Belgian Regulatory Guidance On The Use Of Genetically Modified Organisms In A Clinical Trial

Federal Agency for Medicines and Health Products

and

Sciensano

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Contents

Definitions

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:
Contained use is 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:
Deliberate release is 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:
A Comparator product is an investigational or marketed product (i.e. active control), or placebo, used as a reference in a clinical trial (EudraLex volume 4 annex 13).

1. Introduction

1.1 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. This document covers the regulatory requirements to initiate such clinical trials (CTs).

1.2 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 (see section 2.6) and a positive opinion from the Ethics Committee (see section 2.5). 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 authorized 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.

2. Procedures And Timelines

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

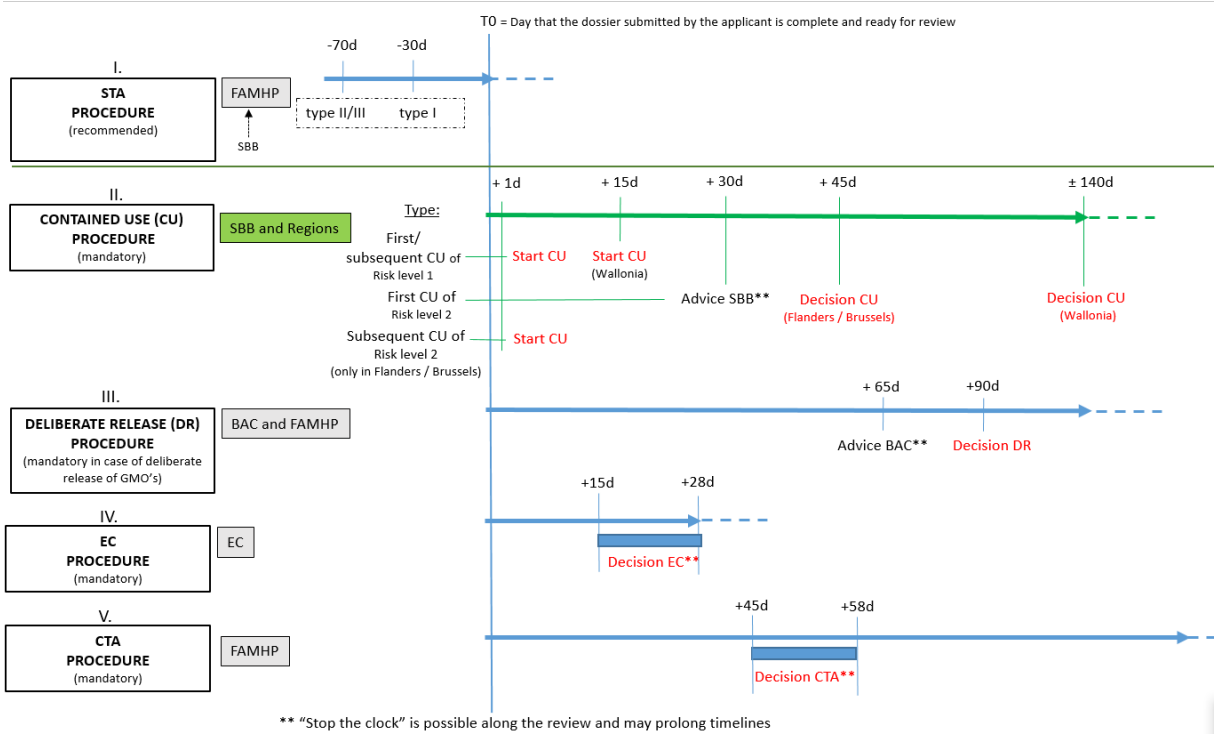

Figure 1: Overview of the Belgian regulatory framework for clinical trials involving an investigational medicinal product containing or consisting of GMOs

- *BAC: Biosafety Advisory Council, CA: Competent Authority, CTA: Clinical Trial Application, EC: Ethics Committee, FAMHP: Federal Agency for Medicines and Health Products, STA: Scientific and Technical Advice, SBB: Service Biosafety and Biotechnology*
- *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 CT will be conducted. Note that the CU procedure and approval are independent of those also associated to a CT.
III. To request an authorization under the DR procedure, an application containing the complete dossier (CTA part and biosafety part) 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 and V. In accordance with the Law of 7 May 2004 concerning experiments on the human person, a clinical trial cannot start in Belgium without a positive opinion from the (leading) Ethics Committee and the competent authority (FAMHP).

