Belgian regulatory guidance on the use of genetically modified organisms in a clinical trial

Federal Agency for Medicines and Health Products
and
Sciensano

Version: October 2023

Contents

1. Definitions

Clinical Trials Regulation (CTR)
CTR is the European Union (EU) pharmaceutical legislation that entered into application on 31st January 2022, repealing the Clinical Trials Directive (EC) No. 2001/20/EC and national implementing legislation in the EU Member States. It aims to ensure the EU offers an attractive and favourable environment for carrying out clinical research on a large scale, with high standards of public transparency and safety for clinical trial participants.

Genetically Modified Organism (GMO)
A GMO is an organism, with the exception of human beings, in which the genetic material has been altered in a way that does not occur naturally by mating and/or natural recombination (Directive 2001/18/EC).

Contained Use (CU)
CU means any activity in which organisms are genetically modified or in which GMOs and/or pathogenic organisms are cultured, stored, transported, destroyed, disposed of or used in any other way, and for which specific containment measures are used to limit their contact with, and to provide a high level of safety for, the general population and the environment (Belgian decrees on the contained use of GMOs and/or pathogens transposing European Directive 2009/41/EC).

Deliberate Release (DR)
DR means any intentional introduction into the environment of a GMO or a combination of GMOs for which no specific containment measures are used to limit their contact with and to provide a high level of safety for the general population and the environment (Directive 2001/18/EC transposed in the Belgian Royal Decree of 21 February 2005).

Comparator Product
An investigational or marketed product (i.e. active control), or placebo, used as a reference in a clinical trial (EudraLex volume 4 annex 13).

2. Abbreviations

- BAC: Biosafety Advisory Council.
- CA: competent authority.
- CTA: clinical trial application.
- CTIS: clinical trials information system.
- EC: Ethics Committee.
- FAMHP: Federal Agency for Medicines and Health Products.
- STA: scientific and technical advice.
- SBB: Service Biosafety and Biotechnology of Sciensano.
- SNSA: simultaneous national scientific advice.

3. Introduction

3.1. Scope of this guidance

This guidance has been created through close collaboration between Sciensano and the Federal Agency for Medicines and Health Products (FAMHP). Its purpose is to guide clinical sponsors and investigators to submit clinical trial applications (CTAs) with Investigational Medicinal Products (IMPs) containing or consisting of genetically modified organisms (GMOs) in Belgium within the framework of the Clinical Trials Regulation (CTR). This document covers the regulatory requirements to initiate such clinical trials (CTs).

3.2. Regulatory Framework

A CT involving an IMP containing or consisting of a GMO can only be conducted if it complies with several regulatory provisions. Mandatory approvals needed to begin such a CT include at least a formal approval of the clinical trial application (CTA) from the FAMHP. As defined in article 83 of the CTR, the FAMHP acts as national contact point for the FAMHP and Ethics Committee (EC) submissions and decisions (see section 2.5) in the Clinical Trials Information System (CTIS). As the IMP contains or consists of a GMO, the CT must also comply with legislative provisions on biosafety, implementing Directives 2009/41/EC and 2001/18/EC. Because for most of the CTs, the IMP is administered in clinical centers or settings, a CT will fall under "the contained use procedure" in Belgium (see section 2.3). If the CT involving a GMO cannot be conducted in authorised "contained use" facilities or the CT involves a release of the GMO into the environment that cannot (fully) be encompassed by the regulations on contained use of GMOs, a "deliberate procedure" needs to be followed (see section 2.4).

Note that a CT involving a medicinal product containing or consisting of a GMO that has been granted a marketing authorisation does not require an approval under the "contained use" nor the "deliberate release" procedure, on the condition that the use of the medicinal product is in accordance with the summary of product characteristics and that the environmental risks are covered by the environmental risk assessment from the marketing authorisation.

4. Procedures and timelines

An overview of the different procedures is given in Figure 1 and will be detailed throughout the entire document.

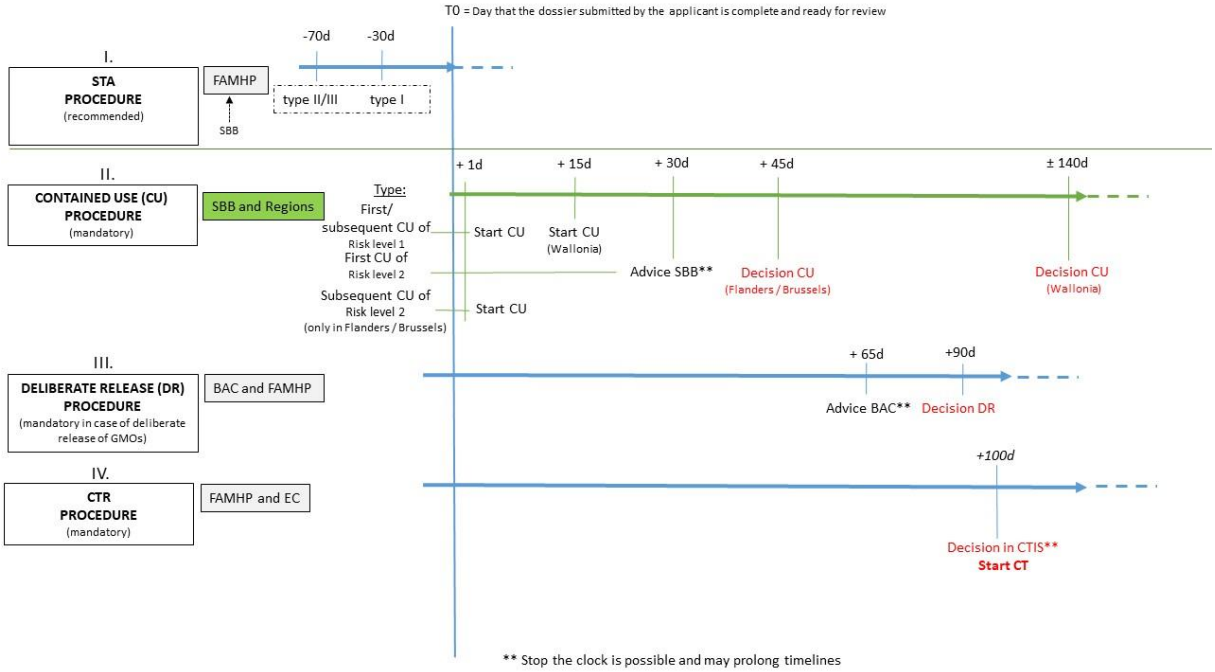

Figure 1: Overview of the Belgian regulatory framework for clinical trials involving an investigational medicinal product containing or consisting of GMOs.

Light grey boxes indicate that the documents to be submitted to this competent authority and advisory body must be completed by the sponsor. The green box indicates that the documents must be submitted by a combined contribution of the sponsor, the investigator and the biosafety officer.

