

SUMMARY REPORT ON THE EXPERIENCE OF BELGIUM WITH DIRECTIVE 90/219/EEC



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Introduction

The implementation of Directive 90/219/EEC regulating the contained use of genetically modified micro-organisms (GMM's) into the Belgian law was historically coupled to the implementation of Directive 90/220/EEC regulating the deliberate release of genetically modified organisms (GMO's) in the environment. It was also harmonised with the parallel implementation of Directive 90/679/EEC regulating the protection of workers exposed to biological agents. International biosafety experience and the expectable progresses of biotechnology were also taken into account.

In order to appreciate the content of the present trisannual report, it might be important for the reader to perceive the scientific complexity of the regulatory puzzle upstream the implementation of Directive 90/219, at least in Belgium. The following summary should help to understand in which spirit and methodology the advisory authority and the competent authorities are presently working.

The Belgian authorities have decided to apply the precautionary and the familiarity principles in the implementation of Directive 90/219/EEC. There were indeed several weaknesses in the European regulations that had to be corrected along the implementation procedure.

First, Directive 90/219/EEC does neither apply to GMO's like transgenic plants and transgenic animals, nor explicitly to new technologies as gene therapy/vaccination vectors or transgenic allo/xenotranplantations used in veterinary or human clinical research. Moreover plants, animals and humans, as carriers of genetically modified micro-organisms were not foreseen in the Directive. The status of cell cultures, lines, strains and defective mutants or variants thereof - used as receptor organisms for further genetic modifications- was undocumented. Finally, the classification of GMM's into group I or II and of the activities of type A or B did not fit well with the internationally accepted basis of classification of biological risks of opportunistic, pathogenic and parasitic agents for humans, plants or animals.

Second, the Belgian authorities considered that the definition of "contained use" of Directive 90/219/EEC had to complement unambiguously the definitions of "accidental or unintentional release" and of "deliberate release" as defined by Directive 90/220/EEC.

Third, laboratories manipulating GMM's also occasionally manipulate gene donors or receptors with pathogenic properties for humans, plants or animals. It was thus essential to avoid discrepancies between the containment levels required under Directive 90/219/EEC and those required -for example- for worker protection under Directive 90/679/EEC. The same concern would also have applied should containment levels and criteria become defined for the uses of plant or animal pathogens as gene donors or receptors.

Finally, the implementation of Directive 90/219/EEC had to integrate the precautionary and the familiarity principles into the executive laws and leave enough room to integrate in the future any potential safety issues emerging from the Rio Convention, notably from the Chapter XVI of the Rio Agenda.

Thus, the implementation of these Directives provided a unique opportunity to build a general, coherent and modern biosafety regulation in our country.

The discussions led the experts to propose -and the authorities to approve- the definition a very general legal frame for biological safety of human activities with GMO's, GMM's and pathogens. In such a frame, the natural integration any Directive, decisions, regulations - or revisions thereof - concerning any genetic modifications of any biological entity and any uses thereof, contained or not, was foreseen.

A juridical tool named "Co-operation agreement", situated between the Constitution and the law levels, was used to address the problem. While the regional authorities had to implement Directive 90/219/EEC, the federal authorities had to transpose Directive 90/220/EEC. However, decisional competencies had to be shared and organised for the part B of Directive 90/220/EEC. Moreover, the implementation of the containment criteria from Directive 90/219/EEC could not conflict with the implementation of the containment measures defined in Directive 90/679/EEC. Finally, a willingness of both mutual and systematic information and transparency was managed in the general model. Therefore, a co-operation agreement was signed between the federal and regional authorities in May 1996 and was confirmed on April 25th, 1997 after advice of the Council of State, about "the administrative and scientific coordination concerning biosafety".

Since December 1993, the spirit and most provisions of the co-operation agreement were already applied. After 6 years of experience, the co-operation agreement appears as providing most of the essential and useful scientific or legal tools necessary to apply not only the Directive 90/219/EEC in the real life but also to easily integrate its revised version 98/81/EC.

These legal tools are:

A definition of Biosafety: "the safety for human health and the environment, including biodiversity protection, of the uses of genetically-modified organisms or micro-organisms and of the contained use of human pathogenic organisms".

A common advisory system composed of the "Biosafety Advisory Council" and its executive body the Service of Biosafety and Biotechnology (SBB). SBB was noteworthy defined by the regions as the "advisory authority" for the review of contained installations and operations.

Guidelines for regulatory interpretation, advisory procedures for both Directives 90/219/EEC and 90/220/EEC, provisions defining the legal frames under which the fate of residual biomass's containing living GMO's must be managed.

1. Notifications and approval systems

1.1. Advisory System

The scientific evaluation system common to all competent authorities consists of a Biosafety Advisory Council and a Service of Biosafety and Biotechnology (SBB).

The Biosafety Council advises the competent authorities on the safety of any activities using GMO's (and also pathogens), including genetic and ecological aspects related to biodiversity.

The Council *can* be consulted by the Regions or the SBB for the contained use activities (laboratories, production plants) but must be consulted for the deliberate release of GMO's in the environment and the placing on the market of all GMO's-based products.

The Council consists of representatives of the Regional and the Federal authorities. The Council is assisted by experts and organises *ad hoc* scientific committees. Actually, four working committees of experts of experts have been created (Recombinant viral vectors, virosomes, Vaccination & Gene therapy / Transgenic plants / Novel Food-Feed/GMM's, Bacteria and Fungi) The SBB is noteworthy in charge of the secretary of the Biosafety Council.

The SBB is composed of an administrative secretariat, a multidisciplinary group of biosafety scientists and a laboratory for Biosafety research and expertise.

Regarding contained use regulation, the SBB defines the specific normative criteria to be applied in a given installation on a case by case basis and advises the Regional authority about the licensing conditions of installation and the authorisations for operations.

Besides, the SBB is also in charge of:

- management of the meetings of expert groups and members of the Council,
- participation to scientific normative programs or meetings;
- drafting of protective measures related to human health and the environment to the attention of the Council or the authorities;
- supporting the petitioners in preparing their petitions and is as such a focal contact point between the Belgian users and the competent authorities
- archiving the dossiers and safeguard confidential information;
- transmitting all necessary information to the European Commission;
- sustaining the Belgian delegations at the international level.

The SBB acts as the advisory authority for the review of the contained use of GMM's, GMO's and pathogens. SBB may request the advice of the scientific committees of the Council in case of need. The SBB directly interacts with the notifiers, the competent administrations and the inspection services thereof. SBB can be (and has been) consulted by any competent or concerned authority from all institutional levels (Municipality, province, Region, Communities, Federal ministers), by other private or public advisory bodies, by the Parliaments, by groups, the press or the public.

