data from field trials. Commercial releases are regulated by EU Directive 90/220, Part C, under which an application has to be submitted to a national authority and subsequently to the European Commission (Figure 1). A guidance document on dossier preparation has been issued by the Scientific Committee on Plants of the European Commission (SCP, 1998).

EU Directive 2001/18, which will replace EU Directive 90/220 in the year 2002, has recently been adopted. The amendments include, among others, the requirement for post-marketing monitoring, the compulsory labelling of the genetically modified products, and the availability of detection methods for the genetically modified plant. In addition, genetically modified plants that are intended for production of medicinal products will be exempted from the risk assessment under EU Directive 90/220 (EP, 2001a).

### 3.2.3. Import of genetically modified crops or crop products

#### *EU*

The import of viable genetically modified products requires the market approval under EU Directive 90/220, part C. If the imported product is to be used as food or food ingredient, additional permission for food use shall be sought under the EU Regulation 258/97 for Novel Foods.

#### *USA*

The import-, movement between States-, and the environmental release- of genetically modified plants and seeds come under the scrutiny of the Animal- and Plant- Health Inspection Service (APHIS), which resorts under the U.S. Department of Agriculture (USDA). Considered, among others, will be the GMO's potential to become a plant pest (Vogt and Parish, 1999). The import of genetically modified foods and feeds fall under the regulatory oversight of the Food and Drug Administration (FDA).

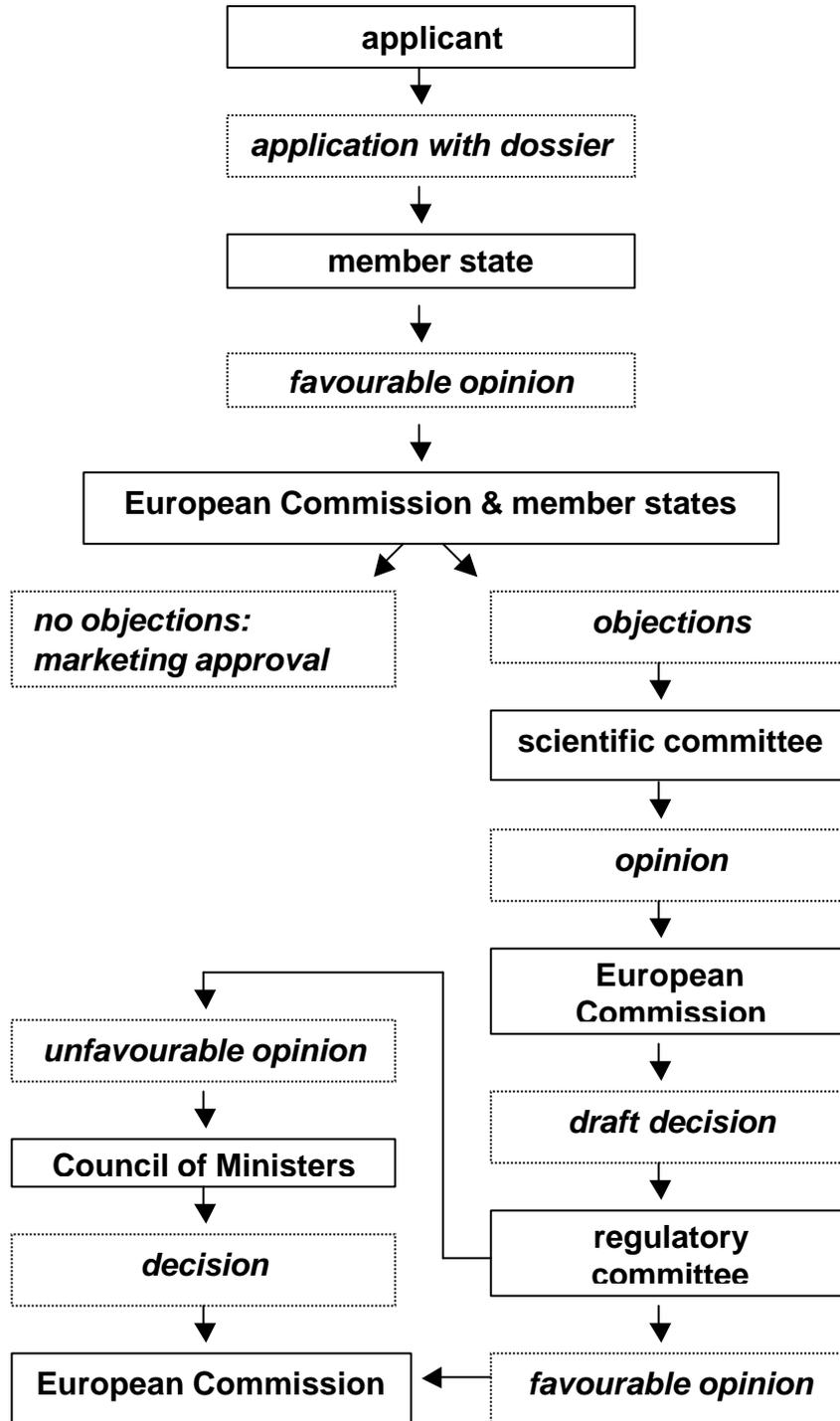


Figure 1 Procedure for market approval of a genetically modified crop under EU Directive 90/220 (EU, 2000)

### 3.2.4. Contained use

#### *EU*

EU Directive 90/219 focuses on the use of genetically modified micro-organisms within a contained facility, such as a fermentor in a factory. This may include genetically modified eukaryotic cells, such as plant cells. The dossier that should be turned in for approval must contain, among others, molecular data on the transgenic insert and data on the organism's safety. This directive may be relevant for those applications that involve the use of a plant cell culture for the production of metabolites. These metabolites should then be purified before being shipped from the factory, *i.e.* without the genetically modified plant cells. Self-cloned micro-organisms that contain inserted self-DNA are exempt from this directive, in other words they are not considered genetically modified.

Greenhouse cultivation of genetically modified plants can be regarded “contained use” too if conditions are similar to “containment” of genetically modified cells described above, as stated in the recently amended EU Directive on genetically modified plants (EP, 2001a).

#### *Netherlands*

Greenhouse cultivation of genetically modified plants is regulated by the Dutch Decision on Genetically Modified Organisms (“Besluit Genetisch Gemodificeerde Organismen”). The requirements for greenhouse facilities are described in Chapter 5.

## **3.3. Food uses**

### 3.3.1. Food, food ingredients, and food additives

#### *EU*

A food or food ingredient derived from a genetically modified organism is considered “novel” in the EU. Other foods considered “novel” in the EU are foods that have not been previously consumed within the EU, derived from micro-organisms, significantly altered, or processed in novel ways. Novel foods should be evaluated for market approval under EU Novel Food Regulation 258/97. Please note that viable genetically modified products need an approval for marketing under EU Directive 90/220 prior to an approval for food applications under the Novel Food Regulation.

The “authorisation” procedure for market approval under the EU Novel Food Regulation 258/97 is very similar to that under EU Directive 90/220. There is, however, an additional short-cut route of “notification” (Figure 2). In the case of “notification”, the applicant supplies evidence for the “substantial equivalence” (see below) of a product derived from genetically modified organisms to a conventional / commercial counterpart. Notifications that have led to market approvals include those for processed oil from genetically modified canola and products, such as starch and oil, from genetically modified maize kernels (EU, 2000).

For the “authorisation” procedure, decision trees will provide guidance on the data required for compiling the dossier (EU, 1997). In all cases, information should be provided on the toxicological and microbiological safety of the novel food, in addition to its nutritive value and its estimated intake.

Substantial equivalence is the central principle in the assessment of the safety of a genetically modified crop, based upon which it is decided which safety tests will be required. The submitted crop or its products are substantially equivalent to a conventional counterpart if they are phenotypically and compositionally comparable. In that case, no further safety testing would be required under the present policy.

If, however, the crop or product is substantially equivalent except for one or a few compounds, the toxicological significance of the altered compounds should be assessed. Crops or foods/feeds that are not substantially equivalent at all should be submitted to a full safety test.

Food additives are defined as substances that do not occur normally in consumed foods, excluding, however, flavourings and, in general, nutrients (minerals, vitamins). Extensive safety testing will therefore be required before a food additive will receive market clearance under EU Directive 89/107. If, by coincidence, the nutraceutical possesses sensory properties, it may be used as a food flavour. Flavourings are used to add odour or taste to foodstuffs. Several substances are allowed as such under EU Directive 88/388, including substances isolated from vegetable tissue by physical means. Specific permissible food uses of sweeteners, colourants, and other additives are described by EU Directives 94/35, 94/36, and 95/2.

For additives and flavourings to be approved, no distinction is made in EU legislation for substances derived from genetically modified organisms.

Foods and genetically modified foods containing detectable transgenic proteins or -DNA should be labelled under EU Regulation 49/2000. The same applies to foodstuffs containing additives or flavourings derived from genetically modified organisms under EU Regulation 50/2000, provided the additives or flavourings have been released on the market after April 2000.

## USA

Genetic modification is not considered different from other technologies for crop improvement in the USA. American legislation is therefore oriented to the safety evaluation of the altered characteristics of the genetically modified food (FDA, 1992). Newly expressed gene products may be regarded “food additives” or “pesticide products” and should therefore be evaluated for their food safety. Food additives are evaluated by the FDA and pesticide residues by the Environmental Protection Agency (EPA) (Vogt and Parish, 1999). Please note that the American definition of a “food additive”, *i.e.* “not generally recognised as safe” (non GRAS, see below), is different from that in the EU. On the other hand, GRAS status may be sought for foods with altered compositions, *i.e.* a vegetable oil with a changed fatty acid profile.



American food additives should always be evaluated for their safety by the FDA, while other foods and food ingredients should be “generally recognised as safe” (GRAS) under the Federal Food Drugs and Cosmetics Act (FFDCA). The determination of GRAS status by the FDA is not mandatory. Moreover, a food substance can be declared “GRAS” by its manufacturer (“GRAS self-determination”). In practice, however, the market will only accept GRAS determinations that are endorsed by recognised institutions in order to avoid legal liability for the use of food substances that may turn out to be unsafe. These recognised institutions include the FDA itself, but also “extramural” associations such as the Federation of American Societies for Experimental Biology (FASEB) and the Flavor and Extract Manufacturers’ Association (FEMA) (Institute of Medicine, 1999). The procedure for food additive petitions is more tightly regulated than for GRAS status. The FDA’s *Redbook* lists the toxicological tests required for safety testing of food additives and – ingredients (FDA, 2000a).

Newly expressed gene products such as viral coat proteins, viral replicases, herbicide degrading enzymes and herbicide tolerant enzymes are regarded “plant pesticides”. These gene products are therefore evaluated by the EPA, which determines the pesticide levels that are tolerable in raw agricultural commodities (Code of Federal Regulations, Title 40, Part 180). The FDA will, in turn, accept the occurrence of these pesticides in food products, provided the pesticide levels in these products do not exceed the tolerable levels determined by the EPA. Transgenic proteins that have thus been tolerated by the EPA in commodities are, however, generally exempted from an upper threshold level of tolerance based on the absence of harm from the estimated human exposure to these pesticides, which are present at low levels in plants.

The FDA recently made a proposal for new legislation, under which the notification of genetically modified food / feed crops by their manufacturers 120 days before market release will become mandatory. In addition, rules are developed for those producers that wish to label genetically modified foods / feeds voluntarily (FDA, 2001a).

### 3.3.2. Food for special uses

#### *EU*

Foods for infants, sportsmen, and hospitalised patients (*e.g.* enteral nutrition) are among the “foods with particular nutritional uses” as defined by the EU. Such foods should be labelled as “dietetic” or “dietary”. Special requirements for the levels of vitamins and minerals in infant formulae have been formulated in amendments to EU Directive 89/398, which regulates these types of food.

#### *USA*

Similar to the EU’s provisions for foods for particular nutritional purposes, the FDA has formulated requirements for the manufacturing-, composition-, and labelling- of “foods for special dietary use”, including infant formulae and weight-loss products (FDA, 2000b). In addition, “medical foods” for oral consumption or enteral nutrition have been defined by American law as foods that provide nutrients to people other than healthy, such as those with diseases or “distinctive nutritional requirements”.

Medical foods are exempt from the regulatory requirements for food labelling, including health claims (FDA, 2000c).

### 3.3.3. Food supplements

#### *EU*

Food supplements are defined by the EU as concentrated forms of nutrients, which serve to supplement the dietary nutrient intake, such as vitamins, minerals, amino acids, fatty acids, fibre, and herbal- and plant extracts. An EU Directive on Food Supplements will likely enter into force in the near future, as a proposed version was recently adopted by the European Commission (EC, 2000a; EP, 2001b). For the time being, the directive gives a limited account of vitamins and minerals permitted to be sold as supplements. Requirements for other ingredients, such as plant and herbal extracts, are still to be defined. For those supplements that are not covered by EU Directives, national legislation of EU member states should apply (EP, 2001b).

Purified vitamins and minerals can also be added to foods rendering these foods “fortified”. Member states’ regulations on food fortification have not been harmonised yet at an EU level.

#### *Netherlands*

Food supplements are considered “health products”, *i.e.* products that look like pharmaceuticals or that are linked to health-functions, but that are no medicines (see section 3.3.4). Similar to conventional foods, health products are regulated by the Commodity Act. Food supplements containing vitamins are more specifically regulated by the Commodity Act Rule waiving Vitamin Preparations (“Warenwetregeling Vrijstelling Vitaminepreparaten”) (Vroom Cramer, 1998).