The submission of application forms or documentation as part of the different **mandatory procedures** can be initiated at the same time, which is shown here as day 0 (**T0**). These applications need to be submitted to the respective advisory bodies and competent authorities who will evaluate and review the activity according to specific timelines, which are indicated by the number (x) of days (**+ xd**).

I. In Belgium, the FAMHP offers the applicant the possibility of requesting an STA prior to other mandatory procedures. An STA is strongly recommended for questions related to the GMO status and/or GMO procedure(s) to be followed.

II. The regional authorities and the SBB as the advisory body are involved in the CU procedure. However, timelines associated with the CU notification are dependent on the region where the trial will be conducted. Note that the CU procedure and approval are independent of those also associated to a clinical trial.

III. To request an authorisation under the DR procedure, an application containing the complete dossier (CTA part via CTIS and biosafety part via CESP) is submitted to the FAMHP. The application will be evaluated by the Biosafety Advisory Council (BAC, the advisory body) which transmits its advice to the FAMHP. Note that an application under the DR framework does not result in an exemption from an application under the CU procedure.

IV. In accordance with the Law of 7th May 2017 on clinical trials on medicinal products for human use, a clinical trial cannot start in Belgium without a positive decision on the CTR dossier in CTIS. Consult the guidance for an overview of the CTIS timelines.

4.1. Determining GMO status of the IMP and procedures

Before undertaking any legal GMO procedural steps, the applicant should determine:

- the GMO status of the IMP and (if applicable) the active comparator: does the GMO meet the definition of a GMO as laid down by GMO legislations?
- the GMO procedure: does a CU procedure suffice, or should both the CU and DR procedures be followed?
- the risk class of the CT (should the CU procedure be deemed applicable): please refer to section 2.3.a) of this guidance for additional information on risk classification.

The flowchart below attempts to assist the applicant in determining the status of the IMP and the procedure(s) to follow.

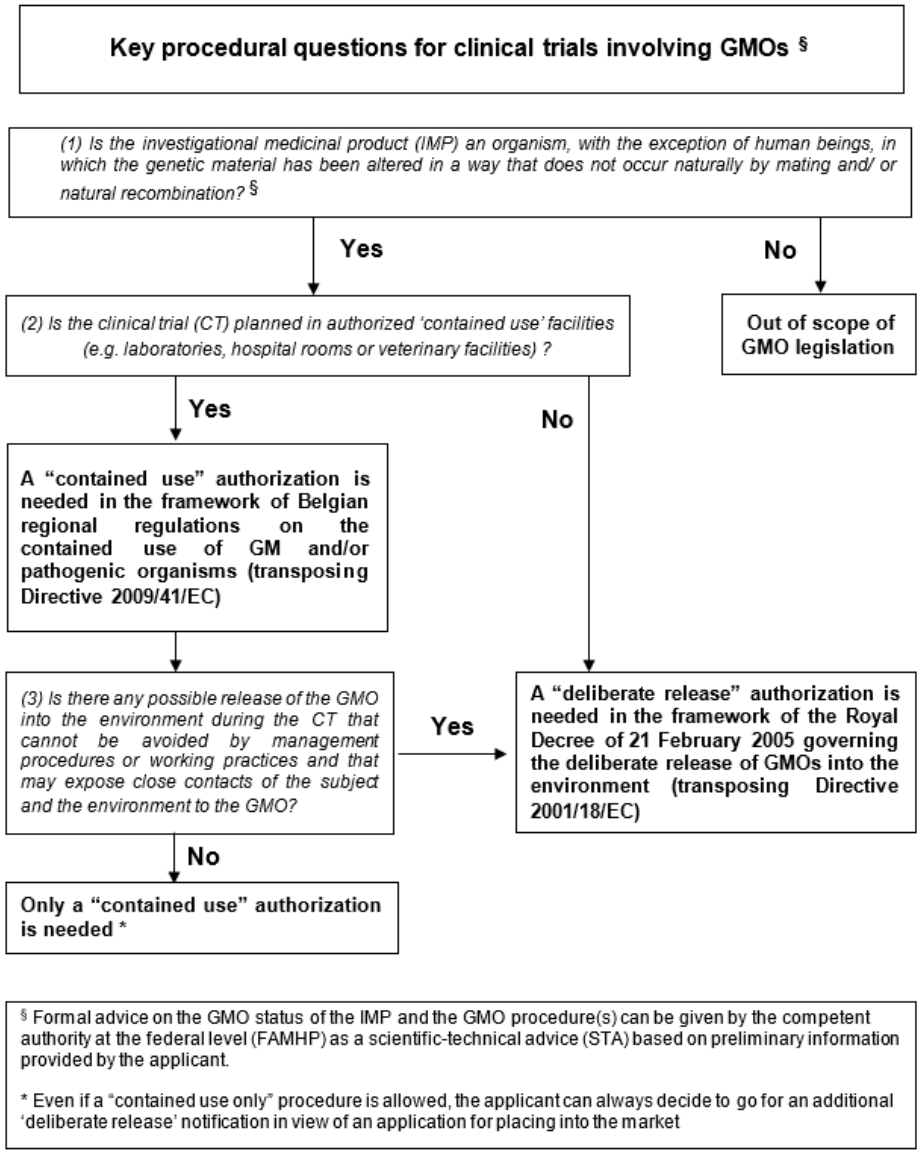

Figure 2: Overview of procedures for submitting an application for clinical trials with GMO-medicinal products in Belgium.

4.1.1. Status of the IMP

The Belgian legislation defines a "genetically modified organism" as an organism, with the exception of human beings, in which the genetic material has been altered in a way that does not occur naturally by mating and/or natural recombination. Within the terms of this definition it should be understood that the genetic modification occurs through the

use of specific techniques. Some of them are listed in the GMO legislation. Other techniques (likewise listed) are not considered to result in genetic modification, and therefore do not lead to organisms with a GMO status. Finally, the legislation also provides a list of genetic modification techniques which yield organisms that have a GMO status but should be excluded from the legislation. Definitions and lists of techniques can be found in the DR and CU legislations and in Directives 2001/18/EC and 2009/41/EC.

Examples of IMPs containing or consisting of GMOs meeting the legal definition of GMO are:

- Virus/bacteria strains genetically modified by recombinant nucleic acid techniques in which the genetic material has been altered (e.g. for attenuation or to express (a) new gene(s)).
- Human T-cells genetically modified to express a chimeric receptor for the treatment of cancers (CAR-T cells): for clinical trials involving the use of genetically modified human cells under the conditions described in a common application form and good practice document, the submission of a biosafety dossier according to the contained use procedure (figure 1-line II) and a submission via the CTR procedure (figure1-line IV) suffice. A submission of a biosafety dossier according to the deliberate release procedure (figure 1-line III) is not necessary.