The SBB has also important tasks to perform with respect to the release and placing on the market of GMO's including the sectorial regulations.

Practically, the SBB is a normative public service carried out by a multidisciplinary group of scientists of post-doctoral level co-financed by the Regions (Directive 90/219/EEC) and the Federal State (Directive 90/220/EEC).

1.2. Procedures for the licensing of installations and the authorisation of operations

1.2.1. Tasks management

All regulatory-related aspects of the uses of GMO's and pathogens are assessed altogether in a coordinated way, inside the same procedures, independently of the implicated specific regional regulation.

Regions are responsible for the public information, the follow-up of administrative procedures, for the legal decisions, the appeals and for the inspections.

The scientific evaluation is made in a centralised way by the SBB. In order to simplify the preparation of the notification dossiers; SBB has designed ad hoc forms gathering all provisions from Directive 90/219/EEC and from regional legislation.

The laboratory of SBB must also assist the regional or federal authorities for the tracing and authentication of GMM's or GMO's in the environment. Therefore, a biosafety research activity is also carried out by the SBB parallel to the regulatory tasks.

1.2.2. General procedures

The contained use of GMM's, GMO's and pathogens is a classified activity requiring an Environmental Permit for classified installations.

Two procedures are foreseen in Directive 90/219/EEC, the "First Use" permit for installation and the "notification" of operations carried out in an installation of a new activity, modification of an authorised activity and renewal of an activity".

In the Regional regulation, the licensing of installation (First use permit) for contained use activities requires an Environmental Permit (new installations) or an update of an existing Permit (existing installations) for contained use activities

The "Notification of a new operation, modification of an authorised operation and renewal of an operation" (Notification of operations) is applied separately (for authorised installation) or together (regularisation of installation) with the procedure of Environmental Permit. When applied separately, it is an extension to an existing valid Environmental Permit.

In order to get an Environmental Permit for contained use in an installation or an extension thereof, a "Biosafety dossier must be submitted to the authorities.

The Biosafety dossier is based on official forms and guidelines and is composed of a "technical dossier" and a "public dossier".

The "technical dossier" is the scientific reviewing tool of the SBB and can contain confidential data. Such a dossier exists as a unique exemplar. It is submitted to administrative classification whose access is restricted to a limited number of persons designated by the competent authorities.

The "public dossier" is a summary of the technical dossier and is written in common language. It is by definition transparent and may be submitted to public hearing according to current Environmental Permit regulation, noteworthy implementing Directive 90/313/EEC.

The *technical dossier* is required both for the first use permit and the notification procedure whereas the *public dossier* is only required for the first use permit. The technical dossier is based on the "TEC" form whereas the public dossier is based on the "PUB" form.

An "Environmental Permit" can concern several contained buildings on one site. In the three Regions, a contained building is defined as the minimal unit of environmental interaction.

The corresponding technical dossier shall include several TEC forms, one TEC form per building concerned.

A contained building can host several teams, each carrying out several operations in several rooms which are either physically grouped (contained zone) or dispersed. One room can be dedicated to a single or several operations.

Each team describe its operation(s) on special forms selected according to the class of biological risk of its operation(s). There is a form for each of the Group I- Type A, Group II-Type A, group II type A operations and Group II-Type B operations.

When pathogenic gene donors or acceptors are involved together with GMM's and/or GMO's, they are described in these forms. When pathogens only are used, a specific form is used to describe the operation.

The forms describing each operation are annexed to the TEC form. The Biosafety dossier is reviewed by the local biosafety committee and further officialised by the responsible of the installation.

The concept of "Operation" is undefined.

An operation can be generic (culture collection, cloning, sequencing or FACS services, DNA manipulation, cell culture, animal husbandry or greenhouse management, etc...) or very specific.

Such flexibility allows the notifiers to modulate their biosafety within long-term and short-term operations and consequently to reduce the administrative burden.

"First Use" procedure, the "public dossier" has to be submitted as an annex of an environmental dossier with respect to the "Environmental Permit", following an authorisation procedure. The procedures differ slightly from region to region.

The public dossier is made available to the public by the Regional authority. It is submitted to public hearing along a special procedure "*commodo incommodo*" by the Municipal authority.

A single copy of the technical dossier is directly submitted by the notifier to the SBB for advice to the competent authority within:

- 45 working days after receipt of the notification for a first use dossier (Directive 90/219/EEC, article 8), and after

- 30-45 days (according to the type of operation) in the case of common notification dossiers (Directive 90/219/EEC, article 9).

The decision of the competent authority must be given within the same delays as those defined by Directive 90/219/EEC.

In **the “Notification procedure of a new activity, modification of an authorised activity and renewal of an activity”**, a technical dossier describing the operation concerned is submitted to the SBB and the competent administration. Activities of type A class of risk 2 and type B class of risk 1 may start 60 days after introduction of the dossier and by default proceed for 3 years. In this case, the notifier/user applies the containment measures he has proposed in his dossier.

N.B. In the practice, the vast majority of the notifiers request a written authorisation from the authority, even if the law allows them not to need it.

1.2.3. Special procedures

a) Certification/Exemption

GMM's or GMO's can be certified as belonging to the class of biological risk 1 organisms or fulfilling the OECD G.I.L.S.P. (Good Industrial Large Scale Practice) status according to the criteria of Annex II. This is possible because Annex II originated word by word from the OECD criteria. This will not be possible anymore when implementing Directive 98/81 since the corresponding annex has been extensively modified and does not comply anymore with OECD criteria for GILSP.

On the same way, GMM's or GMO's of class of biological risk 1 can officially be exempted (at user's request) of the application of the regulations according to the criteria of Annex I B.

Whereas certificates of classification can be delivered by SBB, the competent authorities decide exemption from the contained use regulation.

Both demands (certification and exemption) require a biosafety dossier. With respect to certification, this dossier must contain relevant data demonstrating the GMM fulfils all the criteria defining the Group I of the GMM's.

In order to be excluded from the contained use regulation, a GMM must meet two criteria: 1) the GMM belongs to class of risk1 and 2) the GMM is constructed by means of one of the techniques described in annex IB of the Directive 90/219/EEC, for example selfcloning (the SBB has delivered several certificates of selfcloning upon request of the notifier/user).

b) Gene therapy/vaccination trials

The involvement of genetic manipulation in the design of a gene therapy tool automatically justifies the application of the biosafety regulation *i.e.* the EC Directives 90/219/EEC and - under special circumstances outlined hereafter- the directive 90/220/EEC. The biosafety regulation in Belgium has been designed to cope all types of operations using GMO's including GMO's as gene therapy/vaccination tools: viral-vectors, bacterial vectors, cell-mediated somatic gene therapies, transgenic allo/xenotransplantations and stem cells.

