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Overview of procedures for submitting an application for clinical trials with GMO-medicinal products for human and veterinary use in Belgium

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Overview of procedures for submitting an application for clinical trials with GMO-medicinal products for human and veterinary use in Belgium

Overall, a clinical trial can only be conducted in Belgium if it satisfies several regulatory/advisory requirements. More details about the Belgian law and its implementation decisions as well as about procedures and application content are available on the web site of the Federal Agency for Medicines and Health Products (FAMHP), chapter clinical trials for human medicines (in English - in Dutch - in French) and for veterinary medicines (in English, in Dutch or in French).

When the Investigational Medicinal Product (IMP) used in a clinical trial is based on a **'genetically modified organism' (GMO)**[1] the clinical trial can only be conducted in Belgium if it also complies with the legislative provisions on biosafety regarding deliberate release (DR) of GMOs in the environment and/or contained use (CU) [2] of GMOs[3].

This means that **clinical trials** using GMOs or involving medicinal products containing GMOs have to comply with the Belgian regional regulations on *contained use of GMOs and/or pathogenic organisms* (Flemish Region - Brussels-Capital Region - Walloon Region) which implement Directive 2009/41/EC (in English - in Dutch - in French) as soon as some activities related to the trial, (e.g. preparation and administration of the study medication, conservation of study drug,…) are performed in a 'contained use' facility (e.g. laboratories, hospital rooms or veterinary facilities). The contained use authorization is given by the Regional Competent Authorities, based on a scientific advice given by the SBB[4]. In case the clinical trial (CT) cannot be conducted in authorized 'contained use' facilities OR the CT does not comply with the regional regulations on contained use of GMOs, it has to comply with Directive 2001/18/EC 'on the deliberate release of GMOs into the environment' (in English) (transposed in the Belgian law by the **Royal Decree of 21 February 2005** (in Dutch and French) in which case the authorization is given by the Federal Competent Authority, based on a scientific advice given by the Biosafety Advisory Council[5].

[1] means 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)

[2] 'contained use' means any activity in which micro-organisms are genetically modified or in which such GMMs 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 (Directive 2009/41/EC). e.g. laboratories, veterinary facilities or hospital rooms.

[3] Baldo et al. (2013): General considerations on the biosafety of virus-derived vectors used in gene therapy and vaccination (PMID: 24195604)

[4] SBB or Biosafety and Biotechnology Unit is a multidisciplinary group of scientists (mostly postgraduates) performing scientific expertise in the field of biosafety. As part of a Federal scientific Institute, the SBB holds an independent position with regard to expertise in Biosafety, accessible to any public or private organization. The SBB is also technical expert for the competent authorities. As centre of expertise in Biosafety, the SBB advises the Federal and Regional competent authorities about biosafety-related contained use matters

[5] The Biosafety Advisory Council is one of the two pillars (the other being the Biosafety and Biotechnology Unit - SBB) of the common scientific evaluation system that has been set up in Belgium to advise the competent authorities about the safety of activities involving genetically modified organisms (GMOs) and/or pathogens related to biodiversity. The Council consists of representatives of the Regional and Federal authorities. It is assisted by experts in its scientific work. The secretariat of the Council is ensured by the SBB.

In general, when there is no possible release of the GMO in the environment (GM medication taken at home; probability of shedding, spreading,…) that may confer a risk to human health or the environment or if proper management procedures and/or working practices are taken to prevent any possible release conferring a risk, then a 'contained use' procedure is sufficient. The opposite, when there is a probability of possible release that may confer a risk to human health or the environment which cannot be avoided by proper management procedures or working practices, a notification under 'deliberate release' will additionally be required.

Determination of the GMO status of the IMP('s) and the procedure (DR or CU)

The GMO status and the procedure (DR or CU) should be defined at the time of the submission of the clinical trial application (CTA). However, if the GMO status and/or the procedure to follow are still unclear, the applicant is strongly recommended to request a national scientific-technical advice (STA) at the FAMHP.

To determine the GMO status and/or the procedure a briefing document including some preliminary data that address procedural questions (see fact sheet below), should be provided to the FAMHP as part of the STA procedure. In close collaboration with the SBB, the applicability of one or both Belgian 'GMO' procedures (DR or CU) will be determined.

In general, the STA will be provided to the applicant in writing following the type I STA procedure within a maximum delay of 30 days (i.e. after validation of the STA request). Nevertheless, the FAMHP holds the right to classify the STA request as a type II STA if it concerns a complex matter that requires in depth expertise of multiple experts and, hence, a heavy workload. In such case, the Type II STA will be provided within a maximum delay of 70 days. In general, STA requests are processed as fast as practically possible.

All practical information and guidance on how to submit a request for national STA at the FAMHP can be found on the following website (human medicines: in English - in Dutch - in French; veterinary medicines: In English - in Dutch - in French).

Note:

A 'contained use' authorization is given for a defined 'contained use' activity on a defined site (or facility) for several years . An activity may cover a particular protocol or a whole program of clinical trials, (e.g. phase II and III protocols using one type of vector with one transgene of interest in a determined therapeutic area, etc.) which can be considered equal with regard to biosafety aspects.

