Adviesraad voor Bioveiligheid
Conseil consultatif de Biosécurité

Advice of the Belgian Biosafety Advisory Council on the notification B/BE/18/BVW1 of the company Transgene for deliberate release in the environment of genetically modified organisms other than higher plants for research and development

Final version – 03/07/2018
Ref. SC/1510/BAC/2018_0472

Context

The notification B/BE/18/BVW1 has been submitted by Transgene to the Belgian Competent Authority in April 2018 for a request of deliberate release in the environment of genetically modified organisms other than higher plants for research and development according to Chapter II of the Royal Decree of 21 February 2005.

The planned activity concerns a clinical trial and the title of the notification is: **"*A Phase I/IIa study of TG6002 (VV TK-RR-FCU1) administered by intravenous (IV) infusions in combination with oral flucytosine (5-FC) in patients with advanced gastro-intestinal (GI) tumors*"**. The purpose of the clinical trial is twofold: the determination of the recommended dose for TG6002 (Part I a) (dose-escalation) in patients with advanced GI carcinomas and investigating the efficacy of multiple administrations of TG6002 in combination with flucytosine (5-FC) in patients with colon cancer and liver metastases.
TG6002 is an investigational medicinal product (IMP) developed for oncolytic antitumoral activity combined with targeted chemotherapy. It is a recombinant Vaccinia Virus (VV) with restricted replication to highly dividing cells due to the functional deletion of the thymidine kinase (TK) and ribonucleotide reductase (RR) of the viral genome and genetically modified to express the chimeric yeast FCUI gene encoding a bifunctional protein catalysing the conversion of the prodrug 5-FC into the highly cytotoxic 5-FU and 5-FUMP agents. TG6002 thus induces viral lysis of tumour cells and targeted chemotherapy through in situ conversion of 5-FC into 5-FU and 5-FUMP. TG6002 will be administered as three intravenous infusions in Phase 1 part as well as in the Phase IIa Part.

The parental strain of TG6002 is the Copenhagen strain, a VV that was used for smallpox vaccination in Denmark and the Netherlands in the 1950s. VV are lipid enveloped viruses that are sensitive to inactivation by both physical inactivation (e.g. heat) and disinfectants (lipid solvents and mild detergents). VV is considered as group 2 biological agent.

It is planned to conduct the trial in a clinical site located in Brussels. However, Wallonia and the Flemish Region are also considered as potential receiving environments.

The dossier has been officially acknowledged by the Competent Authority on 18 April 2018 and forwarded to the Biosafety Advisory Council (BAC) for advice.

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Within the framework of the evaluation procedure, the BAC, under the supervision of a coordinator and with the assistance of its Secretariat, contacted experts to evaluate the dossier. Two experts from the common list of experts drawn up by the BAC and the Service Biosafety and Biotechnology (SBB) of Sciensano answered positively to this request. The SBB also took part in the evaluation of the dossier while the Platform Biotechnology and Bioinformatics of Sciensano evaluated the analytical procedure for the detection of TG6002.
The experts and the SBB assessed whether the information provided in the notification was sufficient and accurate in order to state that the deliberate release of the genetically modified organism would not raise any problems for the environment, animal health or human health (people coming in contact with the treated patient and/or with the GMO) in the context of its intended use. See Annex I for an overview of all the comments from the experts.

The scientific evaluation has been performed considering following legislation:
- Annex II (principles for the risk assessment) and annex III (information required in notifications) of the Royal Decree of 21 February 2005.
- Commission Decision 2002/623/EC of 24 July 2002 establishing guidance notes supplementing Annex II to Directive 2001/18/EC.
The pure medical aspects concerning the efficacy of the medicinal product and its safety for the treated patient, as well as aspects related to social, economic or ethical considerations, are outside the scope of this evaluation.

On 29 May 2018, based on a list of questions prepared by the BAC, the Competent Authority requested the notifier to provide additional information about the notification. The answers from the notifier to these questions, including updated instructions for the personnel and for the patient, were received by the Competent Authority on 27 June 2018 and transmitted to the secretariat of the BAC on the same day. This complementary information was reviewed by the coordinator and the experts.

In parallel to the scientific evaluation of the notification, the Competent Authority also made the dossier available on its website for the one-month public consultation foreseen in the abovementioned Royal Decree. The Competent Authority received no reaction from the public.