The SBB defines gene therapy/vaccination as “any type of transfer of genetic material in humans for prophylactic, therapeutic or diagnostic purposes”. It could be extended to animal experimentation if necessary.

As far as biosafety regulations are concerned, any gene therapy/vaccination clinical trials using transgenic material must be authorised.

Specific protocols or a whole program of clinical trials in a given installation for several years (usually 5 years) can be proposed as contained use operations. Such operations may involve several clinical phases, amendments of the previous proposal and variants of the initial GMM when the safety of the GMM and the use thereof remain the same for human health and the Environment.

The notifier could be either a team carrying out a trial in a contained installation or a civil personality organising multi-centric trial with the partnership of different teams acting in different authorised contained installations. This is a basic choice left to the initiative of the notification. In the second case, the application of the regulation under part B of Directive 90/220/EEC is recommended because one single coordinated dossier can be submitted for all installations concerned.

The contained use regulation is applied in all cases. When a release of the therapeutic GMM occurs in the environment, it must also be assessed on basis of part B of Directive 90/220/EEC.

The proposals of clinical trial are reviewed by a multidisciplinary ad hoc scientific committee of the Biosafety Council on demand of the SBB.

The description of the operation includes the protocol(s), the GMP file, the approval of the local Committee of Medical Ethics and the specific questionnaire for gene therapy clinical trials with its scientific annexes. This questionnaire was designed on basis of the US, UK, Swiss and French questionnaires.

The Biosafety Council only reviews the biosafety aspects of the dossier, i.e. the full description of the biological material, the conditions of design, production and uses of the GMM concerned under the proposed trial circumstances in the concerned installation. The balance benefit/risk is not taken into consideration.

The assessment of ethical issues are separately and independently reviewed and approved by an ad hoc local Ethical Committee mandated by the National Committee for Medical Ethics.

If a new protocol involves a GMM - or a substantial equivalent thereof- already reviewed by the Biosafety Council, the dossier is then managed by the SBB as a current affair.

b. 1) Procedure under contained use regulation only

The applicant submits his technical dossier to the SBB; the dossier is reviewed by Biosafety Council for advice to the regional competent authority.

b. 2) Procedure under both contained use and deliberate release regulations:

The application is submitted for approval to the federal Ministry of Public Health as competent authority for Directive 90/220/EEC. The authority acknowledges the dossier and forwards it immediately to the Biosafety Council for advice within 60 days. The SBB immediately forward a defined set of information to the regional authority. The dossier is similar as above except for the part related to a release of the GMM into the environment. When several installations are involved in the proposal, the notification of operation is associated to the dossier.

A co-decision mechanism defined a procedure of authorisation by both the federal and regional authorities. The maximal authorisation delay is 90 days.

c) Amendments to the regional legislation

Since the publication of the regional regulations, new amendments have been made to the Flemish and the Brussels regulation.

The first amendment concerns the decree of the Flemish region (amendment of 24 march 1998) where the major change was the incorporation of the new Annex II of the Directive 94/51/EC. The other change concerns the certification procedure that is taken out of the Flemish legislation and is now managed by the SBB only.

The second amendment concerns the decree of the Brussels-Capital Region (amendment of 22 September 1998) where the previous annexes to the decree were amended. However, this only concerns three annexes: the new annex II derived from Directive 94/51/EEC, and two other annexes, one relating to confinement criteria and the other to a list of micro-organisms and organisms with their maximal biological class of risk as extensively improved by the SBB.

Containment criteria were subdivided into technical characteristics, biosafety equipment and work practices. With respect to (micro-)organisms and their maximal biological class of risk, next to criteria for classification, a non-exhaustive list is given of human-, animal-, and plant pathogens to be considered as gene donors or acceptors.

Whereas procedural differences exist between the three regional regulations, the technical annexes of each regional decree are the same.

2. Overview of activities and installations (GMO's as well as GMM's)

2.1. Reviewed installations and operations.

Since the implementation of the Biosafety regulation in the three Belgian Regions, 236 dossiers of installations have been reviewed by the SBB acting as the advisory authority.

These dossiers have the following distribution:

- 11 dossiers of request for exemption of GMM's under the criteria of Annex IB of the Directive 90/219/EEC

- 7 dossiers of request for certification of GMM's in class of risk 1 under the criteria of Annex II of the Directive 90/219/EEC

- 218 biosafety dossiers of installations carrying out operations of contained use of pathogens, GMM's and/or GMO's (transgenic plants and animals). These dossiers covered 641 receivable operations. 52 operations were either non receivable, cancelled by the notifier or merged by SBB with other receivable operations.

Among the 218 reviewed dossiers of contained use, 121 installations exclusively concerned non genetically-modified, pathogenic micro-organisms and covered 361 operations.

These dossiers were very helpful to develop the reference biosafety expertise of the risk assessment of gene donor and acceptors as human, plant and animal pathogens, parasites or opportunists.

Consequently, 97 installations have been assessed together with 280 operations for the contained use of GMM's and GMO's.

These GMM's/GMO's dossiers are distributed as a function of:**- The procedure and the administrative year**

| Year | 1994 | 1995 | 1996 | 1997 | 1998 | 1999 (15/10/99) | Total |
|--|-------------|-------------|-------------|-------------|-------------|---------------------------|--------------|
| Procedure | | | | | | | |
| First use permits (article 8 of the Directive) | 4 (22) | 8 (23) | 10 (44) | 25 (94) | 13 (43) | 12 (17) | 72 (243) |
| New operations | 0 | 0 | 0 | 0 | 10 (19) | 5 (5) | 15 (24) |
| Modifications of operations | 0 | 0 | 1 (1) | 0 | 3 (5) | 6 (7) | 10 (13) |
| Total | 4 (22) | 8 (23) | 11 (45) | 25 (94) | 26 (67) | 23 (29) | 97 (280) |

Table 1: Distribution of the number of installations (number of operations) as a function of the procedure and the administrative year.

Table 1 illustrates the evolution of the application of the regulations. A plateau was reached since 1996. Interestingly, the "notification" procedure for new operations or for amendments of authorised operations has significantly started in 1998.

- The type of installation:

Private Companies: 32 installations, 73 operations

University campus: 49 installations, 162 operations

Others (Scientific institutions, high schools, etc.): 16 installations, 45 operations

- The Competent Region:

Brussels: 41 installations, 124 operations

Flanders: 32 installations, 61 operations

Wallonia: 24 installations, 95 operations

The higher number of dossiers in Brussels is due to the fact that this Region was the first to implement the Directive 90/219/EEC. The numbers of dossiers and operations submitted in the Flemish and Wallonian Regions are quite similar.