2.1 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.

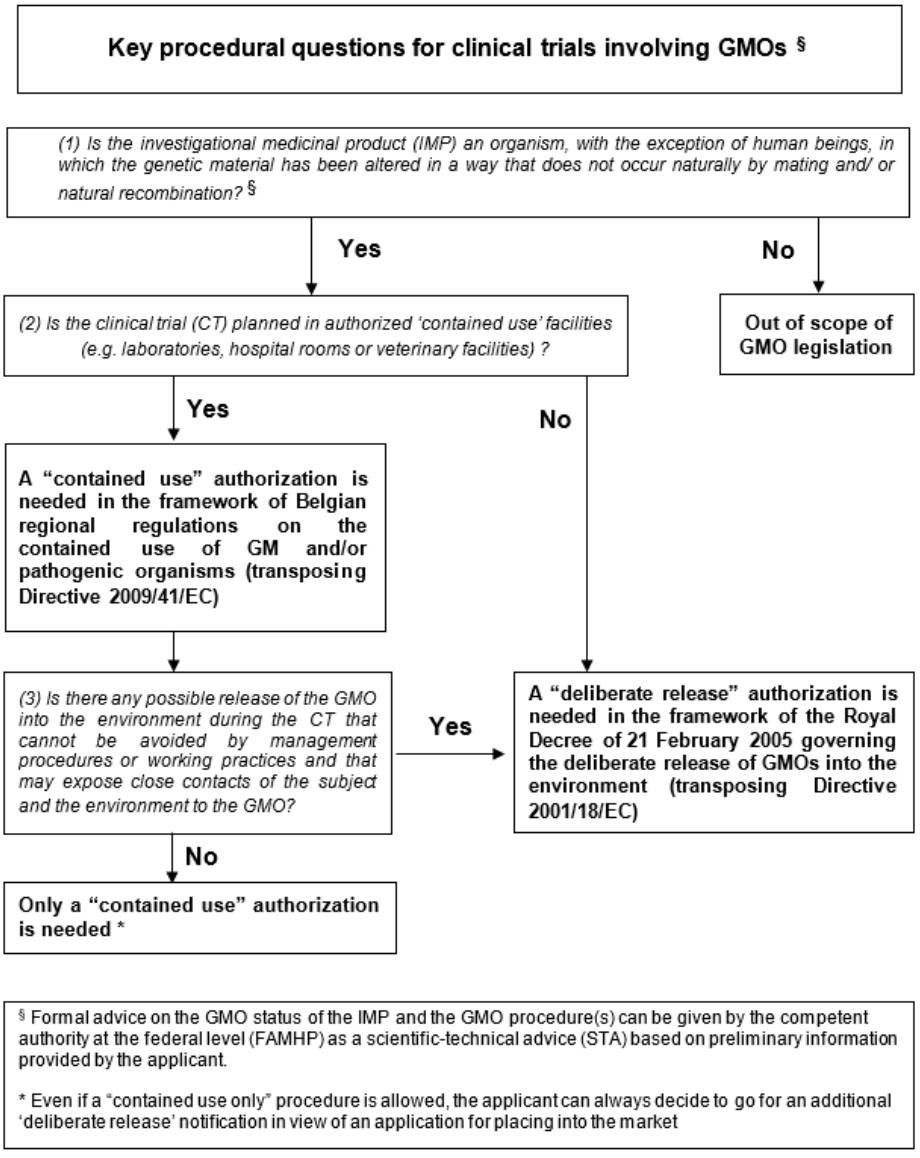

Figure 2: Overview of procedures for submitting an application for clinical trials with GMO-medicinal products in Belgium

2.1.1. Status Of The IMP

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 GMO legislation. There are also techniques (likewise listed) which are specifically not considered to result in genetic modification, and therefore do not lead to organisms that are considered as GMO. Finally, the legislation also provides a list of genetic modification techniques which yield organisms that 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)).
- Autologous human T-cells genetically modified using a retroviral vector to express a chimeric receptor for the treatment of cancers.
- Human cells genetically modified using novel genome editing techniques (e.g. CRISPR/Cas9)

Other examples of GMOs that have been released into the EU environment may be found at the Joint Research Centre website: http://gmoinfo.jrc.ec.europa.eu/gmo_browse.aspx.