Summary of the scientific evaluation

1. The characteristics of the donor, the recipient or parental organism

The donor, recipient and parental organisms were found to be adequately described in the dossier.

2. Information related to the characteristics of the GMO and the medication

Information related to the molecular characteristics of TG6002 including phenotypic and genetic stability of the transgenes were adequately described in the dossier. No particular remarks were raised concerning the information provided in the dossier.

3. The conditions of the release

Because Ibuprofen is a non-steroidal anti-inflammatory drug with potential immunomodulatory effects, the BAC raised a question on the effect of Ibuprofen on the viral replication of TG6002. In its response the notifier referred to data of shedding analysis with another modified vaccinia virus indicating transient shedding in throat swabs, rectal swabs and in urine samples. The BAC concludes an effect on viral replication and hence subsequent shedding. The BAC takes notice that the current study will investigate shedding in saliva, faeces and urine in patients with or without ibuprofen premedication.

The BAC had also several comments regarding personal protective equipment which were adequately answered by the notifier. For example, the subject will receive a hygiene kit to be used in case of appearance of skin pustules and housekeeping personnel as any other persons will need to follow the instructions as described in the patient information note.

In its list of questions addressed to the notifier, the BAC also advised the notifier to further detail the procedures described in the Investigational product instruction manual and the Information for health care personnel (and housekeeping personnel).

4. The risks for the environment or human health

Regarding the possible transfer of genetic material, it was noticed that proposed measures by the notifier were focusing on avoiding transmission to humans, without clearly addressing potential spreading to animals (e.g. pets). In regards the possibility of recombination, the notifier has put the same focus on humans as the host for potential recombinating VV whereas the possible transfer of recombinant VV from humans to animals and the potential of recombination of TG6002 with homologous sequences of viruses present in animal hosts has not been addressed. The BAC considered the latter aspect relevant to assess the potential of generating novel and uncharacterised viruses upon recombination.
Upon request of the BAC the notifier discussed these potential hazards in terms of potentially adverse effects and the likelihood that such an adverse effect would occur. The notifier hereby referred to the immunologically cross-reactive and cross-protective features of OPV infection. Moreover the experience gained with another VV virus administered in more than 350 patients shows no evidence of contamination of patients' pets. There is also an history of use of a recombinant VV, Raboral V-RG, an oral vaccine administered to wild animals to control fox rabies, with no reports of generation of new virus as a consequence of recombination. Furthermore, the notifier completed the Patient Information Note and the Informed Consent Form adding precautions in regards potential contact with animals (e.g. pets or other animals).

5. The monitoring, control, waste treatment and emergency plans proposed by the applicant

Even if the risks are low, the BAC stressed the importance of biosafety precautions to avoid unintended dissemination of the GMO. Upon advice of the BAC the notifier amended the technical sheet with further detailed worker's protection measures and measures in case of accidental spilling.

In its dossier the notifier submitted a detailed PCR protocol for the identification and detection of the GMO. Upon request of the BAC, the PCR protocol was adapted with biosafety recommendations (personal protective equipment recommendations).

Conclusion

Based on the scientific assessment of the notification made by the Belgian experts, the Biosafety Advisory Council concludes that it is unlikely that TG6002 developed for oncolytic immunotherapy, will have any adverse effects on human health or on the environment in the context of the intended clinical trial and provided that all the foreseen safety measures are followed.

Therefore, the Biosafety Advisory Council issues a **positive advice with the following conditions**:

- The notifier and the investigators must strictly apply the clinical trial protocol, and all the safety instructions as described in the dossier also taking into account the suggestions from the Biosafety Advisory Council for improvement of the personnel instructions.

- Any protocol amendment has to be previously approved by the Competent Authority.

- The notifier is responsible to verify that each study centre has qualified personnel experienced in handling infectious material and that the investigator has the required authorizations to perform the clinical trial activities inside the hospital (laboratory, pharmacy, hospital room, consultation room...) according to the Regional Decrees transposing Directive 2009/41/EC on Contained use of genetically modified micro-organisms.

- The Biosafety Advisory Council should be informed within two weeks when the first patient starts the treatment and the last patient receives the last treatment.