The 280 operations of contained use of GMM's and/or GMO's are distributed as follows:**- Operation of type A or B (cf. article 2 d and e of the Directive 90/219/EEC)**

Type A: 264 operations

Type B: 16 operations

- GMM's and/or GMO's (one single operation can involve the use of both GMM's and GMO's)

- GMM's: 219 operations

- GMO's: 28 operations

- GMM's and GMO's: 33 operations

- Group I or II (cf. Directive 90/219/EEC, article 4)

One single operation can imply the use of GMM's and/or GMO's of group I as well as of group II. This explains why the total of operations is higher than 280:

GMM's of group I: 208 operations

GMM's of group II: 109 operations
GMO's of group I: 48 operations
GMO's of group II: 18 operations

The number of operations using GMM's of class of biological risk 1 (group I micro-organisms) is predominant. Among the operations with use of GMM's of group II (classes 2,3,4 of biological risks), only 5 operations implied the use of GMM's in a containment level 3 after risk assessment (genetically modified HIV and production of certain genetically-modified adenoviruses). There are no uses of GMM's of the class of biological risk 4.

- Types of GMO's (61 operations)

Transgenic animals: 28 operations
Transgenic plants: 32 operations
Transgenic animals and transgenic plants: 1 operation

- Type B operations (16 operations)

These operations include the use of different types or categories of organisms:

Transgenic animals : 1 operation
Transgenic plants : 1 operation
Bacteria : 11 operations
Fungi : 3 operations
Cell cultures : 2 operations
Two operations implied the use of bacteria as well as fungi.

- Type B operations with use of GMM's of group II (cf. article 18.1 of the Directive 90/219/EEC):

A single operation is concerned.

This operation implies the use of the bacteria *Yersinia ruckeri* (pathogen for fish – class of risk 3, non pathogenic for humans) genetically modified to produce a surface antigen from another bacteria (pathogen for fish - class of risk 2, non pathogenic for humans). The aim is to produce vaccine for fish farming. The principal risk of environmental contamination is transmission trough liquid effluents.

2.2. Extend of application of the biosafety regulation

At time of report sixteen dossiers of first permit, received in 1998-1999, are still under review by the SBB and involve 120 operations.

The number of installations and activities reported in 2.1 do not cover all existing one.

However, the biosafety regulation of premises and associated activities is progressively but surely applied in Belgium. The advisory authority acquired a significant scientific and regulatory experience in the risk assessment of GMM/GMO-related operations and installations. The administrations have gained a *de facto* training of the technical complexity of biosafety organisation trough their contacts with the notifiers and the SBB.

As far as GMM's and GMO's are concerned, installations and operations of biological class 3-4 implying the use of containment level 3 have all been reviewed and authorised. There is no operation of containment level 4 with GMM's in Belgium.

Most industries and spin-offs have applied the regulations as soon as published.

2.3. Directive 90/219/EEC and clinical trials using GMM's and/or transgenic allo/xenotransplants

Clinical trials activities involving GMM's can be authorised within the Regional Biosafety regulations as soon as genetic engineering is directly or indirectly involved in any proposed clinical trial.

Since March 1996, eight human clinical trial protocols have been approved in Belgium and one application is presently under review. In such cases, the risk assessment always involves meetings of an ad hoc scientific Committee of the Biosafety Advisory Council.

Table II in annex summarises the regulatory parameters of these protocols.

All trials were multicentric and carried out in academic hospitals.

Table III in annex illustrates the most relevant clinical data of the authorised trials. All protocols aimed at testing viral vectors in cancer therapy trials.

3. Classification and risk assessment.

The goal of the risk assessment of a given operation occurring in a given installation is to define the maximal containment measures required to reduce the risk for human health (including workers protection) and the environment to an absolute theoretical minimum.

An assessment strategy has to be followed by both the notifier and the Advisory Authority that is defined in the regulations. The assessment is an “installation by installation - operation by operation” process.

3.1 Assessment of the biological class of risk of an operation in a given installation

As defined by the Directive 90/219, the regional regulation applies to “installations” (article 8) and to “operations” or “activities” (Directive 98/81) carried out in such installations (article 9). The biological risks of each operation involving the contained use of GMO's and their related potentially pathogenic gene receptors or gene donors are assessed taking several risk assessment data into account (see 2.3).

The risk assessment of biological risk ends with the classification of the operation into one of 4 classes of biological risk:

- Risk class 1 includes i) the non-genetically modified, non-pathogenic and non incidentally pathogenic micro-organisms or organisms according to the criteria for classification into Group I laid down in the Commission decision of 16 January 1996, ii) the GMO's which are not disseminating and satisfying the criteria of the annex II, point b and c of the regional legislation's
- Risk classes 2, 3 and 4 include the biological agents, the animal and plant pathogens (referred to in the annex VIII of the legislation), which represent different degrees of hazard (2, 3 or 4), the GMM's and those GMO's not satisfying the criteria for classification into risk class 1, as well as the disseminating GMO's;

Annex VI of regional regulation defines a list of potentialisation factors associated to the type of genetic modification involved in the operation.

Declassification criteria have been established for the containment of GMM derived from animal and plant pathogens and elements thereof. Inversely, transduction of transgenes in multicellular gene acceptors may raise physiological and genetical questions theoretically potentialising the risk of an operation. Similarly, the advisory authority had to define the classes of biological risk of naturally defective pathogenic micro-organisms or made replication defective after genetic modification.

3.2. Definition of an appropriate containment

The risk management addresses the definition of the best containment conditions fitting with the defined biological class of the operation in the context of the installation (building) and the specific staff involved. This includes data provided by the notifier about:

- the available physical primary (equipment's), secondary (Laboratory facilities) and tertiary (Building design) barriers, together with the physical waste inactivation processes;
- the chemical barriers used for disinfection or inactivation
- the biological barriers (work organisation, rooms management, equipment management good practices)
- the scale and frequency of waste production
- the proposed Good Practices and levels of accreditation (ISO 900x, ISO 45001, GLP, GMP)
- the experience and training of the staff and the personal turn-over

The risk management also includes the control of the compatibility between operations occurring within the same building: operations requiring a high degree of aerosol prevention must be physically located in the most access-restricted areas and their laboratory practices and personal training enhanced. The equipment used for virus, viroids, viral vectors, phages manipulations must be dedicated equipment unshared for the experimentation or exploitation of other biological materials.

All these elements are contributing to assign the Biosafety containment levels that reduces to an absolute minimum either the worker's exposure to biological agents and their risk of laboratory-acquired infection or any potential escape of GMM's or GMO's to the environment.