Note that plasmids and DNA vectors that are not integrative and non-replicative are generally not considered to be GMOs, provided that the plasmid does not contain a full viral sequence that is able to replicate. Nevertheless, since this field of expertise is constantly evolving and the definition of a GMO can be interpreted differently across different countries within the EU, it is highly recommended to ask for advice from the FAMHP by requesting a national scientific-technical advice (STA) to clarify this matter (see section 2.2).

Other examples of GMOs that have been released into the EU environment can be found on the Joint Research Centre website.

Answers on frequently asked questions related to the scope of the GMO regulatory framework can be consulted in the questions & answers document.

4.1.2. Determining the procedures

To determine the necessary GMO legal procedure(s), the applicant should evaluate if, at any stage of the CT, the general population and the environment can be exposed to the IMP containing or consisting of a GMO.
In the case where physical barriers, or a combination of physical barriers together with chemical and/or biological barriers, are used to limit the contact with the general population and the environment, the CT and related activities must comply with the Belgian legislation on the CU of GMOs. Generally, activities such as the preparation, administration or storage of the IMP should follow the CU procedure.

In general, a "contained use" procedure is sufficient when there is no possible release of the GMO into the environment either because there is no shedding or spreading of the GMO into the environment by the subject (the human body acts as a biological containment of the GMO), or because proper management procedures and/or working practices are implemented to prevent this release. Conversely, when there is a probability of release into the environment as a result of the shedding and spreading of the GMO into the environment for which no sufficient management procedures or working practices are in place to avoid exposure of close contacts and the environment, a notification under 'deliberate release' will additionally be required. This is the case when the subject leaves the clinical center but still sheds and spreads the GMO, thereby potentially exposing close contacts and the environment to the GMO.

Considerations that are taken into account include the probability of shedding, hazards associated to the shedding should it occur, probability of spreading, probability of

recombination with wild type viruses (in case the IMP contains or consists of a viral vector) or whether the GMO is also administered at home.

If boundaries between deliberate release and contained use remain unclear within the context of clinical trials, it is recommended that the applicant asks for advice from the FAMHP prior to CTA submission by requesting a national scientific and technical advice (STA) to clarify this matter (see below). In case of a multinational clinical trial, applicants are recommended to request for simultaneous national scientific advice (SNSA) from the authorities of the concerned EU member states. For more details on the SNSA procedure see below.

The following chapters are intended to explain each of these procedures in terms of the relevant authorities and advisory bodies, processes and expected timelines in Belgium.

Note that Directives 2001/18/EC and 2009/41/EC use the terms "notifier" or "user" to define the person submitting the notification, or any natural or legal person responsible for the contained use of GMOs, respectively. For the sake of simplicity, both terms will be referred to as "applicant" in this document.

4.2. STA and SNSA procedures – Figure 1 Line I

In Belgium, the FAMHP offers the applicant the possibility of requesting a formal national **scientific and technical advice (STA)** prior to other formal procedures such as CTAs. In the case of a CT or substantial amendment to a CT with a GMO, the STA (in collaboration with the SBB) can provide clarity on, for example, the GMO status of the IMPs and/or active comparator involved, the choice of comparator, the study design, the risk class of the CT and any containment measures related to the conduct of the clinical trial as proposed by the sponsor/investigator of the involved trial site(s), and the necessity of applying for a deliberate release procedure. A formal STA request prior to submission of the CTA is thus **strongly recommended**.

A briefing document should be provided to the FAMHP and might include the following data (non-exhaustive list):

- (draft) study protocol or protocol synopsis;
- study design;
- size and type of the study population;
- timing of the conduct of the study (e.g. in relation to circulating strains, flu season, RSV season, etc.);
- duration of the study;
- location of the involved clinical centers across the Belgian regions;
- characteristics of the parental organism from which the GMO is derived (information on pathogenic properties, host range, transmission route, zoonotic potential, geographic distribution, elements necessary for replication, genetic stability, persistence in the environment);
- characteristics of the GMO (with a focus on information regarding the properties of the GMO that are different compared to the parental organism from which it is derived, such as molecular characterization; biodistribution and possible transmission routes, including information on (asymptomatic) shedding of the GMO; genetic stability; probability of recombination with wild type strains);
- if appropriate, information on the strategies used to avoid the generation of replication competent vectors during production of the IMP;
- pre-clinical data or already available clinical data with the GMO-based IMP or similar constructs that may substantiate any conclusions made with regards to possible transmission routes and potential shedding of the IMP into the environment;
- data that may substantiate any conclusion made with regards to the genetic stability (data on recombination with wild type strains or data on genetic reassortants);

- if appropriate, proposed containment/protective measures at the involved clinical centers (for the trial subjects, the staff, and the human population and the environment) either during the trial, at the time of discharge of the trial subjects or during the post-discharge phase;
- proposed containment/protective measures at the involved clinical centers (e.g. for the trial participants, as well as for the staff of the clinical centres involved and the environment) either during the trial, at the time of discharge of the trial subjects or during the post-discharge phase;
- if appropriate, data/scientific rationale/justification of why the applicant deems such risks to be negligible or not requiring any specific containment measures either during the conduct of the trial or during further follow-up of the trial subjects;
- data on the overall drug development program (e.g. future clinical trials) that may be relevant;
- regulatory status of the (N)IMP/comparator product (e.g. previous or ongoing CTAs, STA requests, other consultations with NCAs and advisory bodies in other EU member states or at international level (e.g. WHO), etc;
- any other information regarding the planned trial or GMO-based IMP/comparator or similar constructs that may be available and deemed relevant (e.g. draft environmental risk assessment (ERA), GMP, GLP status).

As a general rule, the applicant will receive the STA in writing, following the type I STA procedure, within a maximum time limit of 30 days (after validation of the STA request). However, in practice, the formal type I advice is often issued in writing within 15 days if possible. Nevertheless, the FAMHP reserves the right to exceptionally classify the STA request as a type II STA procedure if it concerns a complex matter that requires the in-depth expertise of multiple experts and, hence, a heavy workload, or in case a face-to-face or online advice meeting with the applicant is deemed necessary in order to discuss and clarify critical issues in order to provide more specialized formal advice. In such case, the type II STA will be provided within a maximum of 70 days. In general, STA requests are processed as fast as practically possible and normally within 7 weeks after validation of the STA request.