Food fortification is regulated by the Commodity Act Decision on the Addition of Micro-Nutrients to Foods (“Warenwetbesluit Toevoeging Micro-voedingsstoffen aan Levensmiddelen”). The addition of all micro-nutrients is permitted, except for iodine, fluorine, and amino acids. Three categories of food fortification with micro-nutrients are considered:

?? Restoration: compensating for nutrient losses during food manufacture.

?? Substitution: addition of nutrients of a product to a substitute for that product.

?? Enrichment: addition of nutrients to products that do not contain them.

Limits are posed to the added amounts of micro-nutrients, based on their recommended daily intakes. Fortified foods are allowed to bear claims pertaining to their nutrient contents (Vroom Cramer, 1998).

#### *USA*

American food supplements may consist of vitamins, minerals, herbs and dietary components as tablets, fluid or food. Food supplements are not allowed to be marketed as foods. Supplements are less stringently regulated as they fall under the Dietary Supplement Health and Education Act. Their constituents need not be GRAS, but the manufacturer should be able to prove their safety. In case the supplement contains a novel ingredient, the FDA should receive a notification and data

Exploitation and regulation of plants genetically modified to express nutraceuticals and pharmaceuticals  
<http://www.rikilt.wageningen-ur.nl/nutraceuticals>  
substantiating the novel ingredient's safety 75 days prior to its market release (FDA, 2001b)

American legislation on food fortification is similar to that of the Netherlands (Code of Federal Regulations, Title 21, Part 104.20).

#### *International harmonisation*

In addition, efforts are made by the EU and the US to harmonise legal criteria for food supplements containing vitamins and minerals, in order to ensure marketability of these products in both regions. These criteria will include, among others, Good Manufacturing Practice (GMP) (TABD, 2000).

#### 3.3.4. Health claims

##### *EU*

A recent research report prepared by consultants of Hill and Knowlton analyses the current situation concerning the legislation of health claims on foodstuffs in the EU. For details on the different national procedures for health claims on foods and food supplements we refer to this study (Hill and Knowlton, 2000). In Hill and Knowlton's report, three types of claims are discerned: nutritional-, health- and ethical claims. Nutritional claims pertain to the composition of the foodstuff, while health claims concern the potential health benefits of consumption. Ethical claims say something about the working conditions under which the food has been manufactured, such as for Dutch "Max Havelaar" products.

Two directives are most tightly linked with food labelling, 2000/13 (labelling and advertising of food) and 90/496 (labelling of nutritional value). These directives are, however, not comprehensive on health claims. EU Directive 2000/13, for example, does only define those claims that are *not permitted* as follows: "The labelling and methods used must not ... attribute to any foodstuff the property of preventing, treating or curing a human disease, or refer to such properties". Hence genuine medicinal claims are not allowed on foods. This may change, however, as a recent resolution of the Euro-parliament attached a high priority to the inclusion of all labelling issues into one directive (EP, 2000a).

EU Directive 90/496 regulates nutritional claims on labels. Such claims relate to the nutritional value of the foodstuff, such as the content of vitamins. It does not, however, specify rules for the evidence needed in support of such claims.

Labelling of dietary foods is regulated by EU Directive 1999/21, which extends EU Directive 89/398 on foods for particular nutritional purposes. Health claims for these foods are subject to pre-market clearance.

The legislation on claims in individual EU member states may be more extensive than the rules set out by the EU directives. Scrutiny of health claims may be performed either pre- or post-clearance of the food product.

The European Commission recently proposed to harmonise legislation on (EC, 2001a):

- 1) Nutritional claims. A draft list has been provided, featuring a number of permissible nutritional claims.
- 2) Functional claims, *i.e.* health claims that relate to the positive effect of a nutrient on a bodily function.

### *Netherlands*

Dutch legislation on nutritional claims follows EU Directive 90/496 and pertains only to the nutritional value of foodstuffs.

In the Netherlands, a distinction is made between “health products” and medicinal products. “Health products” bear the shape of a pharmaceutical, such as tablets and tinctures, but they are distinguished from medicines by the attached claims that relate to health without making them medicines. It should be noted that food supplements too fall under the Dutch definition of health products. Health claims for health products can be scrutinised voluntarily. For this scrutiny, three institutions have each developed their specific code of practice. These institutions are:

- 1) Advertising Code Foundation (“Stichting Reclame Code”, <http://www.reclamecode.nl/SRC.asp>) in which the media and consumers participate
- 2) Verification Council (“Keuringsraad”, <http://www.koagkag.nl>) in which branch organisations (producers, media, marketeers, drug retailers) participate.
- 3) Nutrition Centre (“Voedingscentrum”, <http://www.voedingscentrum.nl>), which is independent and disseminates public information on nutrition and food safety.

In all three procedures, relevant scientific data must support the proposed health claim.

A Code of Practice has been developed by the Nutrition Centre, which specifies the criteria that should be fulfilled by the scientific evidence in support of a claimed health benefit of food and drink products. Adherence to the Code is on a voluntary base (Nutrition Centre, 1998).

Criteria for the advertisement of “health products”, *i.e.* products with either a pharmaceutical appearance or attributed health-function, have been formulated by the Verification Council (KOAG/KAG, 2000a). One important criteria in the Verification Council’s evaluations is that no pharmaceutical-like properties may be ascribed to the health product.

Complaints about these advertisements can be assessed by the Advertising Code Committee, which verifies their compliance with the Dutch Advertising Code (Advertising Code Committee, 2000). Previous evaluations by the Verification Council of health claims submitted to the Advertising Code Committee will be taken into account.

Claims pertaining to vitamin preparations, as a category of food supplements, are specifically regulated by the Commodity Act Rule waiving Vitamin Preparations (“Warenwetregeling Vrijstelling Vitaminepreparaten”). These claims have to be

supported by scientific evidence, that the manufacturer or trader must be able to deliver at request (Vroom Cramer, 1998).

In addition, fortification of products with micro-nutrients and the claims pertaining to fortified products are regulated. Fortification is allowed if its purpose is to compensate for micro-nutrient losses during processing or to create a substitute for another product containing the micronutrient, *i.e.* vitamin-fortified margarine *vs.* milk butter. Several micro-nutrients are prohibited (*e.g.* iodine) or allowed only in small amounts (*e.g.* vitamins A-D) due to their narrow safety margins (Vroom Cramer, 1998).

Sponsorship of non-profit health associations provides for an additional opportunity to attract consumers' attention to health-promoting food products. The Dutch Heart Foundation (<http://www.hartstichting.nl>) allows companies to display the foundation's logo on food products exclusively for fund-raising activities. Several conditions must be fulfilled, however, to obtain permission to use the logo. The food product in question should i) be a food of preference for the Nutrition Centre, or ii) bear a heart-related health claim that has been positively evaluated according to the Nutrition Centre's Code of Practice. In addition, the manufacturing company's image should be positive and compatible with a healthy lifestyle (no tobacco companies allowed, for example). The logo should be displayed such that its conjunction with fund-raising is obvious to the consumer and that it's not mistaken for a quality mark. As example, Unilever's phytosterol-enriched margarine spread Becel Pro Activ was allowed to bear the Heart Foundation's logo during several months while the foundation was receiving royalties from the sales of Becel Pro Activ.

In a similar vein, the Dutch Digestive Diseases Foundation (<http://www.mlds.nl>) offers sponsoring companies the opportunity to seal certain food products with the foundation's logo against a fixed fee under the following terms:

- ?? The product should be compatible with the foundation's message; for example, it should be high in fibre and/or moisture.
- ?? Claims should be scientifically supported.
- ?? The foundation logo symbolises the company's support for the foundation and should not be mistaken for a quality mark.

## USA

In the United States, a distinction is made for permissible health claims on foods and on food supplements. Please note that the American definition of a health claim is narrower than ours and limits itself to "substance-disease" claims.

Three types of claims are discerned for both foods and food supplements (FDA, 2001c):

- 1) "Substance-disease" claims, which are also referred to as "health claims" in the USA. These claims pertain to the beneficial effect of a food substance on human health without becoming medicinal (*i.e.* to cure, mitigate, or diagnose disease). A limited number of acknowledged health claims are permitted on foods, such as prevention of cancer by fruit consumption (Kurtzweil, 1998). Fewer acknowledged health claims are allowed on food supplements than on foods.

Exploitation and regulation of plants genetically modified to express nutraceuticals and pharmaceuticals

<http://www.rikilt.wageningen-ur.nl/nutraceuticals>

Novel substance-disease claims can be cleared for labelling through three regulatory pathways:

- ?? Claims may be submitted to the FDA, which will evaluate the scientific background supporting these claims. The FDA requires that “significant scientific agreement” exists for such claims to be cleared (FDA, 2001c).
  - ?? Claims on foods (not on dietary supplements) may be based on authoritative statements from scientific bodies, such as the National Academy of Sciences (NAS) and federal institutions such as the National Institutes of Health. These claims should reflect consensus within these scientific bodies and be based on review of the scientific evidence. The following approved claim, for example, was based on a statement by NAS: "Diets rich in whole grain foods and other plant foods and low in total fat, saturated fat, and cholesterol, may help reduce the risk of heart disease and certain cancers" (FDA, 2001c).
  - ?? “Qualified” claims are allowed on food supplements (not on foods) as a result of a court decision on a recent lawsuit between a supplement manufacturer and the FDA (the “Pearson vs. Shalala” case). The FDA was required by the court to permit claims that did not match the FDA’s standards for “significant scientific agreement”, provided that qualifying language was used that would render these claims not misleading. The qualifying claims that have since then been approved by the FDA contain either qualifying remarks (rendering claims rather lengthy) or disclaimers (FDA, 2001c).
- 2) “Nutrient content” claims on foods and food supplements (such as “high in calcium”), which pertain to the level of a nutrient for which a recommended daily intake or a daily reference value has been established. Such claims have to be submitted to the FDA for evaluation. In addition, nutrient-content claims may be based on authoritative statements, similar to substance-disease claims (FDA, 2001c).
  - 3) “Structure function” claims on foods and food supplements describing the relation between a nutrient and body structures, physiological functions, nutrition deficiencies, and common affections that are associated with “passages of life”. Claims related to severe diseases are, however, precluded. Structure-function claims are not liable to the pre-market scrutiny and should be notified to the FDA within 30 days after market introduction. The burden of proof for these claims lies on the side of the FDA, which has to react to non permissible claims. A disclaimer should be added that, among others, the FDA has not evaluated the claim (FDA, 2001c).

In addition, requirements for ingredient labelling of dietary supplements are less rigorous than for foods and allow for the omission of non-relevant ingredients and for the declaration of special nutrients (FDA, 1999).

In addition to explicit health claims, several American producers of foodstuffs, food supplements, and pharmaceuticals are allowed to seal the logos of non-profit health organisations to their products and advertisements in return for sponsorship. An example is the labelling of Florida fruit products with health logos sponsored by the US State of Florida’s Department of Citrus (see <http://www.ultimatecitrus.com/health.html>). Florida orange juice labels are allowed to display logos of the American Cancer Society (reduced risk of cancer) and the March

Exploitation and regulation of plants genetically modified to express nutraceuticals and pharmaceuticals

<http://www.rikilt.wageningen-ur.nl/nutraceuticals>

of Dimes (reduced risk of birth defects), while Florida grapefruit is allowed to bear the American Heart Association's logo (reduced risk of heart disease). It should be noted that the American Cancer Society will not accept new sponsors for this purpose. The American Heart Association, on the other hand, has a food certification program in place where food manufacturers can acquire permission to label their products with the "heart-check mark" (<http://www.americanheart.org/FoodCertification/>). Eligible food products must be low in fat, cholesterol, and salt, but contain enough nutrients. Fruit juices, fortified beverages, and lean beef are among the food products that have thus been approved. Logos of other American non-profit health organisations not mentioned here have also been linked to products and advertisements.

It should be borne in mind, though, that American consumer laws and Federal Trade Commission standards apply to the use of logos as described above. Both the logo-providing non-profit health organisation and the sponsoring food manufacturer have the responsibility to ensure that the logo display will not mislead the consumer. If, for example, the health organisation and the manufacturer have entered an *exclusive* agreement, this should be stated clearly. In addition, if the health organisation does not specifically endorse a labelled product, this should be stated too (OAG, 1999).

### **3.4. Feed uses**

#### **3.4.1. Feed and feed ingredients**

##### *EU*

A list of materials, including plant products, that are allowed to be marketed as ingredients of compound animal feeds in the EU, is provided within EU Directive 91/357. Additional clearance under EU Directive 90/220 is required for animal feeds and feed ingredients derived from field-tested and commercially released genetically modified crops, as long as the crop is considered a viable organism (see above). A specific EU Novel Feed Regulation, however, is anticipated to replace the animal feed evaluation under 90/220 in the EU in 2001. Contrary to the 90/220 directive, this novel regulation also covers the use of non viable GM products and requires post market monitoring and tracing methods for the novel feed.

##### *Netherlands*

Same as the EU for viable products (cultivation and/or import). For the import of non viable animal feed products, a voluntary notification can be made to the Dutch Ministry of Agriculture, Nature Management, and Fisheries. The outcome is not legally binding and does not apply to other EU Member States.