Along the reviewing process applied by the SBB, the precautionary principle is taken into account as following: in case of relevant scientific doubt, the upper containment level is systematically required by the authority until new data become available demonstrating the possibility of reducing the required containment measures. During each phase of the experiments on the genetic modification of micro-organisms or organisms, the biological risk class considered shall be that corresponding to the highest class, be it that of the donor, the recipient, or possibly that of the vector or insert determined in accordance with technical annexes, providing that the genetic modification does not produce an organism of a higher risk class.

These combinations of criteria are listed in the annex IV of the regional regulations

In certain circumstances, i.e. where a genetically modified bloodborne pathogen of risk class 3 which is not infectious by the air route is manipulated at small scale, a laboratory of biosafety level 2 with work practices and personnel protective equipment corresponding to the biosafety level 3 are accepted as the result of the risk management.

In the practice, definition of appropriate containment also regularly interferes with other -non risk related- containment considerations as protection of the experiment (Clean rooms), Good Manufacturing standards or quality insurance standards (GLP and ISO 45001), which are usually more stringent than the provisions of the Directives 90/219, 98/81 or 90/679. Consequently, on demand of the notifier, several Biotech and pharmaceutical companies requested very low-risk operations to be carried out in containment corresponding to biosafety containment 3 or 4.

Risk management is also addressed at the European group of inspectors (Directive 90/219/EEC enforcement Project) to which a Belgian representative participates (see 4).

3.3. Risk assessment data

The technical annexes used for the risk assessment are:

Annex II : Criteria for classifying genetically modified GMM's (Commission decision of 16 January 1996) and GMO's (animals and plants) into risk class 1.

Annex III : Safety assessment parameters to be taken into account, as far as they are relevant (Annex III of Directive 90/219)

Annex VI: Vectors (viral vectors included), inserts, cell lines of vertebrates, their class of biological risk, the corresponding containment levels and definition of the biological, epidemiological or genetical factors potentialising or reducing the level of biological risk under proposed operation.

Annex VIII : Classification of the human, animal and plant pathogens. This list provides the risk class of about 2,500 pathogenic, opportunistic or allergenic micro-organisms.

All these technical annexes, guidelines of interpretation, forms for notification, examples of operations are published on the Internet via the **Belgian Biosafety Server** (<http://biosafety.ihe.be>).

In 1999, the advisory authority has published a catalogue of existing Internet resources in laboratory biosafety in order to help the notifier in performing his risk assessments. The chapter "Risk assessment data" of the Belgian Biosafety Server gives access to the following topics:

- Antibiotic resistance genes
- Biosafety Associations
- Bloodborne pathogens
- Books
- Categorisation of biological agents
- Clinical Microbiology [Bacteriology - Virology - Mycology - Parasitology]
- Gene therapy
- Guidelines, Recommendations, Standards & Publications
- Immunisation and vaccines
- Journals - Bulletins - Newsletters
- Laboratory-acquired infections
- Literature
- Material Safety Data Sheets for infectious agents
- Packaging and transport of infectious substances and diagnostic specimens
- Recombinant DNA
- Risk assessment
- Search tools
- Teaching Materials
- TSE Agents
- Working safely with research animals

4. Inspections and enforcement issues

4.1. Inspectorates

The regional regulations provide means for surveillance and inspections.

Inspections performed by the "Environment Inspection Services" of the Regions aimed to protect, and where necessary, improve the quality of the physical and biological environment by ensuring that the environmental regulations (included that on the contained use of GMO's and pathogens) are observed.

Repressive actions can also be carried out after complaints by individuals or groups, but also on the request of any authority, the police, the fire brigade, municipal services, political authorities.

The competencies of the Inspection Services cover different types of environmental pollution (air, water, soil, noise, wastes, etc.) and each regional Inspection Service has its own structure and organisation.

As regards the implementation of Article 17 of the Directive 90/219/EEC, the competent authorities invested most of their efforts in the authorisation process. The first operations authorised for a limited period of time will have to be renewed next June 2001. In the meantime, the services in charge with authorisations are coupled to the Inspectorate services. The necessary training and administrative measures aiming at enforcing the good application of authorised activities will be a next step under discussion within the frame of the implementation of Directive 98/81/EC.

4.2. The European Group of Inspectors

The SBB has delegated a representative to participate to the European Group of Inspectors (Directive 90/219/EEC Enforcement Project) which was initiated in 1998 by the Dutch Inspectorate for the Environment and the Physical & Biological Agents Unit of the United Kingdom.

The objectives of this project are:

- Promotion of the exchange of knowledge and expertise between Inspectors through seminars and joint inspection visits
- Creation of an information network to "guarantee" this exchange of knowledge and expertise on the long term
- Identification of bottlenecks in inspection, monitoring and enforcement, both on EU and Member-State level, resulting from the legislation itself
- Intensification of these activities in the EU

During the first conference, different types of actions were considered to improve the exchange of information and expertise, and the harmonisation between the participating countries.

On twelve defined actions, three were committed to Belgium:

- the Collection of governmental or official websites dedicated to biosafety and
- specific biosafety studies (renamed Laboratory biosafety resources) and
- development of a specific private Web site for the Group of Inspectors.

4.3. Tracing and authentication of GMM's or GMO's

The last ten years, the scientists of SBB have developed the laboratory expertise (biosystematics, genome analysis, probe design, PCR primer design, DNA extraction formats for environmental samples, PCR and RAPD or AP-PCR formats) for the tracking of any genes in the environment, industries, wastes, biomass and products like food, feed, seeds, plants and animals.

SBB is presently coordinating the "Network of Federal Laboratories for the Tracing and Authentication of GMO's". Such expertise is ready and made available to Inspectorates in case of need.

5. Problems with the interpretation of the provisions (possibly with conflict in defining work use with respect to Directive 90/220/EEC)

Several terms or provisions in the Directive have generated problems of interpretation and/or of practical application:

5.1. In relation with the "contained use" definition

Some difficulties were met with the status of specific operations limited to the storage of GMM's or GMO's. Indeed, there are cases where storage is only a step (a pause) in transport or distribution without any intermediary use of the GMM or GMO. However, storage is covered by the mentioned definition. In such cases, applying fully the provisions of the regional legislation regulating classified installations would lead to unnecessary administrative burden and disproportionate safety measures considering the risk of such activities. Consequently, it was proposed (initially by the Flemish Competent Authority) that such operations, in accordance with article 5 of the Directive, should be declared but not as extensively notified as current operations. Such a declaration would be assessed by the SBB but would ultimately be more appropriately managed under transport regulations.