Further detailed information regarding the **definition** of a type I, II or III STA request, **legal scope, procedures, timelines,** etc. can be found on the FAMHP website:
- Procedures for the introduction and the follow-up of a scientific-technical advice application (English)
- Procedures voor de indiening en opvolging van een aanvraag voor nationaal WTA (Dutch)
- Procédures pour l'introduction et le suivi d'une demande d'avis scientifique-technique (STA) (French)

As an alternative for purely national STA requests, and particularly in case of a multinational CTs with GMO-based medicinal products, applicants are recommend to consider requesting up front a **simultaneous national scientific advice (SNSA)** from the NCAs and Biosafety authorities of the concerned EU member states in which the CT will be submitted by the Applicant.
SNSA is intended to be used in situations where an applicant wishes to obtain national scientific advice from more than one national competent authority (NCA) at the same time. The SNSA format is designed to enhance the quality and consistency of such advice across the NCAs in Europe and to enhance convergence in scientific opinions and national requirements between the member states where possible. The SNSA format is part of an European pilot project from the EU Innovation Offices Network (EU IN) in conjunction with the Accelerating Clinical Trials in the EU initiative (ACT EU).
The same type of advice questions can be raised in an SNSA request as described above for purely national STA requests. At current 17 NCAs within Europe are participating on a voluntary basis in the SNSA procedures (cfr. list of participating NCA included below). Where needed, the NCAs involved in a SNSA request related to GMO-based medicinal

products will liaise with their respective national authority competent for the biosafety/GMO specific aspects if not falling within the remit of that NCA.

All detailed information on the procedural aspects and expected content of a SNSA request can respectively be found in the **guidance for applicants on the pilot project for simultaneous national scientific advice (SNSA)** and in the **guidance on SNSA briefing book format and content** which are available on the FAMHP website.

The **list of NCAs participating in the SNSA pilot procedures** can be found on the HMA website.

4.3. Contained use procedure – Figure 1 Line II

"Contained use" (CU) refers, in Belgium, to activities involving the use of genetically modified or pathogenic microorganisms, as well as genetically modified plants or animals, in a "closed environment" such as laboratories, hospital rooms, animal units, greenhouses and production units. Manipulating and administering GMOs in the framework of a CT are considered "contained use" activities. In Belgium, contained uses of GMOs and pathogens are regulated by decrees transposing Directive 2009/41/EC on the CU of genetically modified micro-organisms (GMMs) at regional level and as a part of the environmental laws for classified facilities. Note that Belgium decided to expand the scope of Directive 2009/41/EC to encompass pathogenic microorganisms and genetically modified organisms (plants and animals).

The regional decrees on CU (Flanders, Brussels-Capital and Wallonia)[1] describe various notification and authorisation procedures, which vary depending on the risks of the CU for the environment and human health, and whether the CU is either a first or a subsequent use. These procedures will be explained per region hereunder in broad outline to help the applicant identify administrative steps, deadlines and interlocutors.

Note that throughout this document several webpages will be provided and, at the time of initiating the CT, it is of primary importance to read through them for the detailed procedures. Alternatively, a consultation meeting with the advisory body (Service Biosafety and Biotechnology of Sciensano, SBB) may be requested.

4.3.1. Risk analysis

A common starting point for the three regional regulations is the obligation for the applicant to proceed with a risk analysis of the CT (figure 3). The purpose of the risk analysis, which consists of risk assessment and risk management steps, is to determine the risk class of the involved organism, the risk class of the CT, and the required containment level which are key determinants of the notification and authorisation procedures.

[1] Arrêté du Gouvernement wallon du 4 juillet 2002 déterminant les conditions sectorielles relatives aux utilisations confinées d'organismes génétiquement modifiés ou pathogènes.
Besluit van de Vlaamse regering van 6 februari 2004 tot wijziging van het besluit van de Vlaamse regering van 6 februari 1991 houdende vaststelling van het Vlaams reglement betreffende de milieuvergunning, en van het besluit van de Vlaamse regering van 1 juni 1995 houdende algemene en sectorale bepalingen inzake milieuhygiëne.
Arrêté du Gouvernement de la Région de Bruxelles-Capitale du 8 novembre 2001 relatif à l'utilisation confinée d'organismes génétiquement modifiés et/ou pathogènes et au classement des installations concernées.

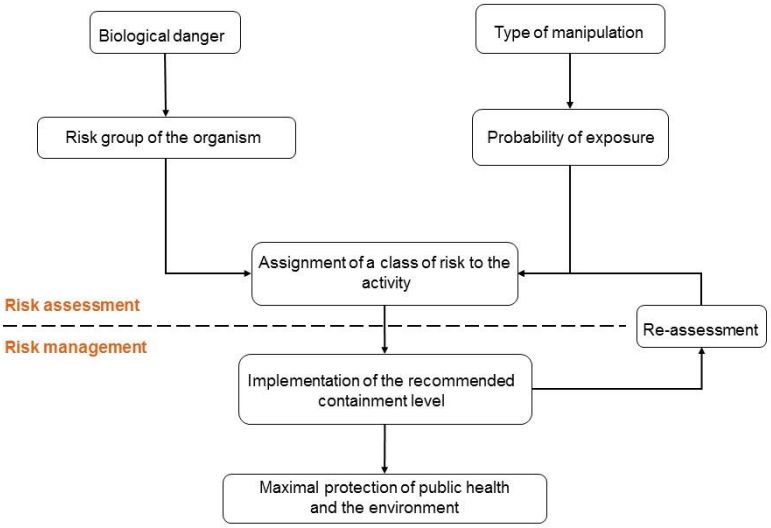

Figure 3: Application of risk assessment and adoption of risk management measures in CU of GMOs or pathogens.

Risk Assessment

The biological risk assessment is a process that includes the identification, the probability of occurrence and the severity of a potential adverse effect on human health or on the environment associated with a specific use of a GMO (or a pathogen). This analysis leads to the classification of the activity into one of the 4 existing risk classes (RC, level of risk increasing from 1 to 4). These classes are defined in Directive 2009/41/EC and Belgian regional decrees transposing it as follows:

- Risk class 1 activities present **no or negligible risk**, that is to say activities for which level 1 containment is appropriate to protect human health and the environment.
- Class 2 activities present a **low risk**, that is to say activities for which level 2 containment is appropriate to protect human health and the environment.
- Class 3 activities are activities of **moderate risk**, that is to say activities for which level 3 containment is appropriate to protect human health and the environment.
- Class 4 activities are of **high risk**, that is to say activities for which level 4 containment is appropriate to protect human health and the environment.

Risk Management

Once the risk is identified and characterized, the appropriate containment level and other prevention measures are determined to ensure the maximum protection of the general population and the environment.
Containment levels are described in the Directive and regional legislations on the CU of GMO and/or pathogens and set out the minimal requirements for the facility with regards to the technical and biosafety characteristics of the facility, the professional work practices, the training of the personnel and the treatment of waste and biological residues. These requirements, which are set in order to mitigate risks, must be determined in a case-by-case manner.

For the sake of simplicity, **only risk class 1 and 2 (RC1 and RC2) CU procedures will be discussed in this guideline** as they currently represent the most frequent risk classes encountered in Belgium for a CT involving a GMO.

