Medicinal products containing genetically modified organisms - Clinical Trials in the Czech Republic

Introduction

According to the Czech legislation on medicinal products, applicants for authorization to conduct a clinical trial/study involving products containing genetically modified organisms (GMOs) are required to obtain an authorization for the use of GMOs as specified by the Act No. 78/2004, on the Use of Genetically Modified Organisms and Genetic Products. Such authorization, issued by the Ministry of the Environment (MoE), should either be attached to the documentation of the application to the State Institute for Drug Control (SUKL) for a clinical trial authorization, or submitted subsequently, however, no later than three days prior to the final outcome of the SUKL assessment process. Should the applicant fail to submit the authorization for the GMOs use by the end of clinical trial assessment process, the application for clinical trial authorization will be refused.

- SUKL website: http://www.sukl.cz/

Legislative Framework on GMOs

The Czech Act No. 78/2004 Coll., on the Use of Genetically Modified Organisms and Genetic Products, as amended, covers the contained use of all genetically modified organisms (GMOs), deliberate release of GMOs into the environment and placing on the market of GMOs as such or in products, including the export and import. The Act transposes EU Directives 2001/18/EC and 2009/41/EC and complies with the Cartagena Protocol on Biosafety. Medicinal products containing GMOs are exempted from the authorization procedure for placing GMOs on the market (authorization procedure for these products falls under Regulation (EC) No 726/2004 and is centralized at EU level).

Formats of notifications, the risk assessment procedure and other specific requirements are laid down by the implementing Decree No. 209/2004, on Detailed Conditions for the Use of Genetically Modified Organisms and Genetic Products, as amended.

- Website of the Ministry of the Environment on GMOs: http://www.mzp.cz/cz/geneticky_modifikovane_organismy

- Czech Biosafety Clearing House - information in English on Biosafety legislation, national contacts and GMO authorisations in the Czech Republic: http://www.mzp.cz/biosafety

State Administration on GMOs

The Competent Authority receiving notifications and regulating the use of GMOs (Competent Authority under EU Directives 2001/18/EC and 2009/41/EC) in the Czech Republic is the Ministry of the Environment (MoE). An expert advisory body to the Ministry, the Czech Commission for the Use of GMOs and Genetic Products (CzC GMO), deals with the environmental risk assessment of GMOs. The Competent Authority on state supervision of

the use of GMOs is the Czech Environmental Inspectorate (CEI) that co-operates with other state supervision bodies as well.

Authorisation for the use of GMOs

General requirements set by the Czech Act on GMOs:

- Only a legal person or a natural person authorized to operate a business can be authorized for the use of GMOs. That means the **notifier has to be a person established in the European Union.**
- Prior to submitting a notification, the notifier has to appoint a **biosafety officer** – a person responsible for risk assessment of the use of GMO and a contact person for the Czech authorities. The biosafety officer has to meet the requirements set by the Act on GMOs as regards his/her education and experience with GMOs and has to be available in case consultations are needed. Whether he/she is an employee of the notifier does not matter for the Competent Authority (the Ministry of the Environment).
- A separate notification has to be submitted by each institution that will participate in the clinical trial/study. Each subject (e.g. a hospital) that will handle the GMOs has to be authorized - including the company importing and distributing the medical product. However, one person (e.g. the sponsor) can be empowered to submit all the notifications and one biosafety officer can deal with the whole project. The notifiers can refer to data included in any other notification of the same study (e. g. a hospital can refer to the risk assessment data provided by the producer of the medicine in its notification).
- The notifier can discuss his notification prior to its submission with the staff of MoE (see contacts below).
- The notification is submitted by the notifier (or the empowered person) to MoE. The notification has to be signed by an official representative of the notifier. The risk assessment has to be verified (signed) by the biosafety officer. If the notification is submitted in a printed format it has to be provided to MoE also electronically (eg. on CD, by email). The dossier has to be in the Czech language, except literature annexes.

Authorization Procedure

The administrative procedure for authorization of the use of GMOs is more complicated, longer in case of deliberate release (under EU Directive 2001/18/EC, Part B) than in case of contained use (under EU Directive 41/2009/EC).

As the first step, the company planning the study must decide which path to take, based on the way and conditions of application of the product to humans, metabolism of the product (shedding), nature of the GMO, etc. The reasons for the chosen procedure have to be described in detail in the notification dossier.

A. Contained use of GMO

The risk assessment of the contained use results in the assignment or the activity to one of the **four risk classes** specified in Annex 3 to the Act on GMOs (= **biosafety levels**). The

contained area must comply with the requirements on containment and protective measures laid down for the pertinent or higher risk class of the contained use in Decree 209/2004.