5.2. Type A and B operations

There has been a permanent and clear lack of understanding among users concerning the distinction between type A and type B operations, which resulted in a lot of information requests to the SBB. Moreover, the differences in terms of procedural requirements (and corresponding delays) between type A and type B operations, particularly for subsequent uses, did raised some concerns in the industrial world, where fast approval is often expected.

On the basis on the specific guidance developed by the Commission (document XI/535/91), Belgium has always adopted a flexible and realistic approach both in defining the concept of "small scale" and in discriminating between non-production and non-commercial activities on the one hand and production/ commercialisation activities on the other hand.

For example, operations aiming at setting up the upscaling of bioreactors or fermentors, even involving volumes up to 350 litres, have been handled as "small scale" operations provided such activities were clearly limited in number and frequency. However, since the present wording was a source of sterile debate unrelated unequivocally to biological risk, Belgium certainly welcomes the abolition of the current categorisation of activities according to purpose and scale in the new Directive 98/81/EC.

5.3. Annex III

In relationship with the prior risk assessment as requested under Article 6, §§ 2 and 3 of the Directive, the SBB has been regularly confronted with very poor and limited scientific information provided by the notifiers. This despite of the availability of standardised template forms for the dossiers, and the basic information given to notifiers or to local biosafety committees along audits or seminars.

The structure and content of Annex III of Directive 90/219/EEC was certainly one of the reason for that situation. Annex III is more a catalogue of criteria than a real tool for risk assessment. It is hoped that Annex III of the revised Directive, which in our view clarifies the elements and the procedure to be used for the risk assessment, will contribute to improve the quality of the assessment by notifiers and simultaneously speed-up the reviewing and authorisation procedures.

5.4. Status of recycled biomass

The recycling of residual materials from industrial operations into products delivered to third parties gave rise to important legal and administrative problems and uncertainties. Should or not Directive 90/220/EEC or other sectorial regulations be applied to such residual materials?

There is an obvious "grey borderline" at the interface between products and recycled residual materials. One practical example is the use of fermenter cakes in agriculture as soil amendments.

If there is a requirement under Directive 90/219/EEC to inactivate wastes by validated means, it is widely recognised that inactivation does not mean that all organisms are killed.

One can expect such problems to be amplified under the revised Directive 98/81/EC. Indeed, at containment level 1, inactivation of waste is foreseen to be optional but it shall be "contained".

It will be important to clarify this borderline and to understand how to interpret the terms "containment" and "inactivation" in such a context.

6. Public consultation and information

Public consultation according to Article 13 of Directive 90/219/EEC has been implemented in the regional legislation in the following way.

The dossier for notification of operations involving the contained use of genetically modified micro-organisms or organisms is based on standardised template forms and guidelines and is composed of a "technical dossier" and a "public dossier".

The "technical dossier" is the technical and scientific evaluation tool for the SBB (the advisory authority) and may contain confidential information. Such a dossier exists as a single exemplar. The access to the technical dossier is restricted to SBB as single advisory authority and to the persons designated by the competent authorities.

The "public dossier" provides the same generic information as the "technical dossier" but written in standard language and without any reference to confidential information. The "public dossier" is only required along the procedures granting a first use permit. As part of this procedure, the "public dossier" is made available to the public by the authorities, the concerned county or municipality for local and time-limited consultation.

The main purposes of that consultation are to provide general information to the neighbourhood regarding contained use and to give to the public the possibility to express comments, observations or objections regarding these operations. The Competent Authority takes these comments, observations and objections into account when drafting its final decision, occasionally upon additional advice of the advisory authority.

All decisions are made available to the public for a time-limited period, allowing introduction of appeals by the public or the petitioner.

Public consultation and information may soon become more effective and more wide in the future through the use of electronic media and the Internet. The revision of Directive 90/220 and the recent evolution of public perception or industrial responsibilities do create a technically more permissive context.

Belgium was one of the first Member States to develop (in March 1996) an Internet site fully dedicated to biosafety and targeting the notifiers, the authorities and general public. The site has a recognised international audience with 50% of the connections from USA, Canada, Japan, and Australia. It has been reviewed by several scientific journals of international size including noteworthy Nature B-Biotechnology. It is found at high frequency by most Internet search engines and back-linked or partly mirrored by more than 100 other Web sites.

The "Belgian Biosafety Server" (<http://biosafety.ihe.be>) essentially provides for the time being general scientific and administrative information such as full text of regional laws and EU Directives, procedural aspects, co-ordinates of Competent Authorities, notification forms.

As a function of the implementation of Directive 98/81 and the future revised Directive 90/220, the site could become a major tool of public information/consultation by the competent authorities.

7. Accidents and emergency plans

Up to now, no accident has been reported to the authorities.

As far as emergency plans are concerned, the Flemish regional regulation (Regulation of 1/6/95) and the Brussels regional regulation (Regulation of 9/12/93) implementing Directive 90/219/EEC mention respectively in Art. 5.51.7.1 §1er and in Art. 14 §1er that the user must submit the information needed to establish emergency plans outside the contained installation in cases of type B operations with a class of risk 2, 3 or 4. The Wallonian regulation (Regulation of 13/6/96) takes into account the guidelines fixed by the EC regulatory committee of article 21 (Regulation of 13/6/96), where the need of emergency plans was restricted to operations requiring containment levels 3 and 4.

Up to now, a single type B operation with GMM's of group II (operation of class of biological risk 2) has been notified in the Walloon Region. But the nature of the operation and of the GMM involved did not require an emergency plan.

To illustrate that the obligation of emergency plans is not a theoretical problem in Belgium, 5 type B operations, consisting in the large scale production of human pathogens (for vaccines purposes) belonging to the class of biological risk 2, have been fully notified together with their specific emergency plans and authorised.

8. Protection of confidential information

In accordance with article 19 of Directive 90/219/EEC, the regional laws transposing the Directive give the possibility to the notifier to indicate, if necessary, the information in the notifications the disclosure of which might harm his competitive position.

However, the following general information can not be regarded as confidential:

- the name and address of the notifier;
- the summary of the purpose of the contained use, the designation and type of operations which will be undertaken and the installation map;
- the biological identity of the genetically modified organism; the identity of the donor and recipient organisms, of the type of vector and of the biological function(s) encoded by the insert(s) or by the deleted targeted gene;
- a short description of the GMM or GMO which are stored, used or whose construction is foreseen;
- a brief description of the allocation and organisation of premises as well as of specific containment measures which are or will be applied;
- control measures adopted for GMM and GMO, and emergency plans;
- the summary of the prior assessment of the contained uses as regards the risks to human health and the environment that may *incur*
- any information already published in the press (scientific or not, paper or electronic), by a patent office or in a public thesis.