Note that the containment levels of the room where the IMP containing or consisting of GMOs is prepared (generally the pharmacy) and the room where this IMP is administrated to patients (generally a hospital room) may be different due to a different risk of exposure of persons and environment to the IMP.

More information on risk assessment and management of contained uses with genetically modified organisms and/or pathogens can be found on the following webpages:

- Assessment of biological risks;
- Contained use of GMOs and/or pathogens: Tools for risk assessment and risk management.

Specific pages on the criteria for containment levels and other protective measures depending on the risk class and the type of facility are described on the following webpages (available in French and Dutch only):

- Utilisation confinée - Critères de confinements et autres mesures de protection;
- Ingeperkt gebruik - Inperkingscriteria en andere beschermingsmaatregelen.

Specific pages on containment levels for hospital rooms and laboratories for risk classes 1 and 2 CU are available in English on the following website:

- Contained use - Criteria for containment levels and other protective measures.

4.3.2. The biosafety dossier

When submitting an application for a CU with GMOs (or pathogens), regulations require that the applicant gathers specific administrative, technical and scientific information and performs the risk assessment and risk management of the CT. This information is reported in a biosafety dossier that must be submitted to the regional competent authorities and to the SBB experts for advice. The SBB will carry out an evaluation of the CT risk assessment on the basis of the information provided in the dossier and will inform the competent authority of whether or not the containment level proposed by the applicant is adequate. The SBB acts here as a scientific and technical expert for the competent authorities who will take its advice into consideration when delivering, if appropriate, the authorisation to proceed with the CT in a specific location (mostly clinical centers).

In order to facilitate the information and notification procedures and to keep administrative constraints to a minimum for the applicants, the SBB has, in collaboration with the competent authorities, developed notification forms based on both the requirements of the regional decrees, as well as the experience gained of implementing this regulation. Since the advice from the SBB and the subsequent authorisation from the competent authorities will be written in Dutch or French, two of the Belgian official languages, forms are available in these languages. However, within the framework of CTs, the scientific and technical part of the dossier can be completed in English (form available upon request at the SBB).

The biosafety dossier must be filled out in close collaboration between those who hold the scientific and technical information on the CT (investigator and/or sponsor) and the person responsible for biosafety in the hosting facility, in general the local biosafety officer. The biosafety officer of a specific site is generally aware of the procedures to follow to request an environmental permit and/or authorisation for a new CT with a GMO.

4.3.3. Notification procedures

Generally, clinical centers are already covered by an environmental permit. However, in order to specifically perform CU activities with GMOs (or pathogens) such as a CT involving an IMP containing or consisting of a GMO, an extension or an addition to the existing environmental permit covering this type of activity may be required. Moreover, a specific authorisation to perform a CT with a GMO may also be required.

4.3.3.1. Brussels-Capital

Competent authority of Brussels-Capital is **Brussels Environment (BE)**.

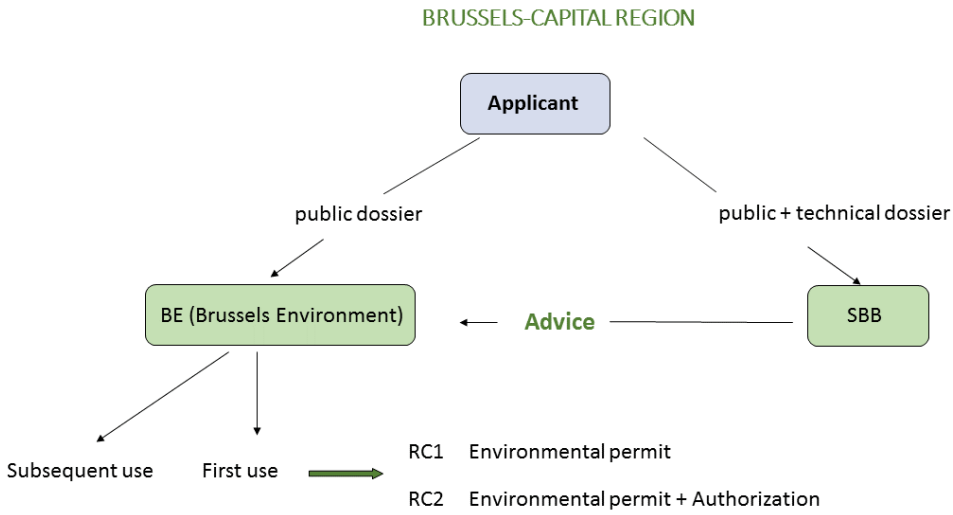

Figure 4: CU notification procedure in Brussels for RC1 and RC2 activities.

In Brussels-Capital, CU activities involving GMOs (or pathogens) can only take place in facilities that hold an **environmental permit**. More specifically, an environmental permit is required according to section 85b of the list of classified facilities[2]. It is usually issued for 15 years, renewable once.

Two procedures exist depending on whether the CU is either a "**first or a subsequent use"**:

- When a CU activity is reported for the first time to the competent authority, the "first use" procedure applies. The facility needs the environmental permit for CU (section 85b), and an authorisation for an RC2 CU. An RC1 CU does not require an authorisation.
- If the facility already holds an authorisation for RC2 CU (and the environmental permit covering CU activities) and has completed the "first use" procedure, the "subsequent use" procedure applies. The procedure for a subsequent use may be followed either in case of:
    - a new CU activity of the same (or lower) RC;
    - a change in an existing activity that does not modify the RC;
    - a continuation of an activity for which the authorisation term has elapsed.

The environmental permit and the authorisation are issued by the same competent authority: BE.

Both procedures start by the submission of a biosafety dossier to the competent authority (BE) and to the SBB for advice. In Brussels-Capital the biosafety dossier is composed of two parts:

- the technical biosafety dossier sent to the SBB which provides a detailed description of the CU activities (including confidential information if any), the infrastructure, the containment measures, the laboratory practices;

[2] Ordinance of 5.6.1997 modified by the Ordinance of 26.3.2009, Belgian Official Journal of 16 April 2009.
Ordinance in French.
Ordinance in Dutch.

- the public biosafety dossier sent to the competent authority and to the SBB which is a non-confidential summary of the technical dossier that can be submitted to public hearing.

The SBB advice is always required and is sent to the competent authority within 30 calendar days after receipt of the validated biosafety dossier.

Tables 1 and 2 summarize the requirements and timings for RC1 and RC2 CU in a first use and subsequent use.

All information regarding the contained use procedures in the Brussels-Capital region and forms to put together the biosafety dossier can be found on the following webpages:

- Contained use of GMOs and/or pathogens: Notification procedure in the Brussels-Capital Region;
- Bioveiligheidsregels voor het gebruik van pathogene en/of genetisch gewijzigde organismen;
- Règles de biosécurité pour l'utilisation d'OGM et/ou de pathogènes.