##### *USA*

American regulations on animal feed differ from their European counterparts. Feed ingredients that are allowed to be included in animal feeds are listed in the "Official Publication" of the Association of Animal Feed Control Officials (AAFCO), a voluntary organisation that advises authorities' officials (<http://www.aafco.org/>). Each State of the USA may have its own feed regulations, additional to those of the Food and Drug Administration (FDA) (USDA, 2000).

“Nutraceuticals” as feed ingredients have apparently not been regulated yet, given the discussion inside AAFCO on whether or not nutraceuticals should be registered as feed ingredients and, consequently, evaluated for their safety (AAFCO, 1999).

#### 3.4.2. Feed additives

##### *EU*

Prior to market approval in the EU, new feed additives are evaluated for their safety and efficacy, *i.e.* animal performance and welfare. To this end, animal tests should be carried out (EU Directive 87/153; SCAN, 2000).

Feed additives from genetically modified organisms that are similar to any on the market are not specifically regulated and are regarded as safe. The presence of transgenic DNA containing antibiotic resistance genes is, however, not allowed (SCAN, 2000). Proposals have been amended by the European Parliament to install mandatory labelling of feed additives that contain- or consist of- genetically modified organisms (EP, 2000b). This would imply that purified additives lacking transgenic components would not fall under this labelling requirement.

##### *USA*

Feed additives are considered animal medicines in the USA, hence they should be approved as a new animal medicine. The marketing of a feed additive that is generally recognised as safe (GRAS) by the FDA will, however, only require an expert’s opinion, eventually supported by literature data (USDA, 2000).

#### 3.4.3. Feed for special uses

##### *EU*

Feedingstuffs for particular nutritional purposes serve the nutrition of metabolically impaired animals. These feedingstuffs may consist of feed additives and should be distinguishable from ordinary feedingstuffs and medicated feeds. A number of applications for these feedingstuffs are permitted, including “reduction of acute intestinal absorptive disorders”, under EU Directive 94/39.

##### *USA*

To our knowledge, no specific regulations exist for special dietary feeds in the USA.

### **3.5. Medicinal uses**

#### 3.5.1. Human medicines

##### *EU*

Approval for the production of medicines by genetically modified organisms can only be granted by a “centralised” EU procedure as described by EU Directive 2309/93. A

comprehensive dossier should support the application for a medicine derived from genetically modified organisms. Guidance for applicants on the content of dossiers is provided by the European Agency for the Evaluation of Medicinal Products (EMA) (EC, 1997).

Three types of data must be collected for the marketing application dossier: quality-, preclinical-, and clinical- data.

Quality includes medicine composition and stability, while special requirements have been formulated for vegetable products.

Preclinical data comprise *in vitro* data, such as mutagenicity, and animal test data, such as pharmacokinetics and toxicity; the latter includes single dose- and repeated dose- tests, teratogenicity, and carcinogenicity. Specific guidance is provided for the pre-clinical testing of biotechnology-derived medicines (CPMP, 1997).

Clinical trials are human trials in which pharmacokinetics, efficacy and toxicity are assessed. The order in which data are collected is not random, *i.e.* clinical trials are only permitted *after* safety and efficacy in animals have been assessed by preclinical trials.

Human medicinal products are classified into two categories by EU Directive 92/26:

1. Prescription medicines, which can only be sold through pharmacies.
2. Non prescription (“over the counter”, OTC) medicines, *i.e.* medicines that can be obtained with- or without- a physician’s prescription (EU Directive 92/26). Several criteria are considered before a medicine is granted the OTC status, including the safety of the medicine, the ability of the patient to self-diagnose and to self-medicate with little or no professional instructions.

Advertising is only possible for OTC medicines, not for prescription medicines.

After their market release, medicines should be monitored for side effects. The “market authorisation holder”, together with health professionals and government officials should report side effects to the Member States and EMA. Serious adverse effects have to be reported within 15 days, whereas other side effects are reported periodically (PhVWP, 1999). No special additional requirements have been formulated for the monitoring of biotechnology-derived medicines.

### *Netherlands*

Advertisements for OTC medicines are under scrutiny of the Verification Council (Keuringsraad KOAG/KAG) in the Netherlands (KOAG/KAG, 2000b). The Dutch Medicine Evaluation Bureau recently advised the Dutch Minister of Health Welfare and Sports to allow the general sales (*i.e.* outside pharmacies and drug stores) of certain OTC medicines, such as vitamins and minerals (CBG, 2000a).

In the Netherlands, pharmacovigilance is carried out by health professionals, medical specialist organisations, the marketing authorisation holder, and official bodies. For human medicines, these official bodies are the Medicine Evaluation Bureau and the Health Inspectorate (CBG, 2000b).

## USA

Under American legislation, the same stages in medicine testing prior to marketing can be discerned as in EU legislation (see above): quality, pre-clinical, and clinical.

In the clinical stage, the medicine is tested as an “investigational new drug (IND)”. All relevant details of the preclinical tests and the IND-tests should be submitted in the “new drug application (NDA)”. If the NDA is approved by the reviewers, the new medicine is allowed to be marketed.

A short-cut route can be followed if the medicine for which a marketing approval is sought is a “generic drug”, *i.e.* a medicine that has already been approved and that lacks patent protection. This route is named “abbreviated new drug application (ANDA)”. Apparently, USA legislation does not exempt biotechnology-derived medicines from this possibility, unlike EU legislation. For an ANDA, the “innovator” medicine should be proven to be bio-equivalent to the approved medicine, *i.e.* it should display the same uptake from the dosage (FDA, 2000d). Bio-equivalence studies should involve 24-36 human volunteers, in which the bloodstream uptake of the medicine is measured. These studies can substitute for preclinical- and IND-studies. ANDAs for “biologics” (*e.g.* proteins), however, are still a matter of discussion in the USA, as reported recently (Dove, 2001).

Similar to the EU, the FDA discerns “prescription (Rx)” medicines and “over the counter (OTC)” medicines. OTC medicines are not classified into active compounds but into their indication or purpose. At present, “OTC drug monographs” are compiled, which stipulate composition and quality of approved OTC medicines (FDA, 2000e). If a new medicine’s composition concurs with that described in an OTC monograph, a simplified OTC medicine application can be filed instead of an NDA.

Botanical products that have been marketed as food or food supplements and that are “generally recognised as safe (GRAS)” by the FDA (see section 3.3.1) can also be sold in the USA as OTC medicines (FDA, 2000f).

Similar to the EU, pharmaceuticals must be monitored post-market for adverse effects. The FDA has programs in place for reporting adverse reactions, *viz.* the Adverse Event Reporting System (<http://www.fda.gov/cder/aers/default.htm>) for manufacturers, packers and distributors, and MEDWATCH for health professionals (<http://www.fda.gov/medwatch>).

### *International harmonisation*

Regulatory authorities of the EU, USA, and Japan have joined forces in the International Conference on Harmonisation (ICH) to harmonise the requirements for medicine applications. The ultimate goal is the mutual acceptance of medicine application data that have been compiled in accordance with ICH guidelines (Nutley, 2000). Consensus has already been reached on requirements for preclinical (S6 of [ICH, 2001]) and clinical data. Moreover, ICH guidelines have been prepared for the production of biotechnological medicines from genetically modified cell cultures (Q5 & Q6 of [ICH, 2001])

### 3.5.2. Veterinary medicines

#### *EU*

The requirements for dossier data for the registration of veterinary pharmaceuticals are quite similar to those for human pharmaceuticals (see section 3.5.1) (EC, 1997). Human toxicity is also relevant to veterinary medicines with regard to consumer safety. It should be noted that for veterinary medicines a maximum residue limit in food animals must be defined according to EU Regulation 2377/90. In addition, a withdrawal period has to be determined during which the medicinal product should not be administered to food animals prior to slaughter.

Similar to human medicines, veterinary medicines can be either “prescription” or “OTC”, as EU Directive 90/676 defines which medicines can only be administered on prescription. OTC status of veterinary medicines has not been harmonised, though, in the EU.

#### *Netherlands*

Veterinary medicines that can only be dispensed through the pharmacist or the veterinarian have been defined by the “canalisation” rules under the Dutch Law on Veterinary Medicines. After the market release of veterinary medicines, adverse reactions should be reported to the Centre for Veterinary Pharmacovigilance.

#### *USA*

The American legislation on veterinary pharmaceuticals by and large resembles that of human pharmaceuticals. Hence American legislation discerns “investigational new animal drugs (INADs)”, “new animal drugs (NADs)”, and “abbreviated new animal drug applications (ANADAs)” (FDA, 2000g). Guidance documents on the various issues surrounding veterinary medicines, *i.e.* specific uses and clinical testing, have been published by the FDA’s Center for Veterinary Medicine (FDA, 2000h).

Similar to the EU, a distinction is made between prescription (“Rx”)- and OTC veterinary medicines. A veterinary medicine may be changed, however, from prescription- to OTC- status if long-term experience warrants its safe use (FDA, 2000i).

Once a medicine has been approved for commercial release, post-market reporting to the FDA’s Center for Veterinary Medicine of adverse reactions of veterinary medicines is mandatory for medicine manufacturers and voluntary for animal owners and veterinarians (FDA, 1998).

#### *International harmonisation*

Similar to ICH for human medicines, the International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Products (VICH) seeks to establish mutual recognition of veterinary medicine dossiers between the EU, USA, and Japan. Guidelines have already been implemented for quality requirements of

Exploitation and regulation of plants genetically modified to express nutraceuticals and pharmaceuticals  
<http://www.rikilt.wageningen-ur.nl/nutraceuticals>  
veterinary medicines, while draft guidelines have been prepared for clinical trials, antihelminthics, and pharmacovigilance (VICH, 2001).

### 3.5.3. Health economics

One aspect that is currently receiving much attention of professionals involved in the human medicine approval process is that of *health economics*, also known as *pharmacoeconomics*. Pharmacoeconomic studies on pharmaceuticals take various economic and social aspects of the novel medicine into account, such as its cost effectiveness and its effect on the “quality of life”. Cost effectiveness include the pricing of the medicine compared to other medicines, but also savings made in other sections of healthcare, such as hospitalisation of patients, by use of the novel medicine. Cost-effectiveness considerations are nowadays pivotal for a medicine to get incorporated, for example, into reimbursement schemes of health insurance providers.

#### *EU*

There is no common EU guidance on the issue of pharmacoeconomics that we are currently aware of. A recent French study reviews pharmacoeconomic guidelines of, among others, EU member states and the USA (Baron, 2000).

#### *Netherlands*

Guidelines have been issued for pharmacoeconomic data to be supplied with the medicine application in The Netherlands (CVZ, 2000a; Riteco et al., 1999).

It may be worth noting that dietary preparations are reimbursed by Dutch healthcare insurance companies under certain conditions, *e.g.* if they alleviate severe diseases, such as cow’s milk allergy in children till 2-3 years of age. The Dutch organisation for healthcare insurance companies is currently reviewing this policy of reimbursing dietary preparations.

#### *USA*

In the USA, pharmacoeconomic data provided by medicine companies to committees and other bodies that decide on eligibility of the medicine for therapy or reimbursement are considered “promotional” data. The quality of these data should fulfil the requirements formulated in Section 114(a) of the FDA Modernization Act of 1997 amending Section 502(a) of the Food, Drug & Cosmetics Act.

It may be interesting to note here that pharmacoeconomic studies show that specific diets can alleviate medical costs, as projected recently for American diabetes patients receiving special diets under “medical nutrition therapy” (Sheils et al., 1999). It has therefore been argued that special diets should be eligible for reimbursement under healthcare insurance programs.

### **3.6. Production Chain (GMP and similar conditions)**

#### **3.6.1. Foods and food ingredients**

Chemical and microbiological contamination of foods should be prevented to avoid illness of the consumers. Current food hygienic standards are nowadays implemented by food industries in the frame of Good Manufacturing Practice (GMP) and Hazard Analysis at Critical Control Points (HACCP). The Codex Alimentarius Commission of the FAO / WHO has adopted such standards (Codex, 1997).

The hygienic practices described by Codex involve, among others, the use and design of apparatus and machines that allow for cleaning, the prevention of contamination by personnel and training of personnel. For HACCP, a flow diagram of the food manufacture process is made. Critical control points (CCPs), *i.e.* essential points in the food production chain where samples can be drawn and possible contamination can be controlled, are then assigned in this process. Records are stored of data sampled at the CCPs, and instructions for control measures should be available in case a contamination is noted.

#### *EU*

EU Directive 93/43 stipulates the hygiene rules that food businesses should comply with in general, such as HACCP as described by the FAO/WHO Codex Alimentarius. A recent proposal of the European Commission for an EU General Food Regulation will also incorporate hygienic standards such as HACCP. This proposal will probably be implemented by the year 2002.

#### *Netherlands*

HACCP is mandatory for the Dutch food industries under the Dutch Commodity Act Rule on the Hygiene of Foodstuffs (“Warenwetregeling Hygiëne van Levensmiddelen”), implementing EU Directive 93/43.

#### *USA*

GMP is mandatory for the American food industry (Code of Federal Regulations, Title 21, Part 110). In addition, HACCP is mandatory too for a number of foods, including fruit- and vegetable- juices. Guidance on HACCP has been published by the FDA (FDA, 2000j).

#### **3.6.2. Food supplements**

#### *Netherlands*

Food supplements fall under the scope of the Dutch Commodity Act (“Warenwet”) and HACCP is therefore required for their production.

## *USA*

GMP is mandatory for food supplements containing more than 30 mg iron per dosage (Code of Federal Regulations, Title 21, Part 110.50).