A 'deliberate release' authorization may cover a particular gene therapy clinical trial conducted in different sites or a whole program of clinical trials.

Fact sheet GMO procedures

This fact sheet provides key procedural questions to determine the GMO status of the IMP and GMO procedure(s) to follow [§].

(1) *Is the investigational medicinal product (IMP)* 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)

Yes ↓

↓ **No**

Out of scope of GMO legislation

(2) Is the clinical trial planned in authorized 'contained use' facilities (e.g. laboratories, hospital rooms or veterinary facilities) ?

Yes ↓

↓ **No**

A "deliberate release" authorization is needed in the frame of the Royal Decree of 21 February 2005 governing the deliberate release of GMOs into the environment (transposing Directive 2001/18/EC).

Links: *GMO medicinal products ; application content 'deliberate release'*

(3) Is there any possible release of the GMO in the environment (e.g. GM medication taken at home; probability of shedding, spreading,…) that may confer a risk to human health or the environment which cannot be avoided by proper CU management procedures or working practices?[£]

Yes →

No* ↓

A "contained use" authorization is (also) needed in the frame of the Belgian regional regulations on contained use of GMOs and/or pathogenic organisms

Links: *website: contained use of GMOs and pathogens ;*
'contained use' procedure (Flemish Region - Brussels-Capital Region – Walloon Region)

[§] Formal advice on the GMO status and the acceptability and conditions under which a clinical trial can be considered eligible or not for the 'contained use only' procedure can be given by the competent authority at the federal level (FAMHP) in close collaboration with the SBB as a scientific-technical advice (STA) based on preliminary information provided by the applicant.

[£] To address this question the applicant is invited to consult guidelines of GMO environmental risk assessment ; http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003964.pdf (HUMAN); http://ec.europa.eu/health/files/eudralex/vol-6/ne_en_doc/vol6c_env_risk_gmo_200603_en.pdf (VETERINARY)

* Even if a "contained use only" procedure is allowed, the notifier can always decide to go for an additional 'deliberate release' notification.

Overview of procedures (A-D) for submitting an application for clinical trials (CTA) with GMO-medicinal products for human and veterinary use

(A) For an optimal progress of your application, it is strongly recommended to submit prior to the formal CTA submission some preliminary data that address key procedural questions (see fact sheet) as part of a scientific-technical advice (STA) request to determine in advance the GMO status and/or procedure if this is unclear.

The preliminary data is submitted by the sponsor to the competent authority at the federal level (FAMHP). The FAMHP will forward a copy of the data to a team of technical experts (of the SBB) for reviewing. SBB transmits a GMO procedural determination report to the FAMHP for final decision. The final decision on the GMO procedure to follow will be formalized, generally, in a written STA (type I) and communicated to the applicant by the FAMPH.

In case the GMO procedure to follow is clear for the applicant or has been communicated by the FAMHP as part of a STA, the formal CTA can progress by submitting (B, C and D) [§]:

(B) An application by the sponsor to the FAMHP

(C) An application by the principal investigator to the Ethics Committee

(D) "GMO" application(s) according the STA on GMO procedures to follow*:

(D1) If a "contained use" authorization is needed in the frame of the Belgian regional regulations on contained use of GMOs and/or pathogenic organisms

A notification of the clinical trial by principal investigator / exploitant of each participating "contained use" facility according to the "contained use" procedures is requested. This dossier will be reviewed by technical experts of the SBB which transmits their advice (via the notifier) to the competent authority at the regional level for final decision.

It is recommended to complete the biosafety dossier with the clinical trial protocol to provide extra information for proper risk assessment.

(D2) If a "deliberate release" authorization is needed in the frame of the Royal Decree of 21 February 2005 governing the deliberate release of GMOs into the environment

A notification of the clinical trial by the sponsor to the competent authority at the federal level (FAMHP) according to the "deliberate release" (DR) procedures is requested (usually submitted together with the CTA part of the dossier). The FAMHP will forward a copy of the dossier to the Belgian Biosafety Advisory Council (BAC) for advice; this dossier will be reviewed by the BAC which transmits its advice to the competent authority at the federal and regional level for final decision. The clinical trial may not begin in Belgium before the sponsor has received the positive advice of the ethics committee and the formal approval from the FAMHP (CTA approval and "deliberate release" authorization). The "tacit approval" principle is not applicable for clinical trials with GMO products.

[§] Any previous STA issued by the FAMHP in relation to the CTA should be included in the formal CTA submission as supportive documentation.

More details about the Belgian law and its implementation decisions as well as about procedures and application content are available on the websites of the Federal Agency for Medicines and Health Products (FAMHP) and/or the Belgian Biosafety Server of the Biosafety and Biotechnology Unit of the Scientific Institute of Public Health:

Useful links

1. 'FAMHP': Clinical trials for Human medicines (English, Dutch or French)
   Veterinary medicines (English, Dutch or French)
2. 'Contained use': contained use of GMOs and pathogens ;
   'Contained use' procedure (Flemish Region - Brussels-Capital Region – Walloon Region)

* Even if there is only a "contained use " procedure allowed, the applicant can decide to go for an additional 'deliberate release' notification
Note: "contained use" and "deliberated release" procedures can run in parallel but "deliberate release" authorization is mandatory before authorization under contained use.