The provisions of article 19 of Directive 90/220/EEC are fully integrated in the Forms used for the Technical and Public dossiers along notification procedures.

The SBB, on the basis of a justified proposal of the notifier, takes the final decision as to which information has to be kept confidential.

Confidential information must be gathered in a specific, distinct and identifiable annex of the "technical dossier". Confidential information is never referred to in public advices or the text of authorisations relating to contained use activities.

At SBB level, electronic mail/ irc/ ICQ/ AOL interactions, Faxes and telephonic calls: Only reference to the dossier code is authorised. Any wording or comment related to confidential data is forbidden.

9. Waste disposal

So far, and before the implementation of Directive 98/81/EC, there is an explicit legal requirement to inactivate all types of GMM's to be disposed of in wastes by validated means. Such requirement is mandatory even if the GMM is deemed safe and is considered to have a reduced fitness and therefore a limited ability to survive in the environment.

Moreover, Article 13 of the Cooperation agreement between the competent authorities defines the status of residual matters containing living GMM/GMO's when recycled as product delivered to third parties. The legal frame applied in such a case is clearly Directive 90/220/EEC as well as pertinent sectorial regulations.

However, according to SBB's experience, inactivation of waste does not mean that all organisms are killed although the majority can be. It is also widely recognised that the concept of absolute absence of any living organism conflicts with the concept of probability of destruction. Indeed, it is admitted, both by the US and European Pharmacopoeia, that when the chance of survival is not more than one in a million, the level of risk is low enough in order to consider an object as "sterile".

In industrial processes, GMM's are grown in fermenters. On basis of the notifications and authorisations, most of the fermenters or bioreactors are used for enzyme production. One single installation for example can produce up to 3_9 tons of solid waste/week. These are typically operations of Group I-Type B.

According to Belgian regulations, the solid, liquid and gaseous effluents are certified as inactivated as a result of the enzyme extraction method and/or pasteurisation processes.

Although quality control will help in limiting the escape at all stages of the fermentation process, as well as during the waste management, non-intentional release of GMM's can occur especially when the production occurs at containment level 1. At this containment level, aerosol leaks from fermenters under pressure are admitted (minimise escape).

However, when biohazardous, the control measures, production and safety equipment are designed to prevent the escape of GMM's. From such a view point, Belgium has acquired with the pharmaceutical industry a large experience in the prevention of GMM escape from fermentation process, since GMP (Good manufacturing practices) standards are more stringent than those required by the related biosafety containment level.

The required inactivation process also implies for production at large scale that controls are carried out to check that the number of viable microorganisms in the treated waste stream does not exceed specific acceptable levels established by the risk assessment.

The final draft for the European norm for the “Guidance for handling, inactivating and testing of waste” (prEN 12461) mentions that appropriate statistical methods should be used to make inferences from these tests because it is practically impossible to verify the complete absence of microorganisms.

Specific studies on the inactivation of GMM in wastes and on the fate of DNA have been carried in Belgium by a group independent from the industry. It is actually usual that fermenter cakes issued from large scale productions of GMM's of group I are reused in agriculture as soil fertilisers after inactivation.

There is no systematic monitoring of inactivated effluents and wastes in Belgium.

As regards research facilities, wastes are either heat treated in autoclaves, or chemically inactivated by validated protocols, or disposed of in specific containers to be incinerated by third parties.

10. Progress with the transposition of Directive 98/81/EC into national legislation

In the frame of reviewing the regional legislation on environmental regulations, the Flemish region has organised a working group for specific revision of the Flemish decree on contained use with regard to the provisions of Directive 98/81/EC.

This working group consisted of members of the competent authority (CEM), a commission in charge of evaluation of environmental regulations, of the SBB as well as of representatives of the industry and universities.

After a year of discussions, proposals from the Flemish Region and from the SBB together with a set of specific proposals from groups, industries, biosafety experts and local biosafety committees will soon be submitted to general discussion between the Regions in the frame of the Cooperation Agreement.

Several elements of the acquired experience to take into account have been described in previous points of the present report

From the reading of the present report, the existing practice of Belgian Biosafety regulations can be observed as already very close the provisions of Directive 98/81. Whereas the scientific assessment of biosafety is now based on objective acquired experience, the design of the new legal text will occur in a new context created by the Cooperation agreement, the existence of the Biosafety Council and the enhanced sensitivity and awareness of the Belgian public.

For the Regional Competent Authorities,
Dr. W. Moens
Secretariat of the Biosafety Advisory Council

Annexes

Table II. Regulatory data on the approved gene therapy clinical trials in Belgium

The fields of the layout were selected to comply with the confidentiality and transparency provisions of European Biosafety regulations (Art 19 of EC Directives 90/219/EEC and 90/220). The time between the receipt of proposal and the authorisation date by the competent authorities includes the time during which the ad hoc Scientific Committee of the Biosafety Council awaited additional information.

B-GT/1

| | |
|------------------------------|--|
| -Title: | Gene therapy for the treatment of glioblastoma multiforme with in vivo tumor transduction with the herpes simplex thymidine kinase gene /ganciclovir system. |
| - Company or sponsor: | Sandoz Pharma, LTD. |
| - Pharmaceutical study code: | GLIB 201-E-00. |
| - Phase: | II. |
| - Installation: | Hôpital Erasme, Brussels. |
| - User: | Prof. Dr J. Brotchi et Prof. Dr T. Velu. |
| - Receipt date: | 1/2/96. |
| - Authorization date: | 3/29/96. |

B-GT/2

| | |
|------------------------------|---|
| -Title: | Prospective, open-label, parallel-group, randomised, multicenter trial comparing the efficacy of surgery, radiation, and injection of murine cells producing herpes simplex thymidine kinase vector followed by intravenous ganciclovir against the efficacy of surgery and radiation in the treatment of newly diagnosed, previously untreated glioblastoma. |
| - Company or sponsor: | Genetic therapy, Inc., Sandoz Pharma, Ltd. |
| - Pharmaceutical study code: | GTI-0115. |
| - Phase: | III. |
| - Installation: | Hôpital Erasme*, Brussels. Universitair Ziekenhuis Antwerpen°. |
| - User: | Prof. Dr J. Brotchi*, Prof. Dr T. Velu*, Dr E. Van de Kelft°. |
| - Receipt date: | 10/24/96*, 12/9/96°. |
| - Authorization date: | 2/5/97*, 3/5/97°. |