4.3.3.2. Flanders

The competent authorities of Flanders are:

- **LNE-Department Omgeving** for authorisations;
- **Municipalities** and **Provincial Council** for environmental permits.

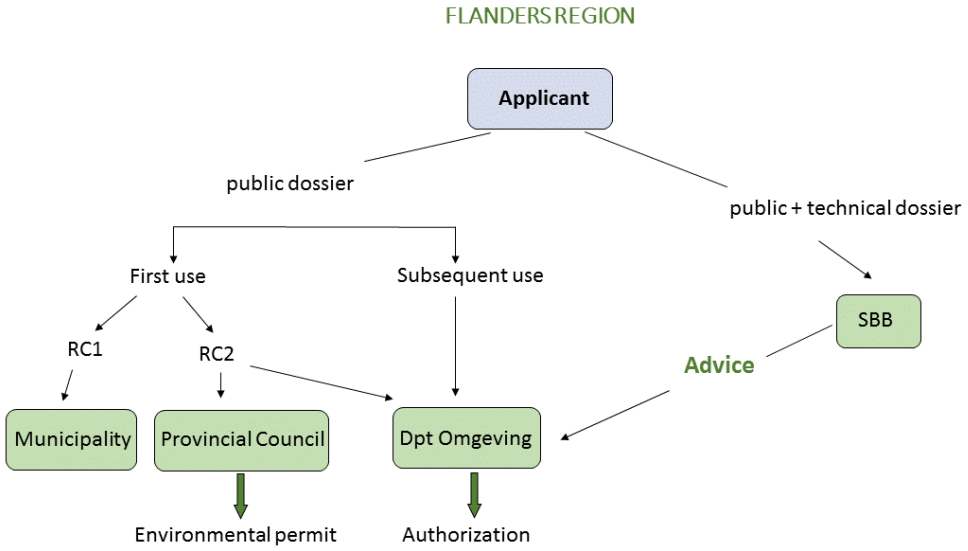

Figure 5: CU notification procedure in Flanders for RC1 and RC2 activities.

In Flanders, facilities hosting CU activities are subject to a preliminary written authorisation in the framework of the **environmental permit covering** sectoral conditions for chapter 51.1 or 51.2 of VLAREM II for the contained use of GMOs or pathogenic organisms, respectively [3]. The environmental permit is usually issued for 20 years or an indefinite duration. Facilities hosting these activities are additionally subject to a written **authorisation** (with the exception of RCI CU). The environmental permit and the authorisation for the CU are issued by different authorities.

[3] VLAREM II
Order of the Flemish Government of 1 June 1995 concerning General and Sectoral provisions relating to Environmental Safety ; Part 5. SECTORAL ENVIRONMENTAL CONDITIONS FOR CLASSIFIED ESTABLISHMENTS ; Chapter 5.51. THE CONTAINED USE OF GENETICALLY MODIFIED AND/OR PATHOGENIC ORGANISMS

Two procedures exist depending on whether the CU is either a **first** or a **subsequent use**:

- when a RC2 CU is reported for the first time to the competent authorities, the "first use" procedure applies. In this case, the applicant has to request an environmental permit specifically covering the RC2 CU involving a GMO and an authorisation;
- if the facility already has the required environmental permit and has already completed the "first use" procedure, the "subsequent use" procedure applies. This involves either a new RC2 (or lower) CU, a change in an existing activity that does not modify the RC or a continuation of an activity for which the environmental permit term has elapsed.

Tables 1 and 2 summarize the requirements for an RC1 and RC2 CU in a first use and subsequent use procedure.

Both of these procedures start by the submission of a biosafety dossier to the competent authorities and to the SBB for advice. In Flanders the biosafety dossier is composed of two parts:

- the technical dossier sent to the SBB which provides a detailed description of the CU activities (including confidential information if any), the infrastructure, the containment measures, the laboratory practices;
- the public dossier sent to competent authorities (Department Omgeving and the Council or municipality) and to the SBB which is a non-confidential summary of the technical dossier that can be submitted to public hearing.

The SBB advice is required and is sent to the Department Omgeving within 30 calendar days after receipt of the validated biosafety dossier.

Consult all information regarding the contained use procedures in the Flanders region and forms to put together the biosafety dossier.

4.3.3.3. Wallonia

The competent authorities in Wallonia are the **Municipalities**:
SPW ARNE -DPA (Service Public de Wallonie – Agriculture, Ressources naturelles et Environnement, Department Permits and Authorisations) acts as technical civil servant.

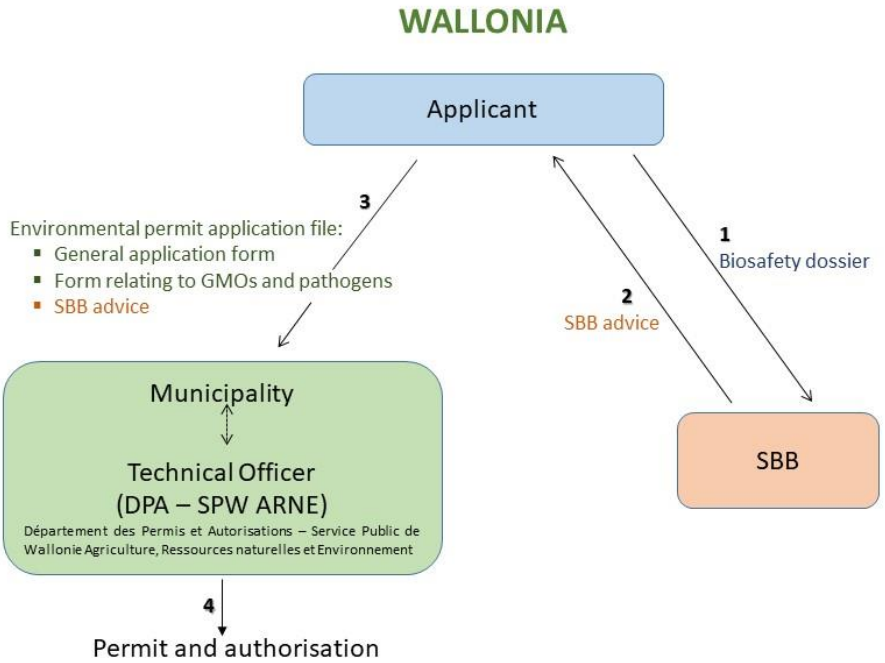

Figure 6: CU notification procedure in Wallonia. For RC1 activities, a declaration to the municipality suffice, no environmental permit is required.

CU activities of GMOs and pathogens are activities mentioned in the list of classified activities that are subject to an environmental permit[4] or to declaration. In Wallonia, the applicant directly requests the advice of the SBB by submitting the biosafety dossier consisting only of a technical dossier. The SBB will send its advice to the applicant within 30 days of receipt of the validated biosafety dossier.