A voluntary quality program for food supplements has been launched by the US Pharmacopeia. This program focuses on the accurate labelling of the composition of food supplements containing vitamins, minerals, and herbal extracts. Manufacturers complying with this program are allowed to display a US Pharmacopeia quality mark on their product labels (USP, 2000).

## *International harmonisation*

Requirements for good manufacturing practices (GMP) are to be formulated in the near future in both EU and USA in the context of the EU-USA harmonisation of legislation on food supplements (TABD, 2000).

### 3.6.3. Animal feeds

#### *EU*

EU Directive 95/69 establishes basic requirements under which manufacturers of commercial feedingstuffs should work, including the requirement to exclude contamination of animal feed by harmful organisms.

#### *Netherlands*

Most (>90%) of the Dutch animal feed producers have voluntarily adopted GMP conditions as established by the national Product Board for Animal Feed. These GMP conditions include the intake and production of feedingstuffs that comply with microbiological- and residue- criteria. Recently, it has been decided that GMP will be extended with HACCP to better adapt feed manufacture to food industry standards (PDV, 1999; PDV, 2001).

#### *USA*

In the US, the Association of Animal Feed Control Officials (AAFCO) provides guidance for implementation of FDA standards for Current Good Manufacturing Practice in animal feed manufacture. These standards include among others the cleaning of manufacturing apparatus, the quality control of raw materials and products, and safety during transport (AAFCO, 2000).

### 3.6.4. Human and veterinary medicines

#### *EU*

In the European Union, good manufacturing practices of medicinal products for both human and veterinary use are quite similar and therefore will be treated together.

It is mandatory that the manufacturers of medicinal products comply with the guidelines for Good Manufacturing Practice. Such practice includes the establishment of a quality control department, the employment and education of qualified personnel, the use and decontamination of appropriate housing and equipment, the storage of records related to the manufacture processes, and the execution of manufacturing instructions, inspection, and monitoring. These requirements are further detailed in the Guide to Good Manufacturing Practice for Medicinal Products (EC, 1997).

Several criteria that have been formulated in the abovementioned guide appear relevant to the production of pharmaceuticals in genetically modified plants:

- ?? Storage of crude plants materials and the products manufactured from them.
- ?? Processing instructions and quality control.
- ?? Characteristics of the crude plants, including active components, contaminants and growth conditions of the crude plant (cultivation areas, separate harvested batches). Impurities that cannot be controlled should be assayed for their toxicity.

Guidance for the determination of quality of crude plants are provided by the Guideline on Quality of Herbal Remedies (pp. 195-202, vol. 3A of [EC, 1997]) and EMEA's Herbal Medicinal Products Working Party (HMPWP, 2000). The forthcoming European Pharmacopeia (fourth edition, to appear in summer 2001) will devote attention to these EU quality guidelines.

The implementation by EU Member States of EU regulations on herbal medicinal products, including those on GMP, and the use of quality standards laid down in monographs (*e.g.* pharmacopeia) are reviewed in a recent study (AESGP, 1998).

Specific guidelines exist for products manufactured with modern biotechnological techniques. In general, full information shall be supplied on any biotechnologically derived compound, including its manufacture and purity. The guidelines, however, restrict themselves to cultures of genetically modified cells (including plant cells) and transgenic animals (pp. 75-80, vol. 3A, and pp. 205-216, vol. 4 of [EC, 1997]).

#### USA

The requirements for the manufacture of medicines from plants are practically the same as in the EU (FDA, 2000f).

### **3.7. Patentability of the new product**

Patents are exclusive rights to commercially exploit an invention. First, the invention should comply with the general conditions of patentability. This means, for example, that the invention should be non-obvious for a person who is skilled in the art, that it contributes to an improvement of present technology, that the invention can be carried out in practice, and that the description allows for reproducibility. Second, special patent rules apply to biological subjects and their constituents in the EU and the USA (Van de Graaf, 1997).

### 3.7.1. Patenting GM plants

Several options are available to attain the exclusive rights to exploit genetically modified plants in the EU (Santaniello, 2000) and the USA (Evenson, 2000). Protection can be attained either for plant varieties (asexually- and sexually-reproducing) or plant materials that are *not* varieties (*e.g.* genes expressed in multiple plant -species or -varieties).

#### *EU*

In the EU, plant varieties cannot be patented as these are covered by plant breeder's rights. This implies that all that does *not* fall under the definition of a plant variety are exempt from this restriction. Examples of plant products that thus can be patented are genes that are expressed in multiple varieties of unrelated plants, fruits that are not used for plant reproduction (such as apples), and non-stable crosses of plants. Although the European Patent Office does not fall under European legislation, the EU has promulgated EU Directive 98/44 on biotechnological inventions which has to be implemented in its member states (Santaniello, 2000; Van de Graaf, 1997).

#### *USA*

American "plant patents" cover the use of a *single* asexually reproducing plant variety and its progeny. Sexually reproduced plant varieties can be protected by plant breeder's rights. Exclusive rights that do not protect plant *varieties*, are "trade secrets" and "utility patents" (Evenson, 2000).

In the USA, parts of the manufacture procedure and resources (*e.g.* parent breeding lines, genetic transformation methods) can be protected as "trade secret", *i.e.* infringement of confidentiality can be litigated (Evenson, 2000).

No utility patents can be granted for nature and therefore only unnatural plants are eligible for patenting in the USA, like it has been the case for maize enriched with the essential amino acid tryptophane. As some genetically modified plants can be considered unnatural too, they may be submitted for a patent (Van de Graaf, 1997).

The claims that are made in the patent define the applications for which the patent confers exclusive rights to the patent owner. The claims, however, should be "reduced to practice", in other words: their practical feasibility should be demonstrated. The US Patent and Trademark Office recently issued revised guidelines to tighten the scrutiny on this aspect (Kowalski, 2000; Smaglik, 2000).

Exploitation and regulation of plants genetically modified to express nutraceuticals and pharmaceuticals  
<http://www.rikilt.wageningen-ur.nl/nutraceuticals>

## **4. Biosafety Considerations of Transgenic Crops Producing Functional Foods, Nutraceuticals and Pharmaceuticals**

### **4.1. Case-by-case**

Above, we distinguished between production of pharmaceuticals, functional foods, or nutraceuticals in crops, and crops to be used entirely (raw or processed) for oral administration of the relevant compounds. Concerning recombinant production, the specific characteristics of the crop and the recombinant compounds, the culture requirements, and the (national and international) guidelines and regulations make each production system an individual case. Biosafety assessments therefore need to be approached on a 'case-by-case' basis. This will be the starting point.

### **4.2. Crop type**

Any crop type, i.e. any food, feed and industrial crop, has the potential to be genetically modified to produce pharmaceuticals or nutraceuticals. Relevant considerations before choosing a specific crop for transgenic medical or health purposes is the familiarity with the agronomic characteristics of the crop, specific methods of crop protection, weed/pest management and possibilities for the removal of agrochemical residues. Major attention should be given to the required containment conditions and the biological containment characteristics of the crop. The biological characteristics of the plant in the field, such as dispersal of pollen, seeds and other diaspores, and its hibernation capacity or the invasiveness are relevant in this respect. Outcrossing to adjacent fields with the same crop cultured for traditional purposes must be prevented. The same holds for outcrossing to wild or weedy crossable relatives. Also possible new effects, due to the presence and characteristics in the plant of the specific health compound, to organisms that accidentally feed on it or live in its phyllosphere or rhizosphere should be considered. Several production systems, especially in the case of pharmaceutical production, will require defined greenhouse facilities. Chapter 5 focuses on the requirements for greenhouses to be used for the culture of crops aiming at the production of pharmaceuticals and nutraceuticals.

### **4.3. Transgene and transgene product**

The type of the functional food, nutraceutical, or pharmaceutical in the plant and its aim needs to be considered. In the case of pharmaceuticals it may be an antibiotic, a hormone, an enzyme, a vaccine or an immunological protein. Active components in functional food crops can involve flavanoids, carotenoids, multiple-unsaturated fatty acids, oligosaccharides, fibres but also increased mineral contents and vitamin level. Each type of compound, when present in unnatural quantities, or in a new host plant, may require its own safety approach.

In the same vein, the “transgene-centred approach to biosafety” described in scientific literature may serve as an auxiliary tool for the biosafety assessment of genetically modified plants (Metz & Nap, 1997; Gilissen et al. 1998). This approach enables to answer concrete questions about ecological and toxicological consequences of the presence of gene xxx or gene product XXX and their metabolites in a genetically modified plant.

#### **4.4. Handling during culture and harvest**

Attention should also be given to the safety of the farmers. Different requirements for handling during culture and harvest may be needed for a crop in its new destination as a medicinal plant or functional food crop.

#### **4.5. Residues**

Each crop produces residues that can play a role in further food chains, as feed, or as manure. The presence and the concentration of a (new) medical or health compound in these residues should be analysed, and its possible effects should be considered. In the case of residues from a food crop used for the production of a pharmaceutical, it might be used for further purposes e.g. as feed or as green manure. In such case, the pharmaceutical should be removed or inactivated completely.

## 5. Blueprint of a Greenhouse

### 5.1. General

The demands put on a greenhouse suited for culturing genetically modified plants for the production of nutraceuticals, functional foods and pharmaceuticals depend on both the legislation related to the GMO status of the produced plants and on specific production requirements claimed by the company that processes the harvested transgenic plant material. For many manufacturing processes these production requirements are laid down in EU Directives describing principles and guidelines of “good manufacturing practices” (GMP). Unfortunately, no GMP directives exist about premises and equipment for transgenic plants that produce pharmaceuticals or nutraceuticals. Production of pharmaceuticals involves legislation related to medicines (see EMEA website: <http://www.eudra.org/emea.html>). Production of nutraceuticals involves legislation related to foods, including novel food (Regulation 258/97). Currently, the EMEA (The European Agency for the Evaluation of Medicinal Products) Working Party on Herbal Medicinal Products agreed to a proposal for guidance on good agricultural and collection practice in relation to the GMP guide for Active Pharmaceutical Ingredients (pp. 95-101 of [HMPWG, 1999]). This document is the only one available that describes cultivation of plants that are used for medicine production and can also be used to outline Good Agricultural Practice (GAP) for both pharmaceutical and nutraceutical production. The GAP guidelines apply to the production of all plant materials used in the food, feed, medicinal, flavoring and perfume industries. It applies to all methods of production including organic production in accordance with the European regulations. Producers, traders and processors of medicinal and aromatic plants should comply with the GAP guidelines, document this, by a Way Bill (batch documentation) and demand that their partners also meet these requirements.

### 5.2. Legislation for production in greenhouses

#### 5.2.1. Legislation in the EU

Combination of the requirements laid down in the GAP guidelines and to the Directives related to the transgenic status of the plant can be used to outline the conditions under which genetically modified plants can be grown in greenhouses for medicinal production. The latter, however, poses a problem: no directives are made that deal with the production of transgenic plants in greenhouses. EU Directive 90/220 is about the deliberate release into the environment of genetically modified organisms and was recently amended by EU Directive 2001/18, which has to be implemented in Member State legislation in 2002. EU Directive 90/219 is about the contained use of genetically modified micro-organisms. Production of pharmaceuticals or nutraceuticals in greenhouses is not about deliberate release in the environment. In contrast, it can have a high level of containment (especially under GAP conditions). On the other hand, contained use of micro-organisms (directive 90/219) involves techniques and risks that are very different from contained growth of genetically modified plants. To fill up this gap in legislation, EU member states have made legislation based on EU Directives 90/219 and 90/220 for the production of genetically modified plants. EU Directive 90/220 consists of four parts. The first part

contains the general provisions: member states must take appropriate measures to avoid adverse effects on human health and the environment which may arise from deliberate release of GMOs in the environment. The second part contains the provisions for the deliberate release of GMOs into the environment for research and development purposes. The third part contains provisions for market release of GMO-derived products and the fourth part contains additional procedural considerations. Further information is provided by Kok et al. (1996). In this study also differences related to implementation of Directive 90/220/EEC into national law are provided. Several differences exist in the application procedures in the different member states (administrative procedures, requirements for field trials, requested information for the technical dossier, necessary measures in field trials related to differences in agro-ecological environment, safety requirement for field trials).

### 5.2.2. Legislation in the USA

Legislation in relation to production facilities in the USA is essentially comparable to that in Europe.

### 5.2.3. Legislation in The Netherlands

In The Netherlands, the COGEM (commission on genetic modification) deals with applications for use of genetically modified organisms. The COGEM evaluates applications via a case by case scenario. The criteria that are used are given in the “Rule on genetically modified organisms and the pertinent COGEM guidelines” (<http://www.minvrom.nl/minvrom/pagina.html?id=1&goto=1489>; published June 1998). COGEM describes the conditions for greenhouses, climate rooms etc. for production of transgenic plants. The greenhouse facilities needed for transgenic plants that produce pharmaceuticals or nutraceuticals are similar. First, the implications of the GAP guidelines for genetically modified plant production will be discussed. For this, the text in this guideline will be discussed in relation to specific demands on the greenhouse facilities and demands for plant production. Hereafter, the greenhouse facilities related to the transgenic status of the plants will be discussed. For this, EU directive 90/219/EEC and 90/220/EEC in combination with the Dutch rules on genetically modified organisms of the COGEM will be discussed. Finally, the information of the GAP guidelines and of the directives related to genetically modified organisms will be combined to set-up a blueprint for a greenhouse for the production of pharmaceuticals and nutraceuticals and functional foods.

