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Regulations in Biotechnology: Administrative Handling and Scientific Content

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Abstract. The administrative handling of regulatory oversight procedures differs from country to country, whereas the scientific data required for the safety assurance are similiar in most instances. Safety issues for contained biotechnology applications are mainly a matter between industry and the government agencies involved. Deliberate release of transgenic organisms and the market introduction of transgenic food, however, produce much public debate. It is assumed that shortcomings related to risk-assessment methodology as, *e.g.*, the lack of accepted protection goals and the continuing discussions about the validity of comparative risk assessment may be reasons for the current situation.

Biotechnology involves the use of modern genetic engineering, which affects many different products and processes. Regulation of biotechnology is designed to provide the necessary legislation to ensure adequate protection of human health and the environment. The regulatory framework can be grouped into contained use (including protection of workers), deliberate release, and product (*e.g.*, medicinal, cosmetics, food and feed) legislation. Legislation on intellectual property protection may also form part of this framework.

Often, regulation is viewed as an innovation obstacle. In fact, regulatory requirements need to be addressed at different stages when a product is developed from basic research to commercialization. If, for example, production involves genetically modified organisms besides the notification of the research project and the registration of the product, the production facility also needs to be approved by an oversight agency. For a food product derived from crop plants, regulatory interventions are even more numerous. Again, it begins with the notification of the research project having the production of the transgenic plant as the objective. Further approvals are necessary, *e.g.*, for field testing, commercial cultivation, and for the novel variety and food status.

The *administrative handling* of regulation differs from country to country. According to an OECD survey [1] on the commercialization of agricultural products derived through modern biotechnology, a number of common features exist. Typically, it is a single government agency (*e.g.*, Ministry of Environment) that is responsible for oversight. However, other governmental agencies may become involved (*e.g.*, Ministry of Agriculture, Ministry of Health, Ministry of Animal Welfare) due to the heterogeneity of biotechnology applications. Formal mechanisms for coordinating oversight activities are then instituted. In addition, advisory councils such as biosafety or even ethics committees may be created for consultation purposes. In *Fig. 1*, the general course of the regulatory oversight procedure for a food product is shown. It is noteworthy that information of the public is usually an element of the regulatory oversight procedure, which in turn may be the basis for the much debated genetic engineering applications in the food sector. The time required for the procedure outlined is at least three months beginning with the submission of the application. The presubmission period and the time required for the submission of additional data may involve substantially more time. Besides the country-specific differences of regulatory procedures, they also depend on the product involved (food, pharmaceuticals, fine chemicals). In the following, some general remarks on the safety assurance of products produced with contained biological systems are given.

Safety Assurance for Products Involving Biological Conversion

Safety of products derived from biotechnological processes is achieved by a holistic system survaillance of the manufacturing process. Initially, quality control was carried out with the final product only, with elimination of batches which did not pass the quality criteria. Now, quality assurance covers the entire manufacturing process. Since biotechnological processes are used in different industries for the production of goods as, *e.g.*, drugs, fine chemicals, enzymes, and foods, the requirements on product safety may differ and have their own tradition and consequently will be of variable formality. Nevertheless, in all applications of biotechnology processes, safety assurance shares some common ground. Generally, quality standards cover

- everything that goes into the product (*e.g.*, starting materials, additives, target product, and by-products),
- everything that could come into contact with the product (*e.g.*, equipment, air, water, packaging material), and

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– everything that has the potential to influence product quality without having an obvious relevance (*e.g.*, personnel qualification, management responsibilities, the validity of methods, documentation).

Generally, safety assessment can be described as the activity of identifying hazards coupled with a state, condition, or process and valuating identified hazards with respect to their damage potential. Due to the comprehensive approach to safety assurance mentioned above, the safety assessment equally covers analytical procedures, the manufacturing process, and organizational measures.

The ultimate aim is to prove that a product can be fabricated reproducibly in a desired quality if certain established production and control methods are obeyed. The formal and documented realization of this evidence is called validation. In the *Table*, a number of elements of a product-safety assurance protocol are listed. These elements are the practical realization of the general product-safety assurance principles mentioned above. The key elements are facility validation, the determination of critical process steps by a safety assessment, and organizational measures. If critical steps or procedures are part of a manufacturing process, measures need to be taken in order to define confidence limits which determine whether a certain process step proceeds in an acceptable range or not. Therefore, the technical safety analysis forms a central element in the safety-assurance concept. It also yields an overall account of the safety standard of a process [2].