- At the latest six months after the last visit of the last patient included in the trial, the notifier must send to the competent authority at the attention of the Biosafety Council a report with details concerning the biosafety aspects of the project. This report will at least contain:
    - The total number of patients included in the trial and the number of patients included in Belgium;
    - A summary of all adverse events marked by the investigators as probably or definitely related to the study medication;
    - A report on the accidental releases, if any, of TG6002 .

Dr. Corinne Vander Wauven
President of the Belgian Biosafety Advisory Council

Annex I: Compilation of comments of experts in charge of evaluating the dossier B/BE/18/BVW1 (ref. SC/1510/BAC/18_0322)

Adviesraad voor Bioveiligheid
Conseil consultatif de Biosécurité

Compilation of comments of experts in charge of evaluating the dossier B/BE/18/BVW1 And comments submitted to the notifier

29 May 2018
Ref. SC/1510/BAC/18_0322

Mandate for the Group of Experts: Mandate of the Biosafety Advisory Council (BAC) of 17 April 2018.
Coordinator: Jozef Anné (KUL)
Experts: Viggo Van Tendeloo (UZA), Jean-Claude Twizere (ULg), Aline Baldo (Sciensano, SBB), Nicolas Willemarck (Sciensano, SBB)
SBB: Didier Breyer, Fanny Coppens, Katia Pauwels.

INTRODUCTION

Dossier **B/BE/18/BVW1** concerns a notification of the company Transgene S.A. for deliberate release in the environment of genetically modified organisms other than higher plants according to Chapter II of the Royal Decree of 21 February 2005.
The notification has been officially acknowledged on 06/04/2018 and concerns a clinical trial with TG6002, a non-integrative, conditionally replicative recombinant Vaccinia Virus derived from the Copenhagen strain. TG6002 differs by three genetic modifications from the Copenhagen strain: 1) deletion of the viral thymidine kinase (TK) gene, 2) deletion of the viral ribonucleotide reductase (RR) gene and 3) insertion of the chimeric yeast FCU1 suicide gene in the TK locus.
The application concerns a phase I/IIa clinical trial involving TG6002 administered by intravenous (IV) infusions in combination with oral flucytosine (5-FC) in patients with advanced gastro-intestinal tumors. It is hypothesized that in addition of the oncolytic efficiency of the tumour-selective Vaccinia Virus, the expression of the FCU1 gene by TG6002 into the tumours generates the FCU1 protein that transforms non-cytotoxic 5-FC, delivered at high concentrations inside the tumours, into cytotoxic 5-FU, thereby lowering undesirable systemic exposure to 5-FU.

♦ INSTRUCTIONS FOR EVALUATION

Depending on their expertise, the experts were invited to evaluate the genetically modified organism considered in the notification as regards its molecular characteristics and its potential impact on human health and the environment. The pure medical aspects concerning the efficacy of the medicinal product and its safety for the treated patient are outside the scope of this evaluation.
The comments of the experts are roughly structured as in
- Annex II (principles for the risk assessment) of the Royal Decree of 21 February 2005
- Annex III (information required in notifications) of the Royal Decree of 21 February 2005
- Commission Decision 2002/623/EC of 24 July 2002 establishing guidance notes supplementing Annex II to Directive 2001/18/EC.

List of comments received from the experts

Remark: The comments below have served as basis for a list of questions that the Competent authority forwarded on 29-05-2018 to the notifier with a request to provide additional information. The comments or remarks highlighted in grey correspond to the questions addressed to the notifier.

List of comments/questions received from the experts

1. INFORMATION RELATED TO THE CHARACTERISTICS OF THE DONOR, THE RECIPIENT OR PARENTAL ORGANISM

(e.g. possibility of natural transfer of genetic material to other organisms, pathological, ecological and physiological characteristics, indigenous vectors ...)

Comment 1

Has evaluated this item and has no questions/comments.

Comment 2

Please add the accession numbers for FCY1 (U55193) and FUR1 (X79811) in Table 1.0

Comment coordinator :

This comment is superfluous because the applicant mentioned the GenBank accession Number for FCU1 (AF312392). See also http://getentry.ddbj.nig.ac.jp/getentry/na/AF312392?filetype=html and Erbs et al., (2000). Via AF312392 the information of the other enzymes can be found.

Comment 3

Has not evaluated this item.