## **5.3. Greenhouse requirements and GAP**

The consequences of the principles and guidelines for GAP for greenhouse construction will be addressed in relation to the different phases of plant production and plant processing.

Whilst the recommendations set out below should be considered to be generally applicable, individual products may present particular quality control issues. Thus, the production and control of each product must be given careful individual consideration taking fully into account any special features.

### 5.3.1. Seeds and propagation material

The occurrence of not species/variety-identical plants and parts of plants has to be controlled in the course of the entire production process. This can easily be performed in greenhouses (better than in the field). No special demands have to be made regarding greenhouse constructions.

### 5.3.2. Cultivation

Depending on the mode of cultivation of transgenic plants for production of nutraceuticals or pharmaceuticals, growers should follow certain Standard Operating Procedures for cultivation. These are not described in any guidelines or directives but have to be elaborated by the growers themselves. In general, care should be taken to avoid environmental disturbances. Greenhouses can be designed in such a way that the probability for such disturbances is at an acceptable level. For instance, the use of gauze in front of windows and the connection of the entrance of the greenhouse compartments to a corridor (atrium) which can only be entered via an air-lock ensures that no insects can enter and that no pollen can exit the greenhouse.

Care has to be taken that no sludge, soil contaminated with heavy metals, residues of plant protection products or any other not naturally occurring chemicals can enter the greenhouse. Irrigation water should be as free as possible from contaminants, such as faeces, heavy metals, pesticides, herbicides and toxicologically hazardous substances. Pesticide and herbicide application should be avoided as far as possible. The use of pesticides has to be documented. It is obligatory that the buyer of the batch be informed of the brand, quality and date of pesticide use in a written form. In greenhouses the use of soil type, fertilizers and pesticides can easily be optimized (especially compared to transgenic plants that grow in the field). In fact, nowadays in the case of regular crop production in greenhouses these demands are already met.

### 5.3.3. Harvest

In the course of the harvest, care should be taken to ensure that no toxic weeds can mix with the harvested crop. Damaged and perished plant parts must be promptly eliminated. The harvested crop must be protected from pests, mice/rodents and domestic animals. Pest control measures should be documented. All these requirements have no extra effects on the demands on greenhouses facilities.

### 5.3.4. Primary processing

Primary processing includes steps of processing such as washing, freezing, distilling, drying etc.. All these processes must conform to European and national regulations. Depending on the production process, primary processing (such as drying) may take place in special compartments of the greenhouse. In many cases specialized companies will conduct primary processing. Requirements for the location for primary processing are comparable to those mentioned under “cultivation”.

#### 5.3.5. Packaging

The harvested product should be promptly packaged according to the demands of the pharmaceutical company that processes the plant material. This can be performed in special compartments of the greenhouse.

#### 5.3.6. Storage and transport

Storage and transport should be according to the demands of the pharmaceutical company that processes the plant material. This can be performed in special compartments of the greenhouse.

#### 5.3.7. Equipment

Equipment should be easy to clean in order to eliminate the risk of contamination. All machinery (preferably non-wooden) should be mounted in an easily accessible way and must be well serviced and regularly cleaned. Fertilizer and pesticide application machinery must be regularly calibrated.

#### 5.3.8. Personnel and facilities

Personnel should receive adequate education before performing tasks that require this knowledge. All processing procedures should fully conform with both EU guidelines on food hygiene (among others EU Directive 93/43) and the general principles for food hygiene of Codex Alimentarius as well as EU Directive 91/356 on good manufacturing practice for pharmaceuticals.

Personnel should be required to have a high degree of personal hygiene (toilets must have hand washing facilities etc.). Persons suffering from known infectious diseases transmittable via food, including diarrhoea, or being transmitters of such diseases, must be suspended from areas where plant processing takes place or wear appropriate protecting clothing, until their complete recuperation. Finally, the welfare of all staff involved in growing and processing shall be ensured.

So, in conclusion, the greenhouses must have proper washing facilities and care has to be taken that the personnel is well educated and does not work when suffering from infectious diseases.

#### 5.3.9. Documentation

The following items must be documented:

- ?? All starting materials and processing steps have to be documented including the location of cultivation. Field records showing previous cropping and inputs should be maintained by all growers.
- ?? All batches from coherent areas should be unambiguously and unmistakably labelled (e.g. by the application of a batch number).
- ?? Batches from differing areas shall be mixed only if it is guaranteed that the mixture in itself will be homogenous. Such mixing procedures should also be documented.

- ?? It is essential to document the type, quantity and the date of harvest of the crop, as well as the chemicals and other substances (e.g. fertilizers, pesticides and herbicides, growth regulators, etc.) used during crop production.
- ?? The application of the fumigation agents such as phosphin must be entered into batch documentation.
- ?? All processes and procedures that could bear an impact on the quality of the product must be entered into the batch documentation.
- ?? All agreements (production guidelines, contracts, etc.) between producer and buyer should be fixed in a written form. It should be documented in a Way Bill (batch documentation) that cultivation, harvesting and production have been performed in accordance with the GAP Guideline. Minimum information included in the Way Bill should cover geographical definition of growth place, country of origin and responsible producer.
- ?? The results of audits should be documented in an Audit Report (copies of all documents, Schlagkartei, Audit Reports, Analyse Reports) to be stored for a minimum of 10 years.
- ?? Special circumstances during the growth period, which may influence the chemical composition like extreme weather conditions, pests - particularly in the harvest period - must be documented. An advantage of greenhouses is that the climate can be controlled.

#### 5.3.10. Education

It is extremely advisable to educate all personnel dealing with the crop or those engaged in the direction of the production regarding production techniques and the appropriate use of herbicides and pesticides.

#### 5.3.11. Quality assurance

Agreements between producers and buyers of medicinal and aromatic plants, with regard to quality questions, e.g. active principles and other characteristic ingredients, optical and sensoric properties, limit values of germ numbers, plant protection chemical residues and heavy metals, must be based on internationally recognized or national specifications and should be laid down in written form.

### **5.4. Implementations of the Dutch regulations on greenhouse requirements**

Implementations of the Dutch regulations on genetically modified organisms on greenhouse requirements for production of pharmaceuticals and nutraceuticals and functional foods is based on Directive 90/219/EEC and 90/220/EEC. The purpose of physical containment is to prevent spreading of genetically modified organisms in the environment. For production of plants three types of greenhouses are described: PK-I (greenhouse ["plantenkas"] 1), PK-II and PK-III. PK-I and PK-II have facilities aimed to limit spreading of pollen, seeds and reproductive parts of genetically modified plants. In PK-I plants may grow in normal soil. PK-II plants need to grow on special substrates (e.g. soil in pots, rockwool). PK-III is suited for activities with normal plants or GMO-plants in combination with genetically modified micro-organisms. Plants that are genetically modified via micro-organisms, for instance *Agrobacterium*

tumefaciens, can only be produced in PK-I or PK-II after they are freed from the genetically modified micro-organisms. This has to be shown with a validated method (is often very difficult).

The type of greenhouse (PK-I, PK-II or PK-III) that needs to be used also depends on the inserted gene, whether or not generative plant parts are covered (paper bags) and the plant type (are related plant species present in the environment?). COGEM gives detailed information about the containment level needed for greenhouses for a particular GMO (appendix C pp 111-114 of the “regeling genetisch gemodificeerde organismen en richtlijnen van de cogem bij deze regeling”, juni 1998).

Construction demands for the different types of greenhouses:

#### 5.4.1. PK-I greenhouse

- ?? Greenhouse has permanent structure with walls and roof, especially made for growing of plants.
- ?? Greenhouse must be entered via a door that can be locked. On this door a sign must be present indicating the GMO status of the plants. Also, the names and telephone numbers of at least one employee involved and of the biological safety functionary must be on the door.
- ?? If plants that can spread via plant parts in the soil, plates must be inserted at least 50 cm deep (or till groundwater level) to prevent spreading.
- ?? If insect-proof gauze is used, the walls and the roof of the greenhouse are allowed to be a construction covered by the gauze.
- ?? If an insect-proof greenhouse is used, the greenhouse needs to be entered via an atrium with a door that can be locked. In the atrium and greenhouse all ventilation canals need to be covered with insect-proof gauze.

#### 5.4.2. PK-II greenhouse

- ?? Greenhouse has a permanent structure with walls, roof and floor especially made for growing of plants.
- ?? Greenhouse must be entered via a door that can be locked. On this door a sign must be present indicating the GMOs status of the plants. Also, the names and telephone numbers of at least one employee involved and of the biological safety functionary must be on the door.
- ?? The floor of the greenhouse is constructed in a way that plant parts can not spread via the soil.
- ?? Ventilation facilities (in- and outlets) are covered with insect-proof gauze.
- ?? If activities with genetically modified micro-organisms are carried out, a washbasin must be present.

#### 5.4.3. PK-III greenhouse

- ?? Greenhouse has permanent structure with walls, roof and floor especially made for growing of plants.

- ?? The contained area is: the greenhouse, an air-lock and workrooms connected to the greenhouse where activities with genetically modified micro-organisms are carried out.
- ?? The workroom is to be entered via an air-lock. The entrance door of the air-lock must have a lock. On the door the biohazard sign must be present and the names and telephone numbers of at least one employee involved and of the biological safety functionary.
- ?? A contained dressing room with washbasin and soap dispenser must be present. Operation of the tap of the washbasin and the soap dispenser must be possible without using hands.
- ?? The windows of the workroom are closed and sealed with kit.
- ?? The floor has to be waterproof. A collection facility is present for waste water of greenhouse, workroom, atrium, washbasin and shower. If air release of this facility is outside the greenhouse, a HEPA filter must be present.
- ?? Appropriate facilities are present for inactivation of genetically modified micro-organisms.
- ?? A ventilation system is present that ensure a air pressure that is 30 Pa lower in the greenhouse than the ambient air pressure. The air pressure in the workroom is lower than in the contained dressing room and shower; these have an air pressure lower than that of the clean dressing room (and outside air pressure).
- ?? Possible additional demand: if the only passage between clean and contained dressing room is an air-lock, a shower must be built in the air-lock.
- ?? Possible additional demand: An air-lock for outlet of materials. This air-lock must have two doors that can not be opened at the same time.

## 5.5. Conclusions for greenhouse facilities

Production of pharmaceuticals and nutraceuticals in GMOs in greenhouses is bound by special rules related to the transgenic status of the plants and according to the guidelines for GAP. GAP must be discussed with the company that processes the harvested transgenic plant material and certain Standard Operating Procedures for cultivation must be agreed upon. The GAP guidelines EMEA/HMPWG/25/99 can be used as a reference. As a result of GAP and GMO legislation, special demands need to be met with regard to the methods for plant production and to the required greenhouse facilities. The demands related to the greenhouse facilities are summarised in the Table 2. PK-I and PK-II conditions can easily be introduced in most greenhouses. GAP demands that extra rooms for primary processing, packaging and storage are made. This is probably possible at reasonable costs. However, PK-III conditions require substantial investments related to the extra rooms, waterproof floors, air-locks, ventilation system with lowered pressure etc.

The type of greenhouse (PK-I, PK-II or PK-III) that needs to be used depends on the inserted gene, whether or not flowers are covered and the plant species. Careful selection of especially the plant species may overcome the need for PK-III facilities. COGEM gives detailed information about the containment level needed for greenhouses for different GMOs.

**Table 2 Facilities related to different levels of containment.**

<b>PK-I greenhouse</b>	<b>PK-II greenhouse</b>	<b>PK-III greenhouse</b>
Normal greenhouse, floor not necessary (see description)	Normal greenhouse with floor	Normal greenhouse with floor
Insect gauze	Insect gauze	Airlock(s) for personnel
Atrium for entrance of the greenhouse	Atrium for entrance of the greenhouse	Workroom(s) (closed rooms etc.)
	Washbasin	Dressing room
		Washbasin + dispensers etc.
		Waterproof floors
		Collection facilities for waste water (HEPA filter)
		Inactivation facilities for micro-organisms
		Ventilation system that ensures lowered pressure (HEPA filter)
		(Optional) airlock for personnel with shower
		(Optional) airlock for outlet of material

## 6. Case: Crop Plants Producing rFSH

### 6.1. Purposes

A recombinant form of follicle stimulating hormone (rFSH) serves as model for a pharmaceutical protein produced by a hypothetical genetically modified crop plant. Follicle stimulating hormone (FSH) is a dimeric glycoprotein that induces ovulation. Together with luteinizing hormone it constitutes “gonadotropin”. Pharmaceutical preparations may contain either “chorionic gonadotropin” or “menopausal gonadotropin”. Chorionic gonadotropin is produced by trophoblast cells and is present in high amounts in serum and urine of females after 7-12 weeks of pregnancy. In addition, serum and urine of postmenopausal females contain elevated gonadotropins, which may serve as source of menopausal gonadotropin. FSH, LH, and gonadotropin have found application for infertility treatment in human females involved in *in vitro* fertilisation therapy, while in animals such as cows it is used as inducer of superovulation. In addition, some preparations are prescribed to treat male infertility as well, since FSH stimulates testosterone production. FSH cannot be applied within the crop as food or animal feed because FSH is orally inactive, which is most likely caused by intestinal degradation of FSH. Preparations containing FSH that have been approved for medicine use in the EU, The Netherlands, and USA are listed in Table 3 (human) and Table 4 (veterinary). In most approved medicine applications, FSH is injected subcutaneously, intramuscularly, or intravenously.