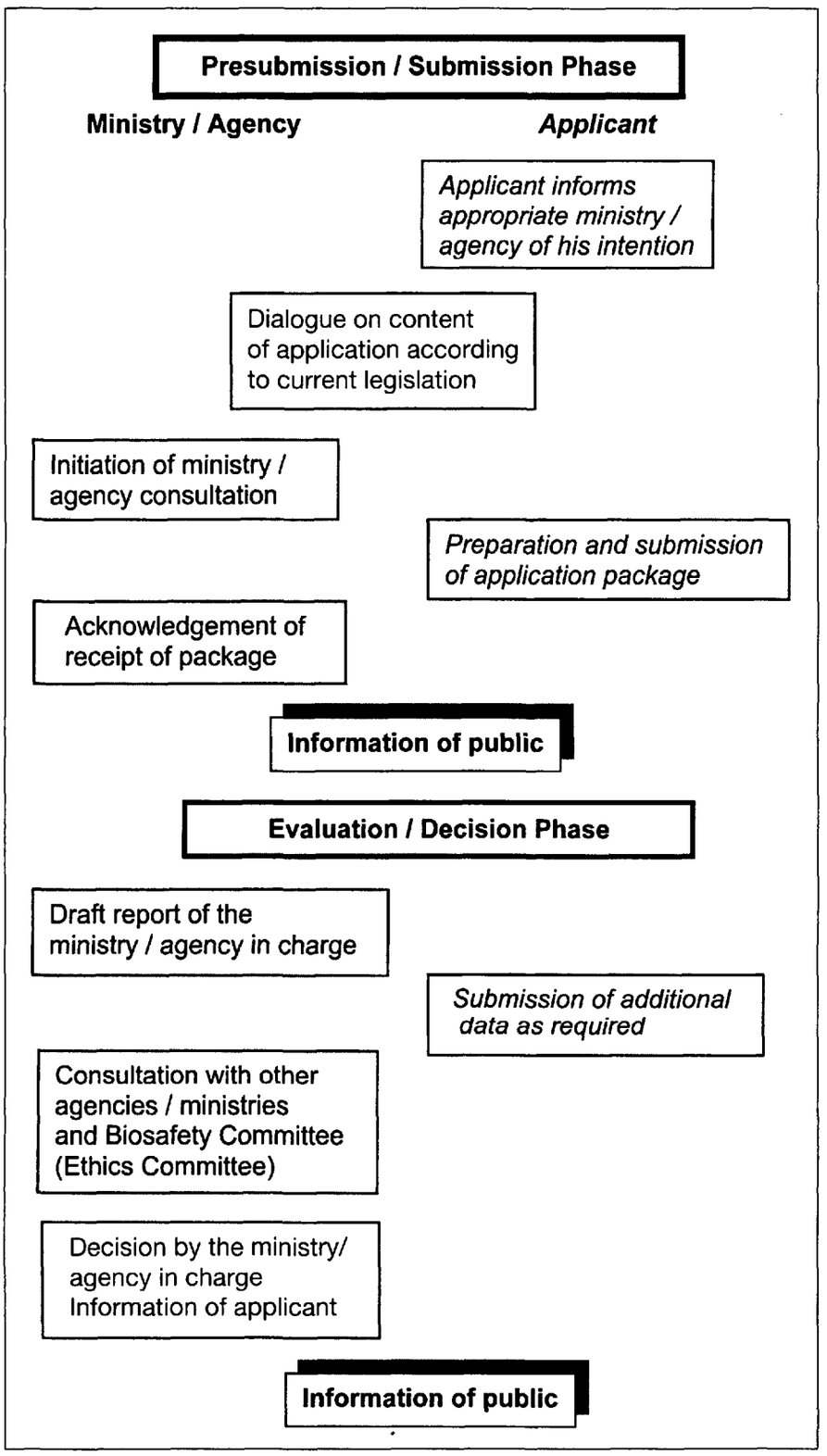

Fig. 1. *General steps of a regulatory oversight procedure for a food product.* The time required from the submission of the application to the decision is usually at least three months.

Environmental Risk Assessment

A risk assessment provides the *scientific information* needed for judging on the environmental safety of an application. The system description is the starting point (characteristics of the donor organisms, of recipient organisms, and of the modified organism), followed by considerations of possible impacts on human health, the environment, and cultivated land. A case-by-case analysis is generally necessary (for details, see [3]).

In an OECD [4] survey, there was remarkable agreement among the countries on the kinds of information that could be used to meet data needs. Scientific literature, published test data, and history of use were cited in all countries. Assessment of data for adequacy and/or quality is done by national expert committees and internal ministerial reviews.

