Do we need new or additional guidance for the assessment of plants used as production platforms for non-food / feed production?

Joachim Schiemann

10th Annual Conference of the European Biosafety Association

Break-out group C: Plant biotechnology – Use of plants as factories for the production of non-food products (PMP, PMI)

Use of plants for the production of PMP & PMI

The presentation will give an overview of

(i) the regulatory framework for plants producing non-food/feed products

(ii) the current risk assessment criteria for GM plants that will form the basis for the safety evaluation of plants producing non-food/feed products

(iii) the activities of the special EFSA working group for additional risk assessment guidance for such plants

Source: Julian Ma, UK

GM Plants as Green Factories

- **Plant cells work like human cells, and they can make complex proteins.**
- **There are some types of protein for which plant production represents the only practical option.**
- **Plants are the only feasible production system for some proteins that are required at massive scale.**
- **Economy of scale, and low cost of initial investment**
- **Prospect of oral delivery**

A matter of cost and scale

- **Current global protein production facilities are limited.**

- **Large greenhouses could be used to grow pharmaceutical crops.**

- **But in the open field, production of pharmaceuticals at agricultural scale would be limited only by the amount of land available.**

Pharma-Planta

An EU Framework 6 Integrated Project (IP)

"Recombinant Pharmaceuticals from Plants for Human Health"

A public consortium comprising
28 Academic Institutes, 3 SMEs
Funding period 2004 - 2009
12M Euros of public funding

Project Objectives

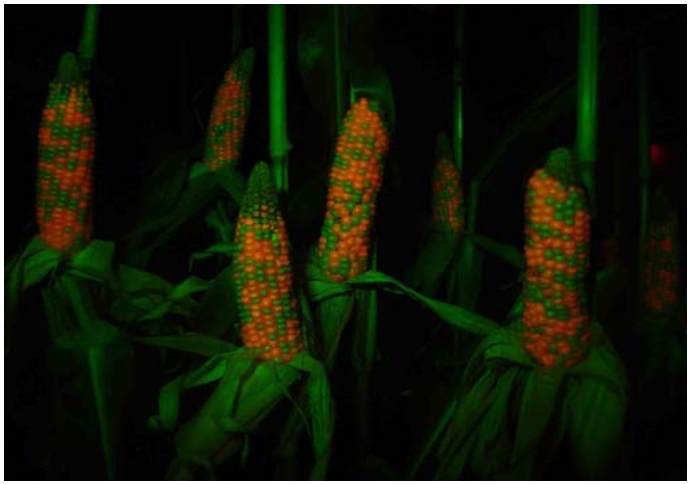
1. To build a plant based pharmacetuical production platform for Europe, and to help the development of appropriate regulatory oversight in the EU.

2. To produce a recombinant monoclonal antibody in transgenic plants at cGMP, for pre-clinical toxicity testing and Phase I human clinical trials in UK.

3. A commitment to humanitarian use by the poor in developing countries.

Two plant production crops

Maize



MAb expression is linked to expression of DS Red

Advantages:

GRAS status

Well established genetics and agronomy

Seeds are optimal for protein accumulation and storage

Disadvantages:

A food crop

Pollen production

Requires 6 generations of breeding to generate a Master Seed (Cell) Bank (currently in the 5th generation)

Two plant production crops

Tobacco

Advantages:

Well established genetics and agronomy

Only 2 generations breeding required to reach homozygosity

High biomass crop

Non-food crop

No pollen

Disadvantages:

High levels of indigenous toxic compounds

Fresh tissue

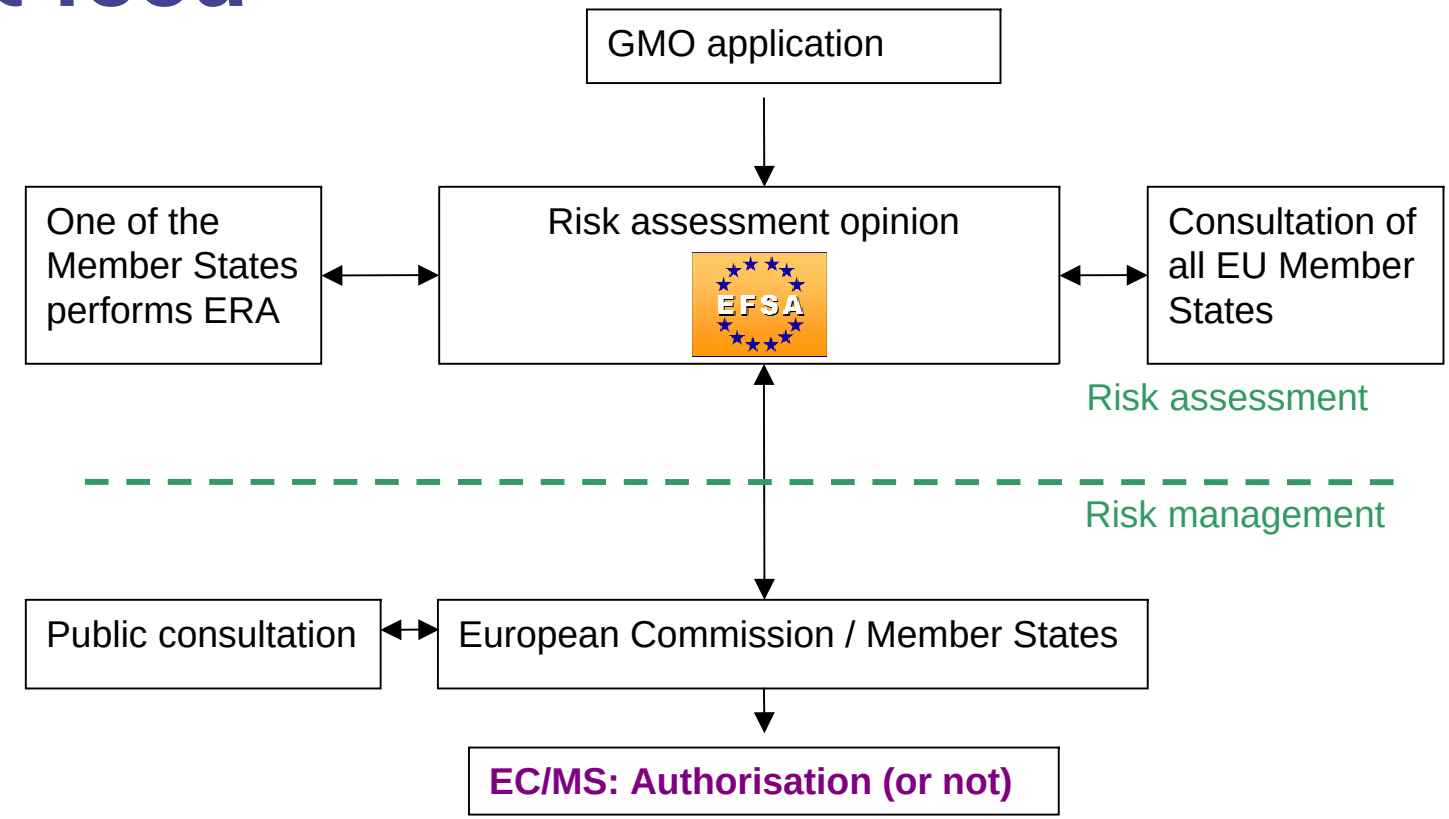
Role of EFSA in risk assessment of GM plants