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).

2.1.2. 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 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 his or her 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 by requesting a national scientific-technical advice (STA) to clarify this matter (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.

2.2 STA Procedure – Figure 1 Line I

In Belgium, the FAMHP offers the applicant the possibility of requesting a formal STA prior to other mandatory procedures. 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 centres across the Regions in Belgium
- 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 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)

2.3 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 micro-organisms and genetically modified organisms (plants and animals).

The regional decrees on CU (Flanders, Brussels-Capital and Wallonia)[1] describe various notification and authorization 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

[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.

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: the SBB) may be requested.

a) 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 authorization procedures.

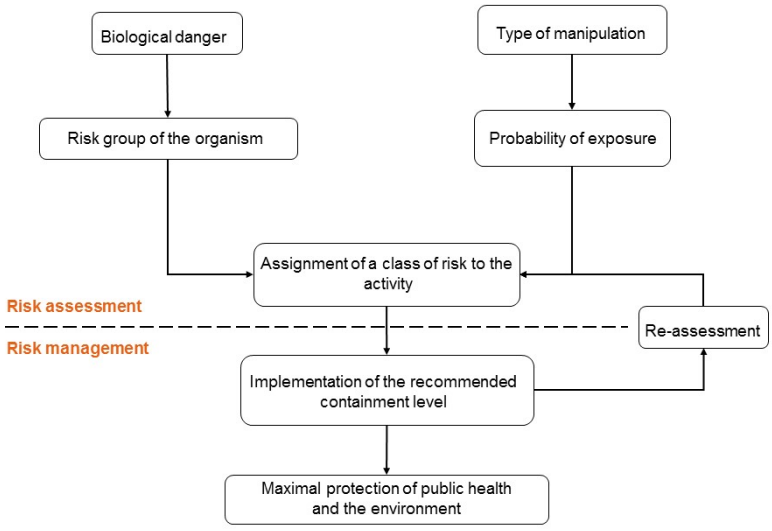

Figure 3: Application of risk assessment and adoption of risk management measures in CU of GMOs or pathogens

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 represent the most frequent risk classes encountered in Belgium for a CT involving a GMO, for the time being, at least.

Note that the containment levels of the room where the IMP containing or consisting ofGMOs 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:

- *https://www.biosafety.be/content/assessment-biological-risks*
- *https://www.biosafety.be/content/contained-use-gmos-andor-pathogens-tools-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):

- *https://www.biosecurite.be/content/utilisation-confinee-criteres-de-confinements-et-autres-mesures-de-protection*
- *https://www.bioveiligheid.be/content/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 https://www.biosafety.be/content/contained-use-criteria-containment-levels-and-other-protective-measures.

b) 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 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 authorization to proceed with the CT in a specific location (mostly clinical centres).

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 authorization from the competent authorities will be written in Dutch or French, 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 authorization for a new CT with a GMO.

c) 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 authorization to perform a CT with a GMO may also be required.