Comment 4

Has evaluated this item and has no questions/comments.

2. INFORMATION RELATED TO THE VECTOR

(e.g. description, sequence, mobilisation ...)

Comment 1

Has evaluated this item and has no questions/comments.

Comment 2

Has evaluated this item and has no questions/comments.

Comment 3

Has not evaluated this item.

Comment 4

Has evaluated this item and has no questions/comments.

3. INFORMATION RELATED TO THE CHARACTERISTICS OF THE GMO

3.1. Information related to the genetic modification

(e.g. methods used for the modification, description of the insert/vector construction ...)

Comment 1
Has evaluated this item and has no questions/comments.

Comment 2
Has evaluated this item and has no questions/comments.

Comment 3
Has not evaluated this item.

Comment 4
Has evaluated this item and has no questions/comments.

3.2. Information on the molecular characteristics of the final GMO

(e.g. number of copies of the transgenes, phenotypic and genetic stability of the transgenes, expression of the new genetic material, re-arrangements in the genome, inclusion or suppression of genetic material ...)

Comment 1
Has evaluated this item and has no questions/comments.

Comment 2
Has evaluated this item and has no questions/comments.

Comment 3
Has not evaluated this ite**m**.

Comment 4
Has evaluated this item and has no questions/comments.

3.3. Considerations for human, animal or plant health

(e.g. invasiveness and virulence, toxic or allergenic effects, possibility of survival outside of receiving host, other product hazards ...)

Comment 1
The FCU1 gene was obtained by fusion of the Saccharomyces cerevisiae FCY1 (encoding for the CDase enzyme) and FUR1 (encoding for the UPRTase enzyme) genes. Is there anything known (eg. preclinical data) about the antigenicity of the resulting CDase/UPRTase fusion enzyme, especially with regard to the possible antigenic peptide sequence of the fusion region?

SBB comment :

This question relates to patient safety considerations and is not directly related to biosafety aspects of the recombinant Vaccinia virus TG6002.
Suggestion : Although out of the scope of the Directive 2001/18, the Biosafety Advisory Council could draw the attention of the notifier on this point (e.g. as 'points to consider') if other questions need to be sent out to the applicant.

Comment coordinator :
Clinical studies with a similar GMO construct have already been carried out (Husseini *et al*., 2017). I think this question doesn't need to be included.

Comment 2
Has evaluated this item and has no questions/comments.

Comment 3
Has evaluated this item and has no questions/comments.

Comment 4
Has evaluated this item and has no questions/comments.

4. INFORMATION RELATING TO THE CONDITION OF RELEASE

(e.g. description of the activity, quantities of GMO to be released, workers protection measures, elimination of any contaminating material in the preparation of the GMO stock, elimination of the GMO at the end of the experiment ...)

Comment 1
Has evaluated this item and has no questions/comments.

Comment 2
Has evaluated this item and has no questions/comments.

Comment 3
Patients received paracetamol or ibuprofen before receiving TG6002. Does the administration of paracetamol or ibuprofen have an effect of viral replication?

SBB comment:
Paracetamol or ibuprofen are non-steroidal anti-inflammatory drugs with possible immunomodulatory effects. A study investigating the effect of Ibuprofen on respiratory syncytial virus in a bovine model indicated that the immunomodulatory effect of ibuprofen was associated with increased viral shedding (Walsh *et al*., 2016).

Concerning workers protection measures:
In the technical sheet, the applicant says that the workers should wear waterproof gloves. Workers should wear protective gloves against micro-organisms conform to the ISO norm 374-5:2016.
A chirurgical mask is considered as a medical device rather than personal protective equipment.
Workers should wear a mask conform with the norm NBN EN 529, a FFP2 type (EN149:2001) with a P2 filter (EN 143:2000) for the administration of TG6002.

They should wear closed and resistant shoes in order to be protected against sharp and syringes that fall.
The internal transport of the vials containing the GMO should be performed in a hermetic transport box containing absorbent paper towels.
Removal of the syringe should occur by means of hands free operation (i.e. hands do not touch the needle) into a closed container.

SBB comment :
Similar comments regarding personal protective equipment have been raised in the context of the dossier B/BE/14/BVW1 involving the use of recombinant HSV-1 (Talimogene laherparepvec). If a list of questions will be sent out, the BAC may consider to ask the notifier to amend the Investigational product instruction manual and the Information for health care personnel accordingly.