In Wallonia, a CU is always considered a first use.

- In case of RC1 CU, an environmental permit is not required. The user must make a declaration to the Municipality, joined with the advice of the SBB (figure 6). The CU can start 15 days after the declaration is submitted to the authority unless otherwise stated.
- In case of RC2 CU, an environmental permit is required.

The applicant should attach the SBB advice to the application form for an environmental permit[5]. This environmental permit dossier is sent to the Municipality which is responsible for transmitting this request to the administration (SPW ARNE-DPA, which acts as technical civil servant). The SPW ARNE-DPA issues its decision within 90 to 140 days. However, the time needed to acknowledge the validity of the notification (20 days) and the time related to the information display must be added to this time limit. The CU can only begin after the permit has been issued.

All information regarding the contained use procedure in Wallonia can be found at:

- Contained use of GMOs and/or pathogens: Notification procedure in Wallonia;
- Demander un permis d'environnement ou un permis unique pour un établissement de classe 1 ou 2;
- Procédure d'instruction des demandes de permis d'environnement ou de permis unique.

[4] Decree of 4/7/2002 defining the list of projects subject to incidence studies and facilities and classified activities - section 73.
[5] Decree of 5/6/2008 amending the Decree of 4/7/2002 related to the procedure and diverse enforcement measures of the Decree of 11 March 1999 concerning the environmental permit.

4.3.4. Overview of the contained use requirements for Brussels, Flanders and Wallonia

Table 1: Requirements for "Contained Use – First Use" in Belgium depending on risk classification.

	Biosafety dossier	SBB advice*	Notification to municipality	Authorisation from competent authority*	Environmental permit*	Start CT
Risk class 1						
Brussels-Capital	YES Public to SBB and BE Technical to SBB	YES Sent within 30 days to BE	NO	NO	YES (section 85b) Usually issued for 15 years	1 day after submission of the biosafety dossier with valid environmental permit
Flanders	YES Public to SBB and municipality Technical to SBB	YES Sent within 30 days to DO	YES	NO	NO	1 day after submission of the dossier
Wallonia	YES Technical to SBB	YES Sent within 30 days to applicant	YES Declaration to municipality	YES, acknowledgment of receipt from municipality	NO	15 days after submission of the declaration
Risk class 2						
Brussels-Capital	YES Public to SBB and BE Technical to SBB	YES Sent within 30 days to BE	NO	YES, from BE	YES (section 85b) Usually issued for 15 years	Can start as soon as the written authorisation is obtained or 45 days after submission of the biosafety dossier to BE**
Flanders	YES Public to SBB, Provincial Council and DO Technical to SBB	YES Sent within 30 days to DO	NO	YES, from DO	YES, from Provincial council Usually issued for 20 years or undefined	After written authorisation is obtained with valid environmental permit (sub-section)
Wallonia	YES Technical to SBB	YES Sent within 30 days to applicant	YES	YES, from the municipality	YES, from the municipality	After environmental permit is obtained (90 to 140 days)

* possible "stop the clock" of the procedure that may stretch the timing.
** if no written authorisation is received.
DO: Department Omgeving, BE: Brussels Environment, SBB: Service Biosafety and Biotechnology of Sciensano.

Table 2: Requirements for "Contained Use – Subsequent Use" in Belgium depending on risk classification.

	Biosafety dossier	SBB advice	Notification to municipality	Authorisation from competent authority	Start CT: on condition that the containment measures are applied
Risk class 1					
Brussels- Capital	Technical to SBB*	YES Sent within 30 days to BE	NO	NO	1 day after submission of the biosafety dossier
Flanders	Technical to SBB*	YES Sent within 30 days to DO	NO	NO	1 day after submission of the biosafety dossier
Risk class 2					
Brussels- Capital	Public to SBB and BE Technical to SBB	YES Sent within 30 days to BE	NO	NO	1 day after submission of the biosafety dossier**
Flanders	Public to SBB and DO Technical to SBB	YES Sent within 30 days to DO	NO	NO	1 day after submission of the biosafety dossier**

* the SBB confirms to the competent authority that the CU is indeed of risk class 1.
** on condition that the facility is already subject to an authorisation and that the containment measures proposed in that first authorisation are applied.

4.4. Deliberate release procedure – Figure 1 Line III

"Deliberate release" means any intentional introduction into the environment of a GMO for which no specific containment measures are used to limit its contact with the general population and the environment. The Directive 2001/18/EC (transposed into Belgian law by the Royal Decree of 21 February 2005) applies to the deliberate release of GMOs and requires that an environmental risk assessment (ERA) should be carried out before release. The objective of an ERA is to identify and evaluate potential adverse effects of the GMO on public health and the environment.

Note that for most CTs, the IMP is administered in clinical centers or settings, and therefore an application under the DR framework will not result in an exemption from an application under the contained use procedure. Hence, most CT under the "deliberate release" procedure will necessitate the submission of a biosafety dossier according to the contained use procedure (figure 1 – line II) and a submission via CESP of a biosafety dossier according to the deliberate release procedure (figure 1- line III), in addition to the submission via CTIS of a CTA dossier to the FAMHP as national contact point for the FAMHP and EC submissions and decisions in CTIS (figure 1- line IV).

4.4.1. Notification procedure

The biosafety dossier for the "deliberate release" procedure is submitted to the FAMHP via CESP in addition to the CTA submission via CTIS according to the Clinical Trials Regulation. The FAHMP, in concertation with the SBB, validates the biosafety dossier and forward it to the Biosafety Advisory Council (BAC) via its secretariat (SBB). This dossier is then evaluated by the BAC which transmits its opinion to the FAHMP for a final decision.

4.4.2. Documentation

The information to be provided in the biosafety dossier for "deliberate release" is listed in article 13 paragraph 2 of the Royal Decree of 21 February 2005 on the deliberate release of GMOs. It includes:

- **A technical dossier** containing the information mentioned in Annex IIIA of the Royal Decree (art 13 paragraph 2 c). According to art 43 of the Royal Decree, not all information mentioned in the technical dossier can be considered confidential. Note that information mentioned in the technical dossier will also be made available in the context of a public consultation (art 17 paragraph 3) excepted part of it that is considered confidential and submitted as such (art 13 paragraph 2 c indent 8). Therefore, the applicant may consider submitting two versions of the technical dossier, with one of the versions containing only non-confidential information.
- **An environmental risk assessment (ERA)** according to Annex II of the Royal Decree (art 13 paragraph 2 e). According to art 43 of the Royal Decree, the environmental risk assessment can never be considered confidential. Note that information mentioned in the ERA will also be made available in the context of a public consultation.
- **The Summary Notification Information Format (SNIF)** according to art 13 paragraph 2 d of the Royal Decree. The SNIF must be completed in English. The SNIF should, for example, refer to all applications/authorisations for deliberate release in Europe. In view of the ESFC platform that was developed by the European Commission, the applicant should also separately submit the SNIF through this ESFC platform when the biosafety dossier is considered complete after validation and a biosafety T0 has been provided. Further questions on this can be raised via the European Commission contact page.