i. Brussels-Capital Region

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

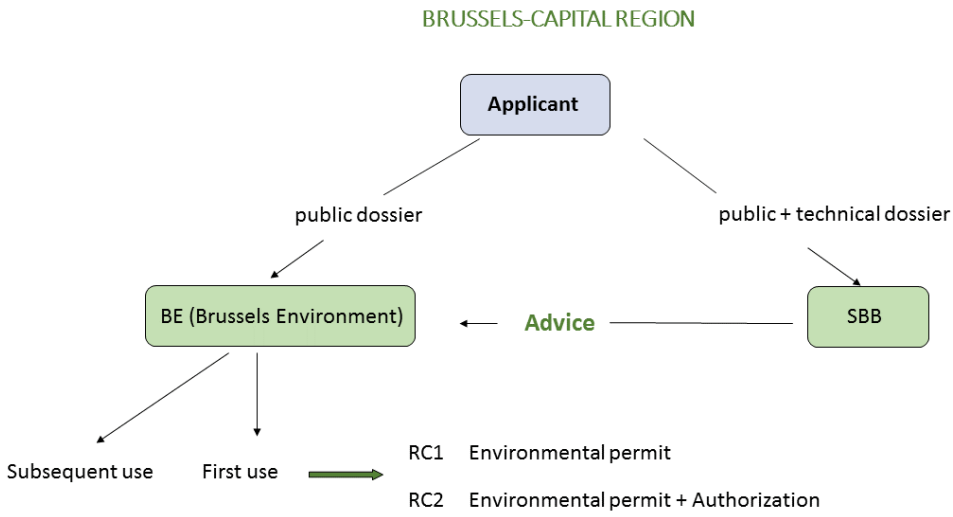

Figure 4: CU notification procedure in Brussels for RC1 and RC2 activities.

In the Brussels-Capital Region, 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 84 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 84), and an authorization for an RC2 CU. An RC1 CU does not require an authorization.

[2] Ordinance of 5.6.1997 modified by the Ordinance of 26.3.2009, Belgian Official Journal of 16 April 2009. https://environnement.brussels/thematiques/sante-securite/laboratoires/biosecurite?view_pro=1&view_school=1 https://leefmilieu.brussels/themas/gezondheid-veiligheid/laboratoria/bioveiligheid?view_pro=1&view_school=1

- If the facility already holds an authorization for RC2 CU (and consequently 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, or
  - a continuation of an activity for which the authorization term has elapsed.

The environmental permit and the authorization 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 the Brussels-Capital Region 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;
- 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 at *https://www.biosafety.be/content/contained-use-gmos-andor-pathogens-notification-procedure-brussels-capital-region*.

ii. Flemish Region

The competent authorities of the Flemish Region are:
- ***LNE-Department Omgeving*** for authorizations;
- ***Municipalities*** and ***Provincial Council*** for environmental permits;

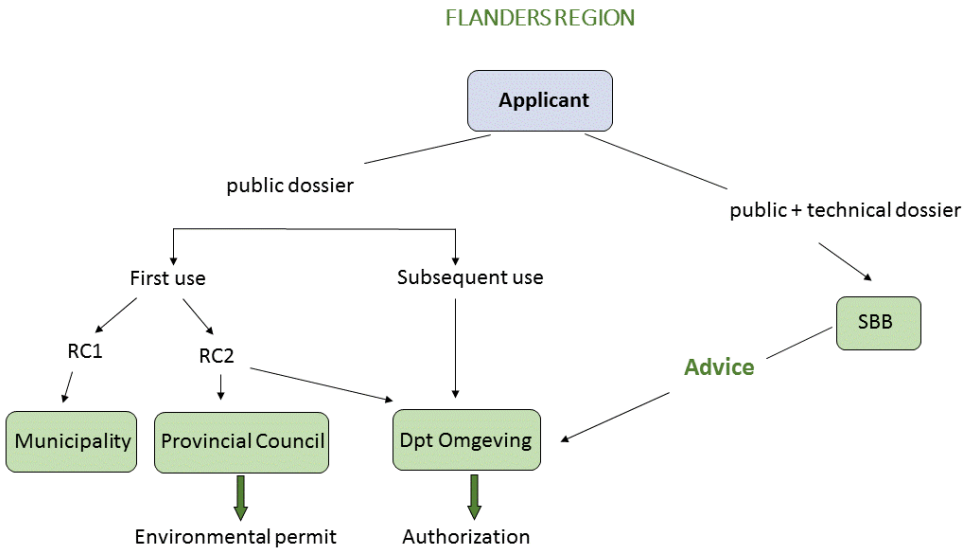

Figure 5: CU notification procedure in Flanders for RC1 and RC2 activities

In Flanders, CU activities of GMOs (or pathogens), with the exception of RC1 CU, can only take place in facilities that hold an **environmental permit** covering the appropriate section. Section 51 covers CU activities in general and sub-sections cover specific CU RCs and specific type of organisms (GMOs or pathogens). The environmental permit is usually issued for 20 years or an indefinite duration. Facilities hosting these activities are additionally subject to a written **authorization** (with the exception of RCI CU). The environmental permit and the authorization for the CU are issued by different authorities.