FSH for pharmaceutical purposes has been isolated from female body fluids and - parts, such as urine, serum, and pituitary glands. The advantages of FSH produced through recombinant DNA technology, however, are that i) the FSH preparation will be free of antagonistic luteinizing hormone activity (Prasmusinto, 1999) and ii) that pure FSH can be combined with other hormones in any desired ratio. The commercial recombinant FSH products are produced by genetically modified Chinese hamster ovary (CHO) cell lines. An additional advantage of the envisioned production of rFSH in crop plants rather than in CHO cells is the avoidance of the risk of transmission of mammalian pathogens (*e.g.* viruses, prions) through CHO cell culture, which eliminates the costs inherent to the efforts to control this risk under good manufacturing practices.

An additional application for rFSH may be in pregnancy testing as reference material for *in vitro* diagnosis of human chorionic gonadotropin (hCG) or its subunits in female urine, plasma, or serum. Kits for hCG-diagnosis are available “over the counter” for clinical- and physician’s office- laboratories in the USA. To acquire marketing permission for such kits, the specificity and sensitivity of the test should be demonstrated in clinical trials (FDA, 2000k).

In the EU, pregnancy tests fall under the definition of an *in vitro* diagnostic medical device and are thus regulated by EU Directive 98/79. For pregnancy tests, a distinction will be made between devices for self-testing (by users at home) or laboratory use. In the case of a self-testing device, a “notified body” (*e.g.* an independent certifying institution) must evaluate the technical data and the quality assurance program for production. Laboratory tests for pregnancy are exempt, however, from evaluation by a notified body. Both self-testing- and laboratory-

pregnancy tests should acquire a CE marking for compliance with European standards.

## 6.2. Cultivation

In The Netherlands, production conditions for a genetically modified crop can either be in-doors (“contained use”) or out-doors (“environmental release”) (see section 3.2. and chapter 5). The transgene product rFSH will possess endocrine activity, hence open-field cultivation of the novel crop may prove unfeasible unless its environmental hazard, *e.g.* for wildlife, can be negated. It may be worth noting here that FSH is orally inactive, hence consumption of the crop is unlikely to cause pharmacological effects. In the case of “contained use”, measures should be taken to avoid environmental escape of viable genetically modified plant material during handling of the harvested crop, else this will be regarded “environmental release”. The time-savings and lesser dossier requirements for “contained use” should be waged against the lower costs of field cultivation, *i.e.* “environmental release”.

## 6.3. Application for medicinal use

FSH and rFSH have already been approved for use as human- and veterinary medicine (Tables 3 and 4). In the EU, full dossiers should be compiled for all biotechnology-derived medicinal products, including pre-clinical and clinical trial data, regardless if they may be “bio-equivalent” to previously approved products. Our hypothetical plant-derived rFSH preparation will therefore require full testing. A “short-cut” route for bio-equivalent biotechnology-derived “biologics” appears possible in the USA, but FDA’s policy on this issue is still evolving. In the most optimistic setting, less extensive testing will be required for the hypothetical “bio-equivalent” rFSH in the USA than in the EU.

rFSH has so far been produced by genetically modified cultures of Chinese hamster ovary (CHO) cells. The fact that FSH is a glycoprotein may complicate the demonstration of “bio-equivalence”, as glycosylation in plants may differ from that in, for example, hamster cells.

It may be worth mentioning here that the difference in chemical composition between a “bio-equivalent” urinary gonadotropin and a reference medicine already approved for medicinal use has been disputed over in a lawsuit between two pharmaceutical companies in the USA. The court finally ruled in favour of the “bio equivalent” gonadotropin (US Court of Appeals, 1998; Biospace, 2000; PR Newswire, 2000). The disputed difference in protein glycosylation between the FSH molecules was described as “microheterogeneity”. The heterogeneity between crop-plant-derived rFSH and CHO-cell-derived rFSH may, however, be larger than the microheterogeneity observed between the urinary FSH molecules. It remains therefore uncertain if this lawsuit has set a precedent for our hypothetical rFSH preparation, if this were to be clinically equivalent to the currently approved CHO-cell-derived rFSH preparations.

To avoid conflict with the protection afforded by patents and exclusivity terms to some FSH preparations already in the market (Tables 3 and 4), care should be taken in choosing the appropriate formulation and uses of the hypothetical rFSH.

With regard to the choice of production conditions, some reference is provided by an EU guideline on the manufacturing through genetically modified cell lines of cytokines, which are comparable to FSH in that they are physiologically active glycoproteins (pp. 223-235, vol. 3A of [EC, 1997]). It is recommended herein to pay attention to the post-translational modification of the cytokines under the manufacturing conditions, and to avoid contamination with viruses and DNA. Each batch should also be tested for activity in animals.

**Table 3 Recombinant FSH and gonadotropin approved for medicinal use**

<i>Active ingredient</i> <sup>1</sup>	<i>Brand name</i>	<i>Manufacturer</i>	<i>Region</i> <sup>2</sup>
Follicle stimulating hormone, recombinant (follitropin-alpha)	Gonal-F	Serono	EU, NL, USA
Follicle stimulating hormone, recombinant (follitropin-beta)	Puregon	Organon	EU, NL
Follicle stimulating hormone, recombinant (follitropin-beta)	Follistim	Organon	USA
Gonadotropin, chorionic, recombinant human	Ovidrel	Serono	EU, USA

<sup>1</sup> Gonadotropin contains both follicle stimulating hormone (FSH)- and luteinising hormone (LH)- activities.

<sup>2</sup> Data from BRD (2001), CVZ (2000b), EC (2000b), EMEA (2001) and FDA (2001d, 2001e).

**Table 4 Approvals for the use of non recombinant FSH and gonadotropin as human and veterinary medicine**

<i>Active ingredient</i> <sup>1</sup>	<i>Target species</i>	<i>Region</i> <sup>2</sup>
Follicle stimulating hormone	human	USA, NL
Follicle stimulating hormone <sup>3</sup>	all food producing animals	EU
Follicle stimulating hormone	cow	NL
Follicle stimulating hormone	cow, dog, mare, sheep, swine	USA
Gonadotropin	human	USA, NL
Gonadotropin	all food producing animals	EU
Gonadotropin	cow, dog, goat, horse, rabbit, sheep, swine	NL
Gonadotropin	cow, fish, swine	USA

<sup>1</sup> Gonadotropin contains both follicle stimulating hormone (FSH)- and luteinising hormone (LH)- activities.

<sup>2</sup> Data from BRD (2001), CVZ (2000b), EC (2000b), EMEA (2001) and FDA (2001d, 2001e).

<sup>3</sup> Synthetic analogues (*i.e.* recombinant FSH) included

Exploitation and regulation of plants genetically modified to express nutraceuticals and pharmaceuticals  
<http://www.rikilt.wageningen-ur.nl/nutraceuticals>

## 7. General Conclusions

### 7.1. Definitions

- ⚡⚡ A functional food is similar in appearance to, or may be, a conventional food, is consumed as part of a usual diet, and is demonstrated to have physiological benefits and/or reduce the risk of chronic disease beyond basic nutritional functions (Health Canada working definition).
- ⚡⚡ A nutraceutical is a product isolated or purified from foods that is generally sold in medicinal forms not usually associated with food and demonstrated to have a physiological benefit or provide protection against chronic disease (Health Canada working definition).
- ⚡⚡ A pharmaceuticals is a single, well-defined medicinal and therapeutic compound that is administered with the purpose to cure, prevent, or diagnose disease. Similar compounds for veterinary application are also categorized to pharmaceuticals.

### 7.2. Biosafety considerations

Concerning production of pharmaceuticals and nutraceuticals transgenically in (crop) plants, the specific characteristics of the plant and the recombinant compounds, the culture requirements, and the (national and international) guidelines and regulations make each production system an individual case. Biosafety assessments therefore needs to be carried out on a 'case-by-case' basis. For pharmaceuticals and nutraceuticals and their producing crops, a case should be considered to include the entire production chain from agricultural production towards the aimed effect of the ultimate product in human or animal.

### 7.3. Regulatory options

Out-doors cultivation- and market introduction- of genetically modified plants in the EU require a more extensive risk assessment than in-doors cultivation (“contained use”). In addition, out-doors cultivation and marketing will require “post market surveillance” under the recently adopted amendments to EU legislation. No specific guidelines have been developed, however, on how to carry out such a surveillance. In-doors cultivation of a genetically modified crop and processing to non-viable products would help to circumvent some of the legal requirements for out-door cultivation, such as post market surveillance and field testing. The additional costs for cultivation in, for example, greenhouses should therefore be waged against the additional time and expenses spent on the preparation of dossiers (*e.g.* field trials, toxicology) for approval of out-doors cultivation. The possibilities for cultivation in greenhouses are discussed below.

With regard to the possible food- and feed- applications (in the broadest meaning) the regulatory options appeared most attractive to us for “functional foods”, “functional feed”, and “nutraceuticals”:

?? Functional foods:

EU

The most attractive appear to be non viable products that are substantially equivalent to conventional products on the market. Such products should either

Exploitation and regulation of plants genetically modified to express nutraceuticals and pharmaceuticals

<http://www.rikilt.wageningen-ur.nl/nutraceuticals>

be imported or produced from in-house cultivated plants within the same facility. The derived food product may follow the short-cut “notification” route for novel foods (Figure 2).

### USA

The food components introduced or altered by the genetic modification should preferably be identical to previously approved “GRAS” substances (generally recognised as safe) or “food additives” to avoid lengthy approval procedures for truly novel components. In addition, safe foods and food ingredients may find application as “medical food” with less stringent requirements for labelling and health-related claims.

An additional opportunity is to market the functional food as a food supplement in the USA. Ingredients of such supplements need not be GRAS, but the manufacturer should be able to prove their safety on request. For novel supplement ingredients, manufacturers should file a notification supported by safety data to the FDA 75 days prior to marketing. Although less “substance disease” claims are permitted than for foods, it is possible to attach “qualified” claims to these products.

?? Functional feed:

### EU

Non viable products from genetically modified plants are exempt from animal feed evaluation under the EU legislation pertaining to such plants. Currently a voluntary notification procedure for these non viable products exists in The Netherlands. This situation will likely change in the near future as proposed EU legislation on Novel Feeds will also cover non viable products for animal feed purposes.

### USA

Safety requirements for animal feeds resemble those for food. Given the low added value for animal feeds in general, efforts to attain a safety status for food, with higher added value, may turn out more rewarding.

?? Nutraceutical:

### Food purposes

Nutraceuticals may be used as food ingredients (see “functional foods”). In addition, nutraceuticals may serve as food additives in the EU and USA, which is an attractive option if they are equivalent to food additives that have been previously found safe; otherwise, elaborate safety testing of the envisioned food additive will be required.

### Feed purposes

Nutraceuticals can be used either as feed ingredients (see “functional feeds”) or as feed additives.

No special requirements have been made for feed additives derived from genetically modified organisms in legislation, contrary to feed and feed ingredients. Feed additives may be an attractive option if the chosen (purified)

Exploitation and regulation of plants genetically modified to express nutraceuticals and pharmaceuticals

<http://www.rikilt.wageningen-ur.nl/nutraceuticals>

additive has previously been approved, because otherwise extensive toxicity- and efficiency- testing will be required. Whereas the presence in feed additives of DNA containing antibiotic resistance marker genes should be avoided in the EU, this may still be allowed for previously approved marker genes in the USA.

In conclusion, most attractive for food- and feed-purposes appear purified products from genetically modified plants that are equivalent to conventional products. Their equivalence to existing products and their non viable nature will simplify the safety evaluation procedure. In addition, applications with high added value, such as “medical foods”, “food additives”, and “feed additives” appear feasible.

With regard to pharmaceuticals, American regulations for biotechnology-derived medicines may be less demanding than EU regulations. The EU namely requires that any biotechnology-derived medicine be evaluated in full. In the USA, shorter procedures are possible in case of “bio-equivalence” to a previously approved “generic” medicine, though this may not apply to “biologics”.

## 7.4. Options for contained culture

Production of pharmaceuticals and nutraceuticals in GMOs in greenhouses is bound by special rules related to the transgenic status of the plants and according to the guidelines for GAP. As a result of GAP and GMO legislation, special demands need to be met with regard to the methods for plant production and to the required greenhouse facilities. PK-I and PK-II conditions can easily be introduced in most greenhouses. GAP demands that extra rooms for primary processing, packaging and storage are made. PK-III conditions require substantial investments.

The type of greenhouse (PK-I, PK-II or PK-III) that needs to be used depends on the inserted gene, the plant species involved and its biological characteristics (especially related to pollination). Careful selection of especially the plant species may overcome the need for PK-III facilities. COGEM gives detailed information about the containment level needed for greenhouses for GMOs.

## 7.5 Conclusions on the case: Crop producing recombinant FSH

The least burdensome option for the purified recombinant follicle stimulating hormone (rFSH) appears to be its use as reference material for pregnancy testing, for which limited clinical testing is required in the USA.

### *Most appealing option*

?? Use as reference material for pregnancy tests in the USA.

**Note:** As this report was being completed, the European Commission released a proposal for a new EU Regulation on genetically modified foods and animal feed, as well as on the traceability and labelling of these foods and feed (EC, 2001bc). Among the proposed changes to the existing EU legislation are:

?? Documenting the use of genetically modified foods and feed throughout the entire production chain.