Comment 4
I have some concerns about the possible occurrence of pustular skin lesion when using this IMP. In my opinion this can be seen as important source/risk of spreading. Prevention measures against this aren't well described in the docs. I would recommend at least (1) the use of bandage to cover the pustular lesions (incl. adequate waste management), (2) avoid (in)direct (skin) contact also with permissive people and/ or possible host animals (cattle and rabbits,…). With regard to the personnel, it is recommended to comply with personal protective measures, such as GLP/hygiene and wearing gloves conform EN374, EN420, EN455 and **ISO 16604 with a** AQL of 0.65 or lower.

SBB comment :
Horizontal transmission of VV and the potential transmission of TG6002 by means of infectious skin papules/vesicles has been addressed in Annex IIIA of the dossier along with a description of the proposed measures to prevent the spread of the recombinant VV (p31, p34-35, p38, p48). The Informed consent form (Patient information Main) also includes detailed instructions on how to prevent dissemination when patients are back home after treatment with TG6002, comprising instructions in case superficial pustules in the skin or in the mouth would appear.
In regards the personal protective measures, the BAC may consider to ask the applicant to complete the Investigational product instruction manual and the Information for health care personnel accordingly.
This can be asked by means of a list of questions addressed to the applicant, alternatively (for example if no list of questions will be sent out) the BAC may consider to mention requirements on ISO norm within the conditions of its advice.
However, it is noticed that proposed measures by the applicant are focused on avoiding transmission to humans, without clearly addressing potential spreading to animals (e.g. pets). In regards the possibility of recombination, the applicant has put the same focus on humans as the host for potential recombinating VV whereas the possible transfer of recombinant VV from humans to animals and the potential of recombination of TG6002 with homologous sequences of viruses present in animal hosts, has not been addressed. The latter aspect needs to be considered to assess the potential of generating novel and uncharacterised viruses upon recombination. Therefore the applicant could be asked to discuss these potential hazards more thoroughly in terms of potentially adverse effects and the likelihood that such an adverse effect would occur. Accordingly, the applicant could be asked to complete the instructions for the patient in regards measures to be taken towards contact with animals (e.g. pets or other animals).

Comment coordinator:

Instructions in regards personnel protection equipment for healthcare workers have been described. However, in the case the patient is returned home after the treatment and presents skin pustules it is not clear from the provided information whether housekeeping personnel will provided with the necessary protection equipment.

5. INFORMATION RELATED TO THE RISKS FOR THE ENVIRONMENT AND HUMAN HEALTH

5.1. Information on spread ("shedding") of the GMO from the treated patient/animal to other persons/animals or to the environment (including indirect/delayed effects due to vertical transmission to offspring).

(e.g. genetic transfer capability, routes of biological dispersal, target organisms ...)

Comment 1
Has evaluated this item and has no questions/comments.

Comment 2
Has evaluated this item and has no questions/comments.

Comment 3
Has evaluated this item and has no questions/comments.

Comment 4
Refers to his comment under section 4.

5.2. Information on possible effects on human health resulting from interactions of the GMO and persons working with, coming into contact with or in the vicinity of the GMO release (carekeepers, patient relatives, immunocompromised people ...).

Comment 1
Has evaluated this item and has no questions/comments.

Comment 2
Has evaluated this item and has no questions/comments.

Comment 3
Immunocompromised individuals will not be allowed to enter in the patient's room and to come into contact with the patient. However, the applicant does not explain the consequences if a patient enters into contact with TG6002.

Comment 4
Refers to his comment under section 4.

5.3. Information on possible effects on animal health or on the environment.

Comment 1
Has evaluated this item and has no questions/comments.

Comment 2
Has not evaluated this item.

Comment 3
Has evaluated this item and has no questions/comments.

Comment 4
Refers to his comment under section 4.

5.4. Information on selective advantages or disadvantages conferred to the GMO compared to the parental organism.

Comment 1
Has evaluated this item and has no questions/comments.

Comment 2
Has evaluated this item and has no questions/comments.

Comment 3
Has evaluated this item and has no questions/comments.

Comment 4
Has evaluated this item and has no questions/comments.

5.5. Information on the possibility of the GMO to reconvert to his wild type form and possible consequences for human health or the environment.