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

- when an 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 authorization;
- 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.
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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.

All information regarding the contained use procedures in the Flemish Region and forms to put together the biosafety dossier can be found at https://www.biosafety.be/content/contained-use-gmos-andor-pathogens-notification-procedure-flemish-region.

iii. Walloon Region

The competent authorities in the Walloon Region are the ***Municipalities***:
DGRNE-DPA (General Directorate Natural Resources – Environment, Department Permits and Authorizations) acts as technical civil servant.

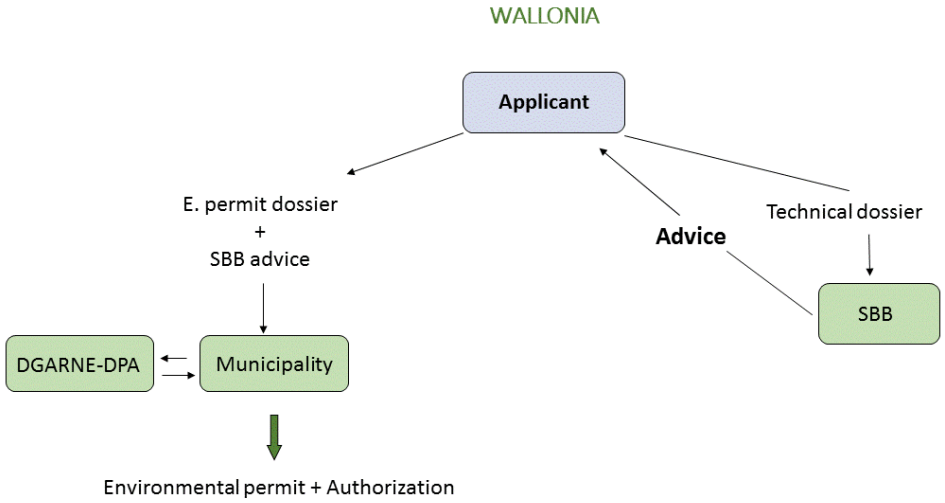

Figure 6: CU notification procedure in Wallonia for RC1 and RC2 activities

CU activities of GMOs and pathogens are activities mentioned in the list of classified activities that are subject to an environmental permit[3] or to declaration. In the Walloon Region, 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 the Walloon Region, 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. 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[4]. This environmental permit dossier is sent to the Municipality which is responsible for transmitting this request to the administration (DGRNE-DPA, which acts as technical civil servant). The DGRNE-DPA issues its decision within 90 to 120 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 *https://www.biosafety.be/content/contained-use-gmos-andor-pathogens-notification-procedure-wallonia* and *http://www.wallonie.be/fr/demarches/20520-demander-un-permis-d-environnement-ou-un-permis-unique-pour-un-etablissement-de-classes-1-et-2*.

[3] decree of 4/7/2002 defining the list of projects subject to incidence studies and facilities and classified activities - section 73
[4] 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

d) Overview Of The Contained Use Requirements for the Brussels-Capital Region, the Flemish Region and the Walloon Region

Table 1: Requirements For "Contained Use – First Use" In Belgium According To Risk Classification.