Exploitation and regulation of plants genetically modified to express nutraceuticals and pharmaceuticals

<http://www.rikilt.wageningen-ur.nl/nutraceuticals>

- ?? Labelling of all products derived from genetically modified organisms, including, among others:
  - Foods and animal feeds without detectable traces of foreign DNA or protein.
  - Food- and feed- additives.
- ?? Abolishment of the “notification” short cut procedure for novel foods.
- ?? Premarket evaluation of non viable animal feed similar to viable feed.
- ?? Post market surveillance for genetically modified foods and feed to detect unforeseen long term effects.

These changes, if they are indeed adopted, will diminish the attractiveness of the options described above for the EU. An alternative option for a functional food or nutraceutical in the EU may be their marketing as food supplements, which are not mentioned in the European Commission’s proposal. No harmonised EU legislation, however, exists on food supplements yet.

## References

AAFCO (1999) AAFCO memo from the Nutraceutical Regulatory Advisory Panel, 01/26/99. Association of Animal Feed Control Officials.

<http://www.localline.com/~aafco/nrapr.htm>

AAFCO (2000) Proposed guidance document for manufacturing, packaging or distribution, of animal feeds and feed ingredients (draft 7/8/00). Association of Animal Feed Control Officials.

[http://www.aafco.org/Proposed\\_Guidance.pdf](http://www.aafco.org/Proposed_Guidance.pdf)

Advertising Code Committee (2000) The Dutch Advertising Code. Dutch Advertising Committee, Amsterdam.

<http://www.reclamecode.nl/pdf/DAC.pdf>

AESGP (1998) Herbal medicinal products in the European Union. Study carried out on behalf of the European Commission. Association of the European Self-Medication Industry, Brussels.

<http://pharmacos.eudra.org/F2/pharmacos/docs/doc99/Herbal%20Medecines%20EN.pdf>

Baron, F (2000) Les guidelines en pharmacoéconomie. GYD Institut, Lyon.

[http://www.medcost.fr/Html/economie\\_sante\\_eco/eco\\_070600.htm](http://www.medcost.fr/Html/economie_sante_eco/eco_070600.htm)

Bijman, J. (1999). Life science companies: can they combine seeds, agrochemicals and pharmaceuticals? *Biotechnology Development Monitor* 40:14-19.

<http://www.biotech-monitor.nl/4007.htm>

Biospace (2000) Generic fertility drug by Ferring gets a boost from Appeals Court. Biospace, October 29, 1998.

[http://www.biospace.com/news\\_story.cfm?StoryID=21513](http://www.biospace.com/news_story.cfm?StoryID=21513)

BRD (2001) Diergeneesmiddelen database. Dutch Board for the Registration of Veterinary Medicines.

<http://www.brd.agro.nl/dbindex.htm>

Brower, V. (1998). Nutraceuticals: poised for a healthy slice of the market? *Nature Biotechnology* 16: 728-731.

CBG (2000a) Advies verkrijgbaarheid zelfzorggeneesmiddelen. Dutch Medicines Evaluation Board.

<http://www.cbg-meb.nl/nl/docs/nieuws/zelfzorg.pdf>

CBG (2000b) Pharmacovigilance. Dutch Medicines Evaluation Board.

<http://www.cbg-meb.nl/uk/reghoudr/pv-indx.htm>

Codex (1997) Basic texts on food hygiene. Food and Agriculture Organisation of the United Nations / World Health Organisation, Codex Alimentarius Commission.

[ftp://ftp.fao.org/codex/standard/Fh\\_basic\\_e.pdf](ftp://ftp.fao.org/codex/standard/Fh_basic_e.pdf)

- Exploitation and regulation of plants genetically modified to express nutraceuticals and pharmaceuticals  
<http://www.rikilt.wageningen-ur.nl/nutraceuticals>
- CPMP (1997) ICH Topic S6. Preclinical safety evaluation of biotechnology-derived pharmaceuticals (step 4, consensus guideline, 16 July, 1997). Note for guidance on preclinical safety evaluation of biotechnology-derived pharmaceuticals (CPMP/ICH/302/95). European Agency for the Evaluation of Medicinal Products, Committee for Proprietary Medicinal Products, London.  
<http://www.emea.eu.int/pdfs/human/ich/030295en.pdf>
- CVZ (2000a) Handleiding voor Kostenonderzoek. College voor Zorgverzekeringen, Amstelveen.  
[http://www.cvz.nl/Pub\\_OverigePublicatiesDetail.asp?InformatieID=233&Title=overigepublicaties](http://www.cvz.nl/Pub_OverigePublicatiesDetail.asp?InformatieID=233&Title=overigepublicaties)
- CVZ (2000b) Positieve lijst geneesmiddelen. College voor Zorgverzekeringen, Amstelveen.  
[http://www.cvz.nl/Wet\\_PositieveLijstZoek.asp?Title=positievelijst](http://www.cvz.nl/Wet_PositieveLijstZoek.asp?Title=positievelijst)
- Diplock, A.T., Aggett, P.J., Ashwell, M., Bornet, F., Fern, E.B. & Roberfroid, M.B. (1999). Scientific concepts of functional foods in Europe: Consensus document. *British Journal of Nutrition* 81 (Suppl. No. 1): S1-S27.
- Dixon, R.A., Arntzen, C.J. (1997). Transgenic plant technology is entering the era of metabolic engineering. *Trends in Biotechnology* 15: 441-444.
- Dove, A. (2001) Betting on biogenerics. *Nature Biotechnology* 19: 117-120.
- EC (1997) EudraLex: The rules governing medicinal products in the European Union. European Commission, Directorate General III. Office for Official Publications of the European Communities, Luxembourg.  
<http://pharmacos.eudra.org/F2/eudralex/index.htm>
- EC (2000a) Proposal for a directive of the European Parliament and of the Council on the approximation of the laws of the Member States relating to food supplements. Amendments. European Commission, Brussels.  
[http://europa.eu.int/eur-lex/en/com/dat/2000/en\\_500PC0222.html](http://europa.eu.int/eur-lex/en/com/dat/2000/en_500PC0222.html)
- EC (2000b) Consolidated version of the Annexes I to IV of Council Regulation n° 2377/90, updated on 07.12.2000. European Commission, Directorate General III, Brussels.  
<http://pharmacos.eudra.org/F2/mrl/index.htm>
- EC (2001a) Discussion paper on nutrition claims and functional claims. European Commission, Directorate General Health and Consumer Protection, Brussels.  
[http://europa.eu.int/comm/food/fs/fl/fl03\\_en.pdf](http://europa.eu.int/comm/food/fs/fl/fl03_en.pdf)
- EC (2001b) Preliminary text of proposal for a regulation of the European Parliament and of the Council concerning traceability and labelling of genetically modified organisms and traceability of food and feed products produced from genetically modified organisms, 25 July 2001. European Commission, Brussels.  
[http://europa.eu.int/comm/food/fs/biotech/biotech09\\_en.pdf](http://europa.eu.int/comm/food/fs/biotech/biotech09_en.pdf)

EC (2001c) Preliminary text of proposal for a regulation of the European Parliament and of the Council on genetically modified food and feed, 25 July 2001. European Commission, Brussels

[http://europa.eu.int/comm/food/fs/biotech/biotech08\\_en.pdf](http://europa.eu.int/comm/food/fs/biotech/biotech08_en.pdf)

EMA (2001) Medicinal products with a Community marketing authorisation. European Agency for the Evaluation of Medicinal Products, London.

<http://www.emea.eu.int/pdfs/general/direct/listprod/3116001en.pdf>

EP (2000a) European Parliament resolution on the Commission White Paper on food safety (COM(1999) 719 - C5-0136/2000 - 2000/2082(COS)). October 25, 2000.

[http://www3.europarl.eu.int/omk/omnsapir.so/pv2?PRG=DOCPV&APP=PV2&SDOCTA=12&TXTLST=1&TPV=PROV&POS=1&Type\\_Doc=RESOL&DATE=251000&DATEF=001025&TYPEF=A5&PrgPrev=TYPEF@A5|PRG@QUERY|APP@PV2|FILE@BIBLIO00|NUMERO@272|YEAR@00|PLAGE@1&LANGUE=EN](http://www3.europarl.eu.int/omk/omnsapir.so/pv2?PRG=DOCPV&APP=PV2&SDOCTA=12&TXTLST=1&TPV=PROV&POS=1&Type_Doc=RESOL&DATE=251000&DATEF=001025&TYPEF=A5&PrgPrev=TYPEF@A5|PRG@QUERY|APP@PV2|FILE@BIBLIO00|NUMERO@272|YEAR@00|PLAGE@1&LANGUE=EN)

EP (2000b) Report on a proposal for a Council Directive amending Directive 70/524/EEC concerning additives in feedingstuffs - Committee on Agriculture and Rural Development. (A5-0015/00).

<http://www2.europarl.eu.int/omk/OM-Europarl?PROG=REPORT&L=EN&PUBREF=-//EP//NONSGML+REPORT+A5-2000-0015+0+DOC+WORD+V0//EN&LEVEL=2>

EP (2001a) Directive of the European Parliament and of the Council on the deliberate release into the environment of genetically modified organisms and repealing Council Directive 90/220/EEC. Joint text approved by the Conciliation Committee - (C5-0685/2000), GMO – 1998/0072COD.

[http://www2.europarl.eu.int/omk/OM-Europarl?PROG=DOC-C&L=EN&SORT\\_ORDER=D&F\\_REFERENCE=\\*&REFERENCE=%](http://www2.europarl.eu.int/omk/OM-Europarl?PROG=DOC-C&L=EN&SORT_ORDER=D&F_REFERENCE=*&REFERENCE=%)

EP (2001b) Report on the proposal for a European Parliament and Council directive on the approximation of the laws of the Member States relating to food supplements, A5-0025/2001, COM(2000) 222 – C5-0234/2000 – 2000/0080(COD).

<http://www2.europarl.eu.int/omk/OM-Europarl?PROG=REPORT&L=EN&PUBREF=-//EP//TEXT+REPORT+A5-2001-0025+0+NOT+SGML+V0//EN&LEVEL=4>

EU (1997) 97/618/EC: Commission Recommendation of 29 July 1997 concerning the scientific aspects and the presentation of information necessary to support applications for the placing on the market of novel foods and novel food ingredients and the preparation of initial assessment reports under Regulation (EC) No 258/97 of the European Parliament and of the Council. Official Journal of the European Communities L253: 1-36.

[http://europa.eu.int/eur-lex/en/lif/dat/1997/en\\_397H0618.html](http://europa.eu.int/eur-lex/en/lif/dat/1997/en_397H0618.html)

EU (2000) Facts on GMOs in the EU, MEMO/00/43. European Union, Brussels.

[http://europa.eu.int/comm/dgs/health\\_consumer/library/press/press63\\_en.pdf](http://europa.eu.int/comm/dgs/health_consumer/library/press/press63_en.pdf)

Exploitation and regulation of plants genetically modified to express nutraceuticals and pharmaceuticals

<http://www.rikilt.wageningen-ur.nl/nutraceuticals>

Evenson, D.D. (2000) Patent and other private legal rights for biotechnology inventions (Intellectual Property Rights – IPR). In: *Agriculture and Intellectual Property Rights. Economic, Institutional and Implementation Issues in Biotechnology* (V. Santaniello, R.E. Evenson, D. Zilberman, G.A. Carlson, eds.), CABI, Wallingford, pp. 11-25.

FDA (1992) Statement of policy: foods derived from new plant varieties. Food and Drug Administration. Federal Register 57 (May 29, 1992): 22984-23005.

<http://vm.cfsan.fda.gov/~lrd/bio1992.html>

FDA (1998) FDA/CVM 1998 adverse drug experience reports - a descriptive overview. Food and Drug Administration, Center for Veterinary Medicine.

<http://www.fda.gov/cvm/index/ade/fdave98.htm>

FDA (1999) Statement of identity, nutrition labeling, and ingredient labeling of dietary supplements; small entity compliance guide. Food and Drug Administration, Center for Food Safety and Applied Nutrition.

<http://www.cfsan.fda.gov/~dms/guidance.html>

FDA (2000a) Toxicological principles for the safety testing of food ingredients; Redbook 2000. Food and Drug Administration, Center for Food Safety and Applied Nutrition.

<http://www.cfsan.fda.gov/~redbook/red-toca.html>

FDA (2000b) Foods for special dietary use. Food and Drug Administration.

<http://www.fda.gov/opacom/morechoices/smallbusiness/blubook/specdiet.htm>

FDA (2000c) Medical foods. Food and Drug Administration. Centre for Food Safety and Applied Nutrition.

<http://vm.cfsan.fda.gov/~dms/ds-medfd.html>

FDA (2000d) Abbreviated new drug application (ANDA) process for generic drugs. Food and Drug Administration, Center for Drug Evaluation and Research.

<http://www.fda.gov/cder/regulatory/applications/ANDA.htm>

FDA (2000e) Over-the-counter drugs. Milestone status of OTC drug review documents. Food and Drug Administration, Center for Drug Evaluation and Research.

<http://www.fda.gov/cder/otc/index.htm>

FDA (2000f) Guidance for industry. Botanical drug products. Draft guidance. Food and Drug Administration, Center for Drug Evaluation and Research.

<http://www.fda.gov/cder/guidance/1221dft.pdf>

FDA (2000g) New animal drug application (NADA), Information and requirements for review and approval. Food and Drug Administration.