B-GT/3

| | |
|------------------------------|--|
| -Title: | A phase I study in patients with recurrent or metastatic squamous cell carcinoma of the head and neck using SCH 58500 (rAd/p53) administered by single intratumoral injection. |
| - Company or sponsor: | Schering Plough NV/SA. |
| - Pharmaceutical study code: | 195-177-03. |
| - Phase: | I. |
| - Installation: | Universitair Ziekenhuis Gasthuisberg, Leuven. |
| - User : | Prof. Dr W. Van den Bogaert, Prof. Dr P. Delaere, Dr K. Haustermans Prof. Dr A.T. Van Oosterom. |
| - Receipt date: | 10/21/96. |
| - Authorization date: | 3/5/97. |

B-GT/4

- *Title:* A phase II gene therapy study in patients with non-small cell lung cancer using SCH58500 (rAd/p53) in combination with chemotherapy for multiple cycles.
 - *Company or sponsor:* Schering Plough NV/SA.
 - *Pharmaceutical study code:* 197-076-03 .
 - *Phase:* II.
 - *Installation:* Akademisch Ziekenhuis, Vrije Universiteit Brussel.
 - *User :* Prof. Dr J. De Grève.
 - *Receipt date:* 8/18/97.
 - *Authorization date:* 2/12/98.
-

B-GT/5

- *Title:* Pilot study of immunisation with recombinant canarypox virus vCP1469A expressing the MAGE-1.A1 and MAGE-3.A1 cytolytic T lymphocytes epitopes in patients with malignant melanoma, non-small cell lung carcinoma, head-and-neck squamous cell carcinoma, oesophageal squamous cell carcinoma or bladder carcinoma.
 - *Company or sponsor:* Pasteur Mérieux Connaught.
 - *Pharmaceutical study code:* MEL01198.
 - *Phase:* I.
 - *Installation:* Cliniques Universitaires St-Luc, Brussels.
 - *User :* Dr M. Marchand.
 - *Receipt date:* 3/26/98.
 - *Authorization date:* 6/9/98.
-

B-GT/6

- *Title:* Phase II randomised study of immunotherapy of advanced breast cancer by repeated intramuscular injection of a recombinant vaccinia virus containing sequences coding for human MUC-1 and interleukin-2 (TG1031) comparing two doses levels.
 - *Company or sponsor:* Transgène.
 - *Pharmaceutical study code:* TG1031.02.
 - *Phase:* II.
 - *Installation:* Universitair Ziekenhuis Gent.
 - *User:* Prof. Dr S. Van Belle.
 - *Receipt date:* 6/4/98.
 - *Authorization date:* 8/6/98.
-

B-GT/7

- *Title:* A phase II, multi-center, open label, randomised study to evaluate effectiveness and safety of two treatment regimens of Ad5CMV-*p53* administered by intra-tumoral injections in 78 patients with recurrent squamous cell carcinoma of the head and neck (SCCHN).
 - *Company or sponsor:* Rhone-Poulenc Rorer.
 - *Pharmaceutical study code:* Ad5CMV-*p53* T-201.
 - *Phase:* II.
 - *Installation:* Hôpital Erasme*, Cliniques Universitaires Saint-Luc°, Brussels, Universitair Ziekenhuis Antwerpen⁺
 - *User :* Prof. Dr T. Velu *, Dr V. D'Hondt°, Dr Dirk Schrijvers and Dr Carl Van Laer⁺
 - *Receipt date:* 6/9/98*, 6/10/98°, 2/3/99⁺
 - *Authorization date:* 7/24/98*°, 23/7/99⁺
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B-GT/8

- *Title:* A phase II/III trial of chemotherapy alone versus chemotherapy plus SCH 58500 in newly diagnosed stage III ovarian and primary peritoneal cancer patients with 0.5 cm and 2 cm residual disease following surgery.
 - *Company or sponsor:* Schering Plough NV/SA.
 - *Pharmaceutical study code:* 198-102.
 - *Phase:* II/III.
 - *Installation:* Cliniques Universitaires Saint-Luc^o, Akademisch Ziekenhuis, Vrije Universiteit⁺, Hôpital Erasme*, Brussel.
 - *User :* Prof. Dr T. Velu *, Dr V. D'Hondt^o, Prof. Dr J. De Grève⁺.
 - *Receipt date:* 10/2/99^o, 19/5/99*.
 - *Authorization date:* tacit authorization (60 days after receipt date)
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Table III. Clinical data on the approved gene therapy clinical trials in Belgium

| n° | Disease | Therapeutic approach | Transferred nucleic acid | Method of transfer | Administered biological material | Route of administration |
|---------------|--|-----------------------------|--|---|--|--------------------------------|
| B-GT/1 | Newly diagnosed or recurrent Glioblastoma multiforme | Suicide gene/ pro drug | Thymidine Kinase (HSV-TK1), neomycin resistance (NeoR) | Amphotropic Murine Leukemia Virus | Retroviral vector producing cells (PA 317) | Intratumoral |
| B-GT/2 | Newly diagnosed previously untreated Glioblastoma | Suicide gene/ pro drug | Thymidine Kinase (HSV-TK1), neomycin resistance (NeoR) | Amphotropic Murine Leukemia Virus | Retroviral vector producing cells (PA 317) | Intratumoral |
| B-GT/3 | Squamous cell carcinoma of the Head and Neck | Tumor suppressor gene | Wild-type p53 | Human Adenovirus serotype 5 | Recombinant Adenovirus _(E3, E1A, E1B, pIX) | Intratumoral |
| B-GT/4 | Non-Small Cell Lung Cancer | Tumor suppressor gene | Wild-type p53 | Human Adenovirus serotype 5 | Recombinant Adenovirus _(E3, E1A, E1B, pIX) | Intratumoral |
| B-GT/5 | Melanoma, Non-Small Cell Lung Cancer, Head and Neck Carcinoma, Esophageal carcinoma, Bladder carcinoma | Immunotherapy | HLA-A1 restricted CTL epitope of MAGE-1 and 3 genes | Canarypox Virus (ALVAC) | Recombinant Canarypox Virus | Intradermal/ Subcutaneous |
| B-GT/6 | Metastatic adenocarcinoma of the Breast | Immunotherapy | Muc-1 and Interleukin 2 (IL-2) | Attenuated Vaccinia Virus (Copenhagen Strain) | Recombinant Attenuated Vaccinia Virus | Intramuscular |
| B-GT/7 | Recurrent squamous cell carcinoma of the Head and Neck | Tumor suppressor gene | Wild-type p53 | Human Adenovirus serotype 5 | Recombinant Adenovirus _(E3, E1A, E1B) | Intratumoral |
| B-GT/8 | Ovarian and primary peritoneal cancer | Tumor suppressor gene | Wild-type p53 | Human Adenovirus serotype 5 | Recombinant Adenovirus _(E3, E1A, E1B, pIX) | Intraperitoneal |