	Biosafety dossier	SBB advice*	Notification to municipality	Authorization from Competent Authority*	Environmental permit*	Start CT
Risk class 1						
Brussels-Capital Region	YES Public to SBB and BE Technical to SBB	YES Sent within 30 days to BE	NO	NO	YES (section 84) Usually issued for 15 years	1 day after submission of the biosafety dossier with valid environmental permit
Flemish Region	YES Public to SBB, municipality and DO Technical to SBB	YES Sent within 30 days to DO	YES	NO	NO	1 day after submission of the dossier
Walloon Region	YES Technical to SBB	YES Sent within 30 days to applicant	YES Declaration to municipality	YES, from municipality	NO	15 days after submission of the declaration
Risk class 2						
Brussels-Capital Region	YES Public to SBB and BE Technical to SBB	YES Sent within 30 days to BE	NO	YES, from BE	YES (section 84) Usually issued for 15 years	Can start as soon as the written authorization is obtained or 45 days after submission of the biosafety dossier to BE**
Flemish Region	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 authorization is obtained with valid environmental permit (sub-section)
Walloon Region	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 120 days)

* possible 'stop the clock' of the procedure that may stretch the timing

** if no written authorization is received.

DO: Department Omgeving, BE: Brussels Environment, SBB: Service Biosafety and Biotechnology (Biosafety and Biotechnology Unit)

Table 2: Requirements For "Contained Use – Subsequent Use" In Belgium According To Risk Classification.

	Biosafety dossier	SBB advice	Notification to municipality	Authorization from Competent authority	Start CT: on condition that the containment measures are applied
Risk class 1					
Brussels-Capital Region	Technical to SBB*	YES Sent within 30 days to BE	NO	NO	1 day after submission of the biosafety dossier
Flemish Region	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 Region	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**
Flemish Region	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 authorization and that the containment measures proposed in that first authorization are applied.

2.4 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 of a biosafety dossier according to the deliberate release procedure (figure 1-line III), in addition to the submission of a CTA dossier to the Ethics Committee (figure 1- line IV) and the FAMHP (figure1-line V).

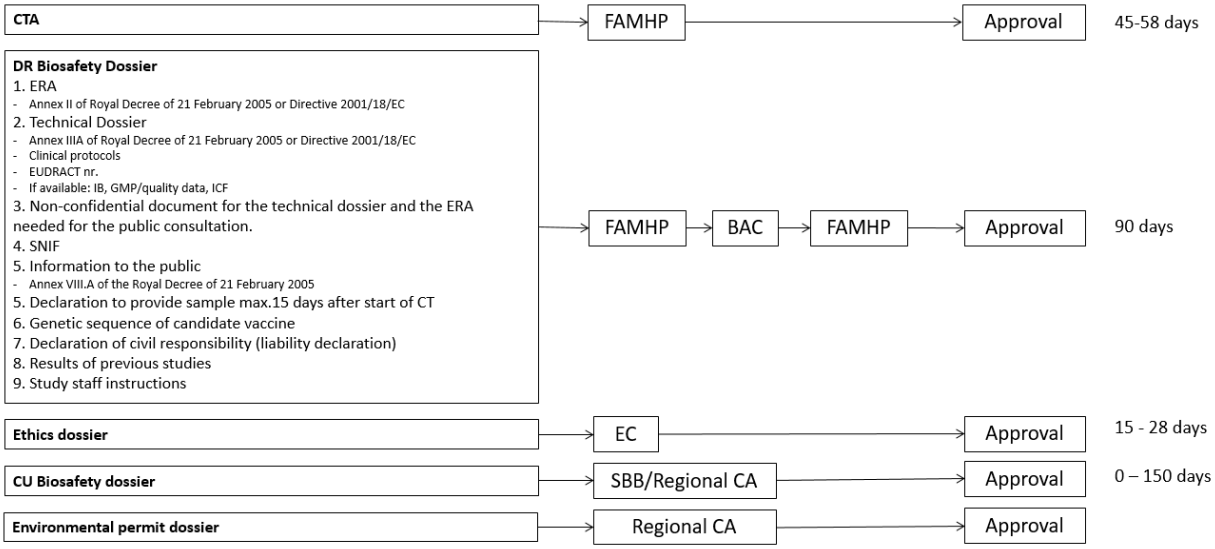

Figure 7: Overview of deliberate release procedure

2.4.1 Notification Procedure

The biosafety dossier for the 'deliberate release' procedure is submitted to the FAMHP in addition to the CTA. 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.

2.4.2. 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 paragraph2 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)** (Art 13 paragraph 2 d)
  The SNIF must be completed in English. This form is forwarded to the European Commission and to the other Member States for potential comments and is published on the website of the Joint Research Center of the European Commission. The SNIF should, for example, refer to all applications/authorizations for deliberate release in Europe.
- **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 Dutch, French, 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** (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.org). 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.