Contained use - Risk classes 1 and 2

For the contained use in classes 1 and 2, the notification does not lead to an administrative procedure; no written decision from MoE is needed to start the activity.

Contained use classified as **class 1 may commence immediately** after the submission of the notification.

Contained use classified as **class 2 may commence 45 days** after the submission of the notification, provided MoE has not raised any objections during this period.

MoE checks the completeness of the notification and acknowledges its receipt within 5 days after the submission. If the notification meets all the requirements pursuant to the Act on GMOs, MoE circulates it to the expert body, the Czech Commission for the Use of GMOs and genetic products (CzC GMO), and to the Ministry of Health and Ministry of Agriculture, if appropriate. The Ministries and CzC GMO can make comments and express their opinion on the notification.

Considering all comments and opinions, MoE may ask the notifier for additional information or require changes in the intended activity or in the assignment of the risk category within 30 days after the submission of the notification.

No administrative fee is required.

MoE makes available to the public only the basic data on the authorized contained use: name and address of the authorized user, GMO(s) used, class of the contained use, date of the authorization and, in case of the second class (BSL 2), the information on emergency response plan are recorded on the List of GMO Users at the MoE website (see above).

Risk classes 3 and 4

Contained use in the third or fourth classes may only be commenced on the basis of written consent issued by MoE, and only within the scope and under conditions laid down in this consent.

Having received a notification, MoE checks its completeness. If the dossier meets all the requirements pursuant to the Act on GMOs, MoE circulates it to the expert body, the Czech Commission for the Use of GMOs and genetic products (CzC GMO), to the Ministry of Health and Ministry of Agriculture and to the Regional Authority of the region where the contained use is planned.

The Ministries and the regional authority as well as CzC GMO provide to MoE their opinions / comments on the notification within 30 days of receiving the dossier. Consequently, MoE may ask the notifier for any additional information. In case the notifier fails to provide the requested information within the set time-period (30 days), MoE terminates the administrative procedure. The additional information is forwarded to the Ministries, Region and to CzC GMO.

MoE shall make the final decision on the notification within 90 days of receiving the dossier.

For the purpose of calculating this time-period, any period of time for completing the notification by the notifier upon request for additional information is not taken into account - the clock stops. It has to be noted that the notification is assessed by different experts from various points. That leads to wide spectrum of comments usually requiring additional information to be provided by the notifier. Therefore the time for issuing the decision is longer than 90 days.

The notifier has to pay an administrative fee for the authorisation CZK 2 000 (approx. 75 EUR). MoE calls on the notifier to pay the fee shortly before issuing the consent. No fee is paid when the notification is rejected or withdrawn.

The contained use is not consulted with the public during the authorisation procedure. The text of the final decision is published on the MoE website and in the municipality of the release after the decision has entered into force.

B. Deliberate release into the environment

Deliberate release of GMO may only be commenced on the basis of written consent issued by MoE, and only within the scope and under conditions laid down in this consent.

Having received the notification, MoE checks its completeness. If the dossier meets all the requirements pursuant to the Act on GMOs, MoE circulates it to the expert body, the Czech Commission for the Use of GMOs and genetic products (CzC GMO), to the Ministry of Agriculture, Ministry of Health and to the Regional Authority of the region where the deliberate release is planned to be carried out. At the same time, MoE makes a summary of the notification available to the public on its website and ensures its publication by the relevant municipality and regional authorities, according to the intended release location. The summary of the notification according to Council Decision 2002/813/EC (SNIF) is also made available to the European Commission and other EU Member States through the JRC WebSNIF database http://gmoinfo.jrc.ec.europa.eu/. Therefore MoE asks the notifier to provide SNIF in English.

The Ministries and the regional authority as well as CzC GMO provide to MoE their opinions / comments on the notification within 30 days of receiving the dossier. Consequently, MoE may ask the notifier for additional information. In case the notifier fails to provide the requested information within the set time-period (30 days), MoE terminates the administrative procedure. The additional information is forwarded to the Ministries, Region and to CzC GMO.

The summary of the notification which is provided to the public in the Czech language corresponds to the information required in SNIF. Anybody can send his/her opinion to MoE or make comments within 30 days of publication of the summary of the notification. If MoE receives a negative opinion / comments from the public, by which any doubt is cast on the results of the environmental risk assessment or an objection to insufficient protection of health or the environment is made, MoE is obliged to arrange a public hearing prior to making a decision on the authorisation.