Despite the high agreement on the scientific content of review documents, the actual outcome of the review process for identical cases may vary from country to country. This is especially true when the safety of deliberate releases is concerned. An important reason for this may be the lack of common protection criteria for biological systems. Contrary to, *e.g.*, chemical systems, there are no thresholds for acceptable damage or risk levels [6]. As a

consequence, debate on acceptance and tolerability criteria is activated each time an application for deliberate release is filed. There are basic deficiencies in the methodology of risk assessment for biological systems [5]. First, it should be evaluated whether the probabilistic approach to risk assessment is adequate for biological systems (*Fig. 2*). Since the damage potential of deliberate releases is mostly not apparent, a damage-oriented approach should be favored with the primary goal to give an idea of the extent of damage. Ideally, projects should be terminated when the safety assessment yields a significant damage potential. Probability has a very relative significance for self-reproducing living systems.

Table. *Elements of a Product-Safety (Quality) Assurance System*

- Product data, *e.g.*
  - Raw Materials
    - Medium additives
    - By-products
- Process flow diagram
- Validation
  - Plant qualification
    - Installation qualification
    - Function qualification
  - Process validation
- Technical safety assessment → Hazards → Critical Process Steps (CPS)
- Assessment of CPS by risk assessment
- Establishment of confidence range (critical limits)
- Adapt operation instructions (human factor)
- Define preventive measures, controls, corrective action, rejection criteria
- Organizational measures
  - Operational / technical level: GMP, GLP
  - management level: ISO 9000-9004
- Documentation

Second, there should be a consensus on whether comparative risk assessment is valid or not. Among scientists, it is widely accepted that transgenic plants do not exhibit any risk quality which is fundamentally different from traditionally bred plants. This assumption needs to be further substantiated by evaluating the criteria for the validity of comparative risk assessment.

Only when safety issues are given adequate attention and the safety assessment methodology is transparent and widely accepted, a more rational debate on genetic engineering can be expected. Those applying genetic engineering should take into account that safety assessment needs special expertise and much scientific input in order to be comprehensive and its results understandable to a wider public.

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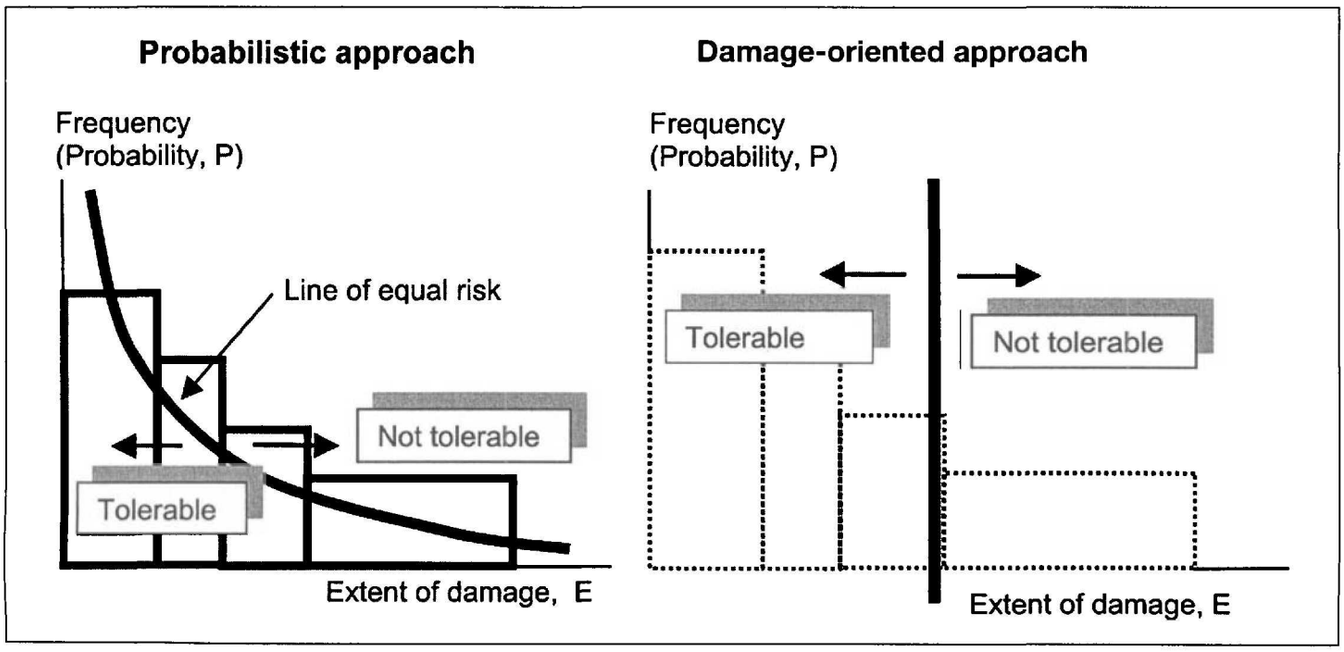

Fig. 2. *Probabilistic and damage-oriented approach to risk assessment.* In the former case, safety is defined based on tolerable risk levels (risk = *f*(P,E)) in the latter case, safety is defined based on tolerable damage extents.