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 EUDRACT number, the investigator's brochure, the GMP/quality data, patient information (patient information 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:

- English: https://www.biosafety.be/content/notification-procedures-clinical-trials-gmos-human-or-veterinary-use
- French: https://www.biosecurite.be/content/procedures-de-notification-essais-cliniques-avec-des-ogm-pour-usage-humain-ou-veterinaire
- Dutch: https://www.bioveiligheid.be/content/kennisgevingsprocedures-klinische-proeven-met-ggos-voor-menselijk-veterinair-gebruik

2.4.3. Timelines

The estimated timeline for a DR authorization 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, which

transmits its advice to the FAMHP and for which the Federal Ministers provide their final authorisation. The Biosafety Advisory Council 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. For the CTA dossier however, only 1 clock-stop is possible, and the applicant needs to provide an answer within 30 days.

2.5 EC Procedure – Figure 1 Line IV

The Law of 7 May 2004 concerning experiments on the human person is applicable for the review of clinical trials by the Ethics Committees in Belgium.

2.5.1 Submission Procedure

The CTA dossier is submitted by the investigator to the EC of each concerned site in Belgium. A circular letter related to the choice of the leading Ethics Committee by the sponsor for multi-centre clinical trials is available on the FAMHP website:

https://www.afmps.be/sites/default/files/content/circulaire_639.pdf

2.5.2 Documentation

The content of the submission dossier for the Ethics Committee is provided in the following guidance available in Eudralex volume 10 (chapter 1):

https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-10/12_ec_guideline_20060216_en.pdf

2.5.3 Timelines

As stated in Article 13 of the Law of 7 May 2004 concerning experiments on the human person, the legal timelines for the review of CTA dossiers are as follows (from T0):

- 15 calendar days in the case of mono-centric phase I trials
- 28 calendar days for multi-centric phase I trials and for phase II, III and IV trials

These timelines are extended by 30 calendar days in the case of trials with investigational medicinal products containing genetically modified organisms.

2.6 CTA Procedure – Figure 1 Line V

In accordance with the Law of 7 May 2004 concerning experiments on the human person and before a clinical trial can start in Belgium, a valid submission of the CTA dossier has to be made to the competent authority. The competent authority in Belgium is the FAMHP. The trial can start if no major objections are received within the predetermined timelines (tacit approval principle). Should any major objections be raised, the applicant must provide satisfactory answers within 30 days. In the case of a clinical trial with a GMO, the tacit approval principle does not apply and the applicant has to wait for the formal approval of the FAMHP.

2.6.1 Submission Procedure

Guidance for the submission of a CTA dossier to the competent authority is provided in the national guidance for the submission of clinical trial applications available on the FAMHP website:

https://www.FAMHP.be/en/human_use/medicines/medicines/research_development/clinical_trials

2.6.2 Documentation

The content of the CTA dossier for the competent authority is available in the following guidance available in Eudralex volume 10 (chapter 1):

https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-10/2010_c82_01/2010_c82_01_en.pdf

2.6.3 Timelines

As stated in Article 13 of the Law of 7 May 2004 concerning experiments on the human person, the legal timelines for the review of CTA dossiers are as follows (from T0):

- 15 calendar days in the case of mono-centric phase I trials
- 28 calendar days for multi-centric phase I trials and for phase II, III and IV trials

These timelines are extended by 30 calendar days in the case of trials with investigational medicinal products containing genetically modified organisms.

During the CTA process, only 1 clock-stop is possible, and the sponsor needs to provide an answer within 30 days.

2.7 Contact Information

Federal Agency for Medicines and Health Products (FAMHP)- – Division Research and Development (Clinical trials)
Contact: ct.rd@fagg-afmps.be
www.FAMHP.be

Service Biosafety and Biotechnology Unit (SBB)
Contact: contained.use@sciensano.be
http://www.biosafety.be

Biosafety Advisory Council (BAC)
Contact: bac@sciensano.be
www.bio-council.be