MoE should make the final decision on the notification within 90 days of receiving the dossier. For the purpose of calculating this time-period, any period of time for completing the notification by the notifier upon request for additional information and/or the period during

which the public hearing is organised are not taken into account - the clock stops. It has to be noted that the notification is assessed by different experts from various points. That leads to wide spectrum of comments usually requiring additional information to be provided by the notifier. Consequently the time for issuing the decision is longer than 90 days. The notifier has to take this possible delay into account when planning the project.

In its decision, MoE is obliged to consider the opinions of the concerned Ministries, regional authorities, CzC GMO and other Member States, as well as the results from the public consultation, if carried out. MoE may lay down special conditions for the release of the GMOs in the decision.

The notifier has to pay **an administrative fee** for the authorisation CZK 20 000 (approx. 750 EUR). MoE calls on the notifier to pay the fee shortly before issuing the consent. No fee is paid when the notification is rejected or withdrawn.

The whole text of the final decision is made available to the public after the decision has entered into force, on the MoE website and in the municipality of the release. The information about the consent is provided to the WebSNIF database as well.

Risk Assessment

Requirements and a procedure of the environmental risk assessment are set in the implementation Decree No. 209/2004, on Detailed Conditions for the Use of Genetically Modified Organisms and Genetic Products, as amended. The risk assessment, carried out or at least verified (signed) by the biosafety officer, must be submitted to MoE as a part of the notification dossier. It is reviewed by the CzC GMO within the authorisation process.

Confidentiality

The notifier may indicate certain data in the notification as confidential business information, provided he is able to justify that disclosure of such information might be detrimental to his competitive position.
Following information cannot be indicated as confidential business information:

- General description of the genetically modified organism;
- Identity of the notifier;
- Location of the premises;
- Risk assessment;
- Information on the emergency response plan if the plan is required.

The information indicated as confidential business information is only accessible to:

- State Authorities referred in the Act on GMOs;
- CzC GMO;
- Laboratories carrying out the detection of GMOs for MoE and CEI;
- Relevant authorities of other EU Member States;
- European Commission.

Emergency response plans

An emergency response plan is required for contained use in the classes 2 and higher (**not** in the class 1) and for deliberate release of GMO. It is a document describing activities and

measures applied in the event of an accident. The detailed requirements for the emergency response plan are laid down in the implementing Decree No. 209/2004.

The notifier is obliged to submit the emergency response plan prior to commencement of the use of GMOs to MoE as a part of the notification and then separately to the municipalities where the contained use is to take place, to the local Fire Rescue Brigade, to the regional authority and upon request also to any persons that may be directly affected by an accident. The authorised user updates and submits the plan every 5 years or in a case any new information on potential risks emerges.

MoE makes information on the emergency response plans available to the public. The scope of such information is laid down by the implementing Decree.

Other Requirements

According to the Act 78/2004 on GMOs, **the notifier is obliged to:**

- In case of contained use, check the **measures for containment** regularly.
- Send to MoE a short **report** on the use of GMOs every year. A final report is required after the end of the trial / study. The formats for the reports (in Czech) are available on the GMO website of the MoE (see above).
- Ensure proper **labelling and packaging of the product during its transport and application.** The text "Genetically modified organism" and/or in Czech "Geneticky modifikovaný organismus" has to appear on the label and in the accompanying documents during the transport.
- Keep the documentation on the use of GMO for 5 years after the end of the contained use or for 10 years in case of deliberate release into the environment.
- Meet any further requirements laid down in the authorisation decision (for classes 3 and 4 of contained use or for deliberate release into the environment).

Import and Export

"Import and export" means transboundary movements **into and out of EU**. Transboundary movements within the EU (e.g. from France to the Czech Republic) are not considered as export or import.

Only genetically modified organisms or genetic products **authorised for placing on the market** in the EU (registered medicinal products) may be imported or exported to and from the Czech Republic without any special approval.

A **person authorised for contained use or for deliberate release of GMOs** may import or export only the GMOs covered by the authorisation, provided that they are exclusively intended for the authorised contained use or deliberate release. Means of transport, country of origin / export etc. have to be described in the pertinent notification.

The authorised person that **intends to import or export** GMOs for contained use or deliberate release is obliged to inform MoE on the species and number / volume of GMOs that will be imported or exported and on the supposed place of entry to or exit from the territory of the Czech Republic, at the latest **5 days prior to** the import or export. This

information can be sent by email (see contacts below).

The notifier is obliged to ensure proper **labelling**: Packaging of the exported / imported GMO or genetic product must have a visible label clearly stating “Genetically modified organism”, in Czech “Geneticky modifikovaný organismus”. This text has to appear also in the accompanying documents during the transport. Any further requirements for the labelling as laid down in the authorisation decision must be observed.

Detailed requirements for import and export documentation are set in § 25 of the Act 78/2004.

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