- Food & Feed Regulation (EC) No 1829/2003
  - **MS → EFSA RA → DGSANCO**

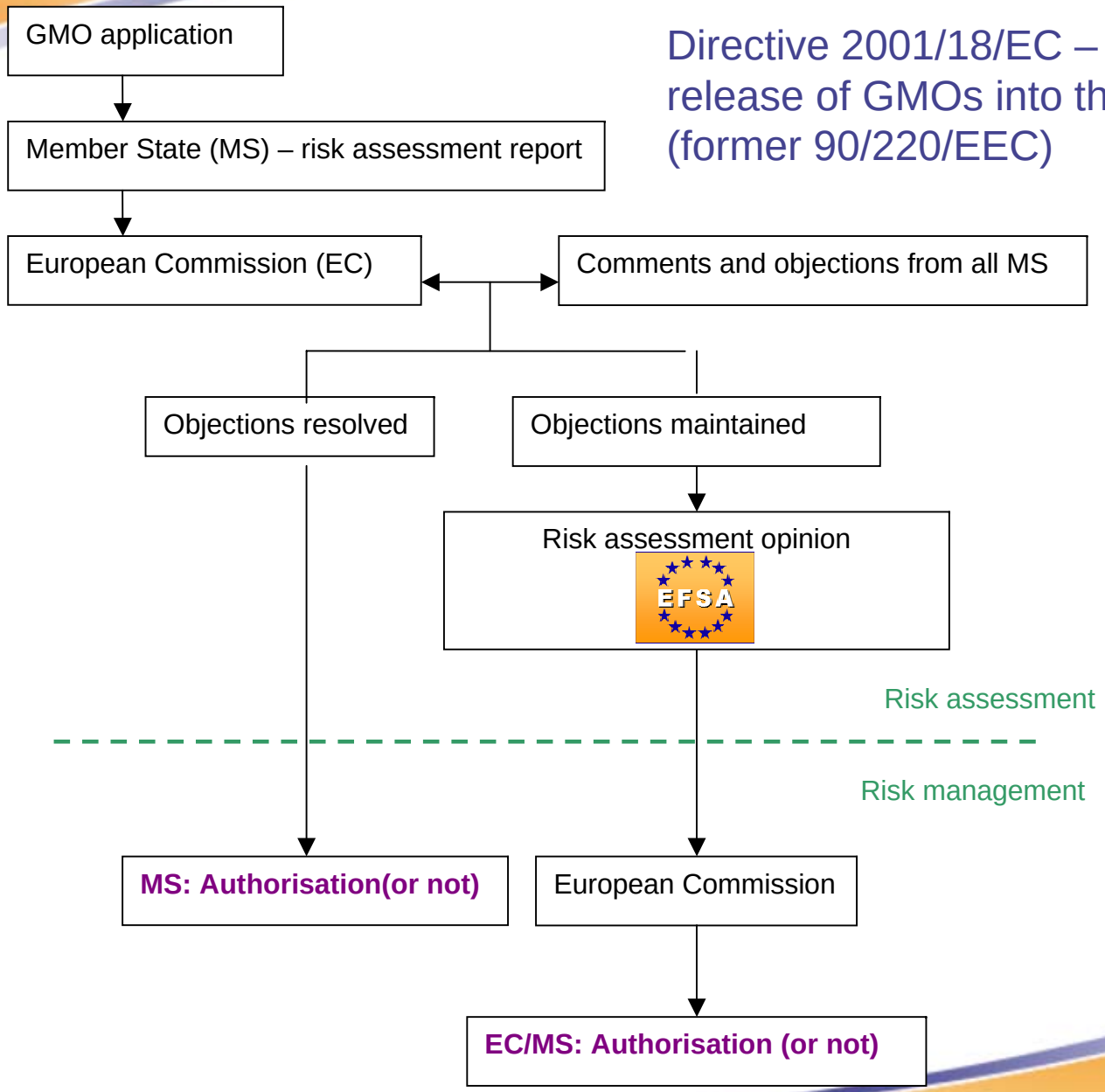
- Deliberate release of GMOs into the environment: Directive 2001/18 for placing on the market **Part C**
  - **MS RA → DGENV → all MS (→ EFSA → DGENV)**
  - **Plants used as production platform for non-food and non-feed products such industrial products**

- EFSA not involved in contained use/field trials

Regulation (EC) 1829/2003 - GM food & feed



Directive 2001/18/EC – deliberate release of GMOs into the environment (former 90/220/EEC)



GUIDANCE DOCUMENT OF THE SCIENTIFIC PANEL ON GENETICALLY MODIFIED ORGANISMS FOR THE RISK ASSESSMENT OF GENETICALLY MODIFIED PLANTS AND DERIVED FOOD AND FEED

Adopted on 24 September 2004
Updated on 7 December 2005
Final, edited version of 28 April 2006

May 2006

European Food Safety Authority

Key Elements in the Assessment of GMOs

- Characterization of donor and host organism
- Molecular characterization of the genetic modification event
- Analysis of agronomical and compositional properties
- Specific toxicity/allergenicity/nutritional testing
- Post-market monitoring
- Environmental risk assessment
- Post-market environmental monitoring

Guidance Document on E.R.A.

- INFORMATION REQUIRED IN APPLICATIONS FOR GM PLANTS AND/OR DERIVED FOOD AND FEED
- **INFORMATION RELATING TO THE GM PLANT**
- **1. Description of the trait(s) and characteristics which have been introduced or modified**
- **2. Information on the sequences actually inserted or deleted**
- **3. Information on the expression of the insert**
- **4. Information on how the GM plant differs from the recipient plant in: reproduction, dissemination, survivability**
- **5. Genetic stability of the insert and phenotypic stability of the GM plant**
- **6. Any change to the ability of the GM plant to transfer genetic material to other organisms**

Guidance Document on E.R.A.