More information about Clinical trials with genetically modified medicinal products.

- **Information for the public** according to Annex VIII.A of the Royal Decree. Information for the public should correspond with the SNIF information. It should be provided in the national languages, and preferably also in English.
- **Declaration of civil responsibility** according to Art 13 paragraph 2 f. This declaration should be provided to cover cases of damage to humans, animals and the environment resulting from the trial.
- **Applicant declaration - control sample** according to art 13 paragraph 2 h. Statement by the applicant that s/he agrees to provide the SBB with a control sample of the GMO and the related scientific documentation at the latest 15 days after the start of the trial.
  In practice, the sample and the documentation should be sent to:
  Sciensano
  Transversal activities in Applied Genomics, GMO lab
  Rue Juliette Wytsmanstraat 14
  1050 BRUSSELS
  Email: GMO-PARTB@sciensano.be
  This sample is requested in order to enable the detection and identification of the recombinant virus or micro-organism in case of inspection or accidental release. The nature and quantity of the sample will depend on the detection method proposed by the applicant in the application. In respect to the scientific information that should accompany the delivery of the control sample, the applicant is requested to provide a detailed protocol for the method of conservation and analysis of the control sample. A quality test is sufficient, there is no need for a quantification test. When adhering to this request, the applicant may consider a guideline describing the data to be presented. This guideline also provides further information on contact points relative to reference material disposition.

Building on the experience gained with certain IMPs containing or consisting of GMOs, a number of documents and common application forms have been created with the aim of streamlining the information that needs to be provided in the context of clinical trials across the EU for both procedures contained use and deliberate release where appropriate. These documents can be retrieved from the European Commission's webpages dedicated to Advanced Therapies Medicinal Products and have been developed for:

- Adeno-associated viral vectors (AAV): common application form and good practice;
- Viral vectors: common application form;
- Human cells genetically modified by means of viral vectors: common application form and good practice.

For IMPs containing or consisting of adeno-associated viral vectors (AAV) or viral vectors, all necessary information for the technical dossier and the environmental risk assessment can be provided by means of the common application form developed for AAV or viral vectors respectively. It is strongly recommended that the technical dossier is accompanied by a number of documents as these greatly facilitate the evaluation of an application by the Biosafety Advisory Council. Such documents may include the clinical trial protocol, the European number attributed to the CTA, the investigator's brochure, the GMP/quality data, patient information (patient information or instruction sheet and informed consent form) and study staff instructions. It is also recommended to provide a copy of the bibliographic references (mentioned in Annex II and Annex IIIA).

This information, including the requested scientific information related to the delivery of the control sample, is also available on the SBB website:

- Notification procedures: Clinical Trials with GMOs for human or veterinary use;

- Procédures de notification: Essais cliniques avec des OGM pour usage humain ou vétérinaire;
- Kennisgevingsprocedures: Klinische proeven met GGO's voor menselijk of veterinair gebruik.

4.4.3. Timelines

The estimated timeline for a DR authorisation by the FAMHP is 90 days from the moment the biosafety dossier is considered valid ("Biosafety T0"). This 90-day time period includes a 30-day public consultation round and the evaluation of the biosafety dossier by the Biosafety Advisory Council (BAC), which transmits its advice to the FAMHP and for which the Federal Ministers provide their final authorisation. The BAC may request that the applicant provides additional information, in which case the timeline will be suspended until the answers have been provided by the applicant. Multiple clock-stops are possible and there are no legal timelines for the applicant to provide an answer. However, in order to streamline the DR procedure with the CTR procedure in CTIS, the applicants are recommended to submit both the DR dossier and the CTR dossier at the same time (respectively via CESP and CTIS), and they will be offered the opportunity to also provide their responses to the BAC validation questions within 10 days, and their answers to additional information within 12 days.

4.5. CTR procedure – Figure 1 Line IV

In accordance with the Law of 7th May 2017 on clinical trials on medicinal products for human use and before a clinical trial can start in Belgium, the CTR dossier must be authorised for Belgium in CTIS. As defined in article 83 of the CTR, the FAMHP acts as national contact point for Belgium. Upon submission of the CTR dossier via CTIS, the applicant is requested to clearly indicate in the cover letter whether the GMO IMP follows the contained use procedure only or both the contained use and deliberate release procedure. In case of a deliberate release IMP, the applicant is advised to submit the biosafety dossier via CESP on the same day as the CTR dossier in CTIS, and to refer to each procedure/submission in the corresponding cover letters.

4.5.1. Submission procedure

Consult the guidance for the submission of a CTR dossier via CTIS.

4.5.2. Documentation

Information on the content of the CTR dossier is available on the FAMHP website.

4.5.3. Timelines

For more information on CTIS evaluation timelines, please consult CTIS Evaluation Timelines.
As stated in the law of 7th May 2017, for phase I mono-national trials submitted for Belgium in CTIS, the 60 days evaluation timeline as foreseen according to CTR is reduced to 20 days. However, in case of a request for information (RFI) during validation, a maximum of 15 days can be added to the reduced timeline and in case of a RFI during assessment (part I and/or part II) a maximum of 31 days can be added to the reduced timeline.
In case of an advanced therapy investigational medicinal product or a medicinal product, as defined in point 1 of the Annex to Regulation (EC) No 726/2004, the reduced timeline can be extended with a maximum of 50 days. As an example, the maximum timeline for a mononational phase I trial in Belgium with a GMO-ATMP product without validation or assessment RFI will therefore be 70 days (i.e. 20 days + extension of 50 days).

4.6. Substantial modifications

Substantial modifications of the CTA dossier for GMO contained use or deliberate release trials will follow the CTR procedure timelines in CTIS.
Substantial modifications of the biosafety dossier for GMO deliberate release trials will also follow the CTR procedure timelines, although the specific biosafety related documents will need to be provided separately via CESP. No separate 90 days-biosafety procedure will be set-up for substantial modifications to the biosafety dossier, but the advice of the Biosafety Advisory Council will be requested within the CTR timelines (together with possible updates to the CTA part of the trial).

4.7. Contact information

Federal Agency for Medicines and Health Products (FAMHP)
Research and Development Division (clinical trials)
Email
Webpage
The FAMHP website

Federal Agency for Medicines and Health Products (FAMHP)
National Innovation Office and Scientific-Technical Advice Unit
Email
Webpage
The FAMHP website

Service Biosafety and Biotechnology (SBB)
Email
The Biosafety website

Biosafety Advisory Council (BAC)
Contact
The Biosafety Advisory Council website