<http://www.fda.gov/cvm/index/other/nadaappr.htm>

FDA (2000h) Guidance documents. Food and Drug Administration, Center for Veterinary Medicine.

<http://www.fda.gov/cvm/guidance/guidance.html>

FDA (2000i) Classification of OTC and Rx drugs (Guide 1240.2220). Food and Drug Administration, Center for Veterinary Medicine.

[http://www.fda.gov/cvm/index/policy\\_proced/2220.pdf](http://www.fda.gov/cvm/index/policy_proced/2220.pdf)

FDA (2000j) Hazard analysis and critical control point. Food and Drug Administration. Centre for Food Safety and Applied Nutrition.

<http://vm.cfsan.fda.gov/~lrd/haccp.html>

FDA (2000k) Review criteria for assessment of professional use human chorionic gonadotropin (hCG) in vitro diagnostic devices (IVDs). Food and Drug Administration, Center for Devices and Radiological Health.

<http://www.fda.gov/cdrh/ode/phcg.html>

FDA (2001a) FDA announces proposal and draft guidance for food developed through biotechnology. Food and Drug Administration, Center for Food Safety and Applied Nutrition.

<http://www.cfsan.fda.gov/~lrd/hhbioen3.html>

FDA (2001b) New dietary ingredients in dietary supplements. Food and Drug Administration, Center for Food Safety and Applied Nutrition.

<http://www.cfsan.fda.gov/~dms/ds-ingrd.html>

FDA (2001c) Labeling of dietary supplements. Food and Drug Administration, Center for Food Safety and Applied Nutrition.

<http://www.cfsan.fda.gov/~dms/ds-labl.html>

FDA (2001d) Electronic orange book: approved drug products with therapeutic equivalence evaluations. Food and Drug Administration, Center for Drug Evaluation and Research.

<http://www.fda.gov/cder/ob/default.htm>

FDA (2001e) The green book. Food and Drug Administration, Center for Veterinary Medicine.

<http://www.fda.gov/cvm/greenbook/greenbook.html>

FUFOSE (1999). FUFOSE developments in understanding functional foods. *Nutraceuticals International* 4 (1): 1-2.

Gilissen, L.J.W.J., Metz, P.L.J., Stiekema, W.J. & Nap, J.P. (1998). Transgene-centred evaluation of genetically modified plants. In: *Past, Present and Future Considerations in Risk Assessment when Using GMO's. Second International CCRO Workshop Proceedings* (De Vries, G.E., ed.), CCRO, Bilthoven, pp. 83-88.

Hammond, J., McGarvey, P., Yusibov, V. (1999). *Plant biotechnology. New products and applications*. Springer, Berlin.

- Exploitation and regulation of plants genetically modified to express nutraceuticals and pharmaceuticals  
<http://www.rikilt.wageningen-ur.nl/nutraceuticals>
- Health Canada (1998) Nutraceuticals / functional foods and health claims on foods (Policy paper). Health Canada, Therapeutic Products Programme and the Food Directorate from the Health Protection Branch.  
<http://www.hc-sc.gc.ca/hpb-dgps/therapeut/htmleng/ffn.html>
- Helsper, J.P.F.G. (1998). Onderzoek aan gezondheidbevorderende stoffen. AB Nota Vol. 114. Research Institute for Agrobiological and Soil Fertility (AB-DLO), Wageningen.
- Hill and Knowlton (2000) Study on nutritional, health, and ethical claims in the European Union. Hill and Knowlton International, Brussels.  
[http://europa.eu.int/comm/consumers/policy/developments/envi\\_clai/envi\\_clai02\\_en.html](http://europa.eu.int/comm/consumers/policy/developments/envi_clai/envi_clai02_en.html)
- HMPWG (1999) Report from the ad hoc working group on herbal medicinal products 1997/1998. EMEA/HMPWG/25/99. European Agency for the Evaluation of Medicinal Products, Herbal Medicinal Products Working Party, London.  
<http://www.emea.eu.int/pdfs/human/hmpwp/002599en.pdf>
- HMPWP (2000) Press releases, draft documents, final documents. European Agency for the Evaluation of Medicinal Products, Herbal Medicinal Products Working Party, London.  
<http://www.emea.eu.int/htms/human/hmpwp/hmpwppr.htm> (press releases)  
<http://www.emea.eu.int/htms/human/hmpwp/hmpwpdraft.htm> (draft guidelines)  
<http://www.emea.eu.int/htms/human/hmpwp/hmpwpfin.htm> (adopted guidelines)
- ICH (2001) ICH topics and guidelines. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, Geneva.  
<http://www.ifpma.org/ich1.html>
- ILSI (1998) Addition of nutrient to food: nutritional and safety considerations : moving towards a scientific consensus : summary of a workshop held in December 1997. International Life Sciences Institute, Washington DC.
- Institute of Medicine (1999) Enhancing the regulatory decision-making approval process for direct food ingredient technologies. National Academy Press, Washington, DC  
<http://books.nap.edu/books/0309064864/html/index.html>
- KOAG/KAG (2000a) Code voor de Aanprijzing van Gezondheidsproducten. Keuringsraad KOAG/KAG, Badhoevedorp.  
<http://www.koagkag.nl/leidraad/cagindex.html>
- KOAG/KAG (2000b) Code voor de publieksreclame voor geneesmiddelen. Keuringsraad KOAG/KAG, Badhoevedorp.  
<http://www.koagkag.nl/leidraad/cpgindex.html>
- Kok, E.J., Bijman, W.J.J., Dale, M.F.B., Noordam, M.Y., Kuiper, H.A. (1996) Evaluation of costs of national registration procedures in traditional and biotechnological breeding programmes. Final report, EU BIOTECH programme,

Exploitation and regulation of plants genetically modified to express nutraceuticals and pharmaceuticals  
<http://www.rikilt.wageningen-ur.nl/nutraceuticals>  
project BIOT2-CT94-0042. National Institute for Quality Control of Agricultural Products (RIKILT), Wageningen.

Kowalski, T.J. (2000) Analyzing the new written description guidelines. With the USPTO's revised guidelines the patent landscape has changed yet again. *Nature Biotechnology* 18: 461-462.

Kurtzweil, P. (1998) Staking a claim to good health. FDA and science stand behind health claims on foods. *FDA Consumer* (November-December, 1998)  
<http://www.cfsan.fda.gov/~dms/fdhclm.html>

Metz, P.L.J., Nap, J.P. (1997). A transgene-centred approach to the biosafety of transgenic plants: overview of selection and reporter genes. *Acta Botanica Neerlandica* 46, 25-50.

Miele, L. (1997). Plants as bioreactors for biopharmaceuticals: regulatory considerations. *Trends in Biotechnology* 15: 45-50.

Nutley, C. (2000) The value and benefits of ICH to industry. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, Geneva.  
<http://www.ifpma.org/pdfifpma/ValueBenefits.pdf>

Nutrition Centre (1998) Code of practice assessing the scientific evidence for health benefits stated in health claims on food and drink products. Nutrition Centre, The Hague.  
[http://www.voedingscentrum.org/gedra\\_en.html](http://www.voedingscentrum.org/gedra_en.html)

OAG (1999) What's in a nonprofit's name? Office of New York's State Attorney General.  
[http://www.oag.state.ny.us/press/reports/nonprofit/full\\_text.html](http://www.oag.state.ny.us/press/reports/nonprofit/full_text.html)

Ohlrogge, J. (1999). Plant metabolic engineering: are we ready for phase two? *Current Opinion in Plant Biology* 2: 121-122.

PDV (1999) Expanding GMP regulations for the Animal Feed Sector with HACCP hazard factors. Product Board for Animal Feed, The Hague.  
<http://www.pdv.nl/PDF/a/948983633.pdf>

PDV (2001) GMP+: HACCP in the animal feed industry. Product Board for Animal Feed, The Hague.  
<http://www.pdv.nl/PDF/a/996042954.pdf>

PhVWP (1999) Notice to marketing authorisation holders. Pharmacovigilance guidelines. European Agency for the Evaluation of Medicinal Products, Committee for Proprietary Medicinal Products, Pharmacovigilance Working Party, London.  
<http://www.emea.eu.int/pdfs/human/phvwp/010899en.pdf>

- Exploitation and regulation of plants genetically modified to express nutraceuticals and pharmaceuticals  
<http://www.rikilt.wageningen-ur.nl/nutraceuticals>
- PR Newswire (2000) U.S. District Court dismisses Serono lawsuit rules in favor of Ferring Pharmaceuticals Inc. PR Newswire, April 25, 2000.  
<http://www.prnewswire.com/cgi-bin/stories.pl?ACCT=104&STORY=/www/story/04-25-2000/0001200654&EDATE=>
- Prasmusinto, D. (1999) The recombinant follicle stimulating hormone : a new alternative for induction of ovulation and treatment of polycystic ovary syndrome.  
[http://matweb.hcuge.ch/matweb/endo/PGC\\_network/Recombinant\\_Prasmusinto.htm](http://matweb.hcuge.ch/matweb/endo/PGC_network/Recombinant_Prasmusinto.htm)
- Riteco, J.A., De Heij, L.J.M., Van Luijn, J.C.F., Wolff, I. (1999) Richtlijnen voor farmaco-economisch onderzoek. College voor Zorgverzekeringen, Amstelveen.  
[http://www.cvz.nl/Pub\\_OverigePublicatiesDetail.asp?InformatieID=164&Title=overigepublicaties](http://www.cvz.nl/Pub_OverigePublicatiesDetail.asp?InformatieID=164&Title=overigepublicaties)  
<http://www.cvz.nl/StaticContents.asp?PageID=40&Title=geneeshulpmiddelen&SubTitle=Farmaco>  
<http://www.cvz.nl/Downloads/Publicaties/FEO-richtlijnen.doc>
- Santaniello, V. (2000) Intellectual property rights of plant varieties and of biotechnology in the European Union. In: *Agriculture and Intellectual Property Rights. Economic, Institutional and Implementation Issues in Biotechnology* (V. Santaniello, R.E. Evenson, D. Zilberman, G.A. Carlson, eds.), CABI, Wallingford, pp. 27-33.
- SCAN (2000) Report of the Scientific Committee for Animal Nutrition on the use of certain enzymes in feedingstuffs. European Commission, Scientific Committee for Animal Nutrition, Brussels.  
[http://europa.eu.int/comm/food/fs/sc/scan/out52\\_en.pdf](http://europa.eu.int/comm/food/fs/sc/scan/out52_en.pdf)
- Schaafsma, G.J. (1994). Een nieuwe voedingsfilosofie: functional foods. *Cahiers Bio-Wetenschappen en Maatschappij* 1(2): 37-45.
- Schmidt Dannert, C., Umeno, D., Arnold, F.H. (2000). Molecular breeding of carotenoid biosynthetic pathways. *Nature Biotechnology* 18: 750-753.
- SCP (1998) Guidance document to facilitate notifiers in the preparation of plant GMO dossiers for consideration by the Scientific Committee on Plants (SCP/GMO/103-Final) - (Opinion expressed by SCP on 18 December 1998). Scientific Committee on Plants, European Commission, Brussels.  
[http://europa.eu.int/comm/food/fs/sc/scp/out31\\_en.html](http://europa.eu.int/comm/food/fs/sc/scp/out31_en.html)
- Sheils, J.F., Rubin, R., Stapleton, D.C. (1999) The estimated costs and savings of medical nutrition therapy: The Medicare population. *Journal of the American Dietetic Association* 99: 428-435.  
<http://www.eatright.org/journal/1999/j0499a1.html>
- Smaglik, P. (2000) ...as US tightens up on 'speculative claims'. *Nature* 403: 3.
- TABD (2000) TABD mid year report (May 23, 2000). Trans Atlantic Business Dialogue.  
<http://www.tabd.com/recommendations/MYM00.pdf>

Exploitation and regulation of plants genetically modified to express nutraceuticals and pharmaceuticals

<http://www.rikilt.wageningen-ur.nl/nutraceuticals>

US Court of Appeals (1998) *Serono vs. Shalala and Ferring* (No. 97-5188). United States Court of Appeals for the District of Columbia Circuit.

<http://www.ll.georgetown.edu/Fed-Ct/Circuit/dc/opinions/97-5188a.html>

USDA (2000) U.S. approach to feed safety. US Department of Agriculture, US Mission to the European Union.

<http://www.useu.be/AGRI/feed.html>

USP (2000) Dietary supplements. United States Pharmacopeial Convention, Rockville MD.

<http://www.usp.org/dietary/index.htm>

Van De Graaf, E.S. (1997) Patent law and modern biotechnology. A comparative study about the requirements and the scope of protection. Thesis, Erasmus University, Rotterdam.

VICH (2001) Welcome to the website of VICH. International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Products, c/o COMISA, Brussels

<http://vich.eudra.org/>

Vogt, D.U., Parish, M. (1999) Food biotechnology in the United States: science, regulation, and issues. CRS report to Congress. United States Information Agency.

<http://www.usinfo.state.gov/topical/global/biotech/crsfood.htm#Table%202.%20EPA%20Registered%20Plant-Pe>

Vroom Cramer, B.M. (1998) Productinformatie over levensmiddelen.

Etiketteringsvraagstukken naar Europees en Nederlands recht. Koninklijke Vermande, Lelystad.

Willmitzer, L. (1999). Plant biotechnology: output traits - the second generation of plant biotechnology products is gaining momentum. *Current Opinion in Biotechnology* 10: 161-162.