- 7. Information on any toxic, allergenic or other harmful effects on human or animal health arising from the GM food/feed
- 7.1 Comparative assessment
- 7.2 Production of material for comparative assessment
- 7.3 Selection of material and compounds for analysis
- 7.4 Agronomic traits
- 7.5 Product specification
- 7.6 Effect of processing
- 7.7 Anticipated intake/extent of use
- 7.8 Toxicology
- 7.9 Allergenicity
- 7.10 Nutritional assessment of GM food/feed
- 7.11 Post-market monitoring of GM food/feed

Guidance Document on E.R.A.

- 8. Mechanism of interaction between the GM plant and target organisms (if applicable)
- 9. Potential changes in the interactions of the GM plant with the biotic environment resulting from the GM
- 9.1 Persistence and invasiveness
- 9.2 Selective advantage or disadvantage
- 9.3 Potential for gene transfer
- 9.4 Interactions between the GM plant and target organisms
- 9.5 Interactions of the GM plant with non-target organisms
- 9.6 Effects on human health
- 9.7 Effects on animal health
- 9.8 Effects on biogeochemical processes
- 9.9 Impacts of the specific cultivation, management and harvesting techniques

Guidance Document on E.R.A.

- 10. Potential interactions with the abiotic environment
- 11. Environmental Monitoring Plan
- 11.1 General
- 11.2 Interplay between environmental risk assessment and monitoring
- 11.3 Case-specific GM plant monitoring
- 11.4 General surveillance of the impact of the GM plant

EFSA

EFSA self-tasking activity

Guidance for the risk assessment of genetically modified plants used for non-food or non-feed purposes

EFSA Mandate self-tasking - Topic 1 Medicinal products

- To establish contact with EMEA to clarify the interplay between Directive 2001/18 and Regulation 276/2004 (former 2309/93) for medicinal products
- Art. 12.2: "As far as Council Regulation (EEC) No 2309/93 is concerned, Articles 13 to 24 of this Directive shall not apply to any GMO as or in products as far as they are authorized by that Regulation provided that a specific environmental risk assessment is carried out in accordance with the principles set out in Annex II to this Directive ….."

Meeting between EFSA-EMEA

- The exception in Dir. 2001/18 is for
  - **GMOs <u>as or in</u> medicinal products**
  - **Meaning the GMO is used as a cure as such**
  - **Reg 276/2004 (former Reg. 2309/93 as amended) applies**

- The exception is not for
  - **GMO producing medicinal products, and the medicinal product is than isolated from the plant.**
  - **Dir. 2001/18 applies**

Risk assessment of the plant and environmental risk assessment (ERA)

- GMO **as or in** medicinal product
  - **Reg. 276/2004 applies**
  - **EMEA – MS for ERA → DGENTR**
  - **EMEA may seek collaboration with EFSA for ERA**

- When medicinal product isolated from the plant
  - **Reg. 276/2004 does not apply**
  - **MS RA → DGENV → all MS (→ EFSA → DGENV)**
  - **EFSA to seek information from EMEA on RA aspects related to the medicinal product**

Mandate - Topic 2

- Identify possible gaps in the present EFSA guidance document concerning the risk assessment of genetically modified plants used for non-food or non-feed purposes
- Examples of non-food/feed products: industrially, medically or scientifically useful biomolecules
  - **Case studies**
    - HIV antibody in tobacco — HIV antibody in Maize
    - Fibre poplar — Fibre maize
    - Vaccine in tobacco — Vaccine in maize
    - Taxol in tobacco — Taxol in oilseed rape
    - Vitamin E in tobacco — Vitamin E in oilseed rape

Mandate – Topic 3

- Potential admixture with food/feed chain
- Biological/physical containment strategies

Mandate – Topic 4

- Develop additional guidance for the applicant to prepare risk assessment dossiers
- Organize stakeholder consultations

Intermediate results

- Current guidance document covers most of the criteria needed to evaluate the case studies
  - **On a case-by-case basis extra studies may be asked to the applicant**
    - *for toxicology and allergenicity*
    - *for environmental risk assessment: impact on non-target organisms*
- Admixture with the food chain: No scientific grounds found to exclude use of food crops
- Confinement / containment: General recommen-dations for the risk manager may be made for certain types of products, e.g. bioactive substances
- Plant molecular farming is not a zero risk technology and approval may depend on the risk/benefit balance.

Ongoing and future activities

- Regular WG meetings
- Write opinion with general recommendations
  - **draft extra risk assessment criteria**
- Organize stakeholder consultations in 2007
  - **Applicants**
  - **Members of the public**

Those who want the world to continue as it is, do not want the world to continue