Comment 1
Has evaluated this item and has no questions/comments.

Comment 2
Has evaluated this item and has no questions/comments.

Comment 3
Has not evaluated this item.

Comment 4
Has not evaluated this item.

5.6. Information on the possibility of the GMO to exchange genetic material with other micro-organisms and possible consequences for human health or the environment.

Comment 1
Has evaluated this item and has no questions/comments.

Comment 2
Has evaluated this item and has no questions/comments.

Comment 3
Has evaluated this item and has no questions/comments.

Comment 4
Has not evaluated this item.

5.7. Information on the possibility of gene transfer to other organisms and about the selective advantages or disadvantages conferred to those resulting organisms (possible consequences for human health or the environment).

Comment 1
Has evaluated this item and has no questions/comments.

Comment 2
Has evaluated this item and has no questions/comments.

Comment 3
Has evaluated this item and has no questions/comments.

Comment 4
Has not evaluated this item.

6. INFORMATION RELATED TO THE MONITORING, SURVEILLANCE AND CONTROL, WASTE TREATMENT AND EMERGENCY PLANS PROPOSED BY THE APPLICANT

6.1. Monitoring plan proposed by the notifier and possibility to identify the occurrence of non-anticipated adverse effects.

(adequation between the monitoring plan and risks identified during the risk assessment, when appropriate measures to minimize the potential risks to offspring ...)

Comment 1
Has evaluated this item and has no questions/comments.

Comment 2
Has evaluated this item and has no questions/comments.

Comment 3
Has evaluated this item and has no questions/comments.

Comment 4
Has evaluated this item and has no questions/comments.

6.2. Surveillance and control of the release

(adequation between the procedures to avoid and/or minimise the spread of the GMO and risks identified during the risk assessment...)

Comment 1
Has evaluated this item and has no questions/comments.

Comment 2
Has evaluated this item and has no questions/comments.

Comment 3
Has evaluated this item and has no questions/comments.

Comment 4
Refers to his comment under section 4.

6.3. Information on the waste generated by the activity and its treatment.

(e.g. type of waste, amount ...)

Comment 1
Has evaluated this item and has no questions/comments.

Comment 2
Has evaluated this item and has no questions/comments.

Comment 3
Waste should be discarded in biohazard bags and incinerated. Lab coat, bedding or any contaminated material should be systematically and adequately decontaminated or discarded and be disposed as biohazard material. When possible disposable material will be preferred.

SBB comment :
If a list of questions will be sent out, the BAC may consider to ask the notifier to amend the Investigational product instruction manual and the Information for health care personnel accordingly.

Comment coordinator :
Ways of disposal are in my opinion clearly described.

Comment 4
Has not evaluated this item.

6.4. If applicable, information on the emergency plan(s) proposed by the notifier.

Comment 1
Has not evaluated this item.

Comment 2
Has evaluated this item and has no questions/comments.

Comment 3

Strict procedures should be provided for medical staff and persons in contact with the patient during the release of the viral vector. These procedures should be posted in the hospital room where the treatment should take place.

A spill kit should be available in the facility, this spill kit should contain appropriate disinfectant, personal protective equipment (PPE, i.e. gloves, safety glasses, laboratory coat, mask), tongs or forceps in order to take broken vials, absorbent paper towels, biohazard waste bags.

In case of accidental spills or breakage of a vial containing the GMO, the medical staff should alert people in the area of the spill, remove contaminated clothes and leave the area for 30 min. He should close the area and post “DO NOT ENTER”. After 30 min, he/she must wear a clean lab coat and wear gloves, glasses and a mask. He/she must cover the spill with towels and other absorbent material starting from the edge toward the centre. He/she must carefully pour the appropriate disinfectant over the absorbent material starting from the edge to the centre. It must allow a sufficient contact time for the disinfectant to inactivate the GMO. After that, he must remove the paper towels and broken vials with tongs or forceps and discard in a biohazard waste bag. The PPE should be discard in the biohazard bag. The lab coat should be decontaminated before disposal.

In case of eye projection: washing the eyes abundantly with water or physiologic liquid for 15 minutes using eyewash, remove contact lenses first. The eyes should be rinsed over a closed basin. Wash water should be collected for decontamination with active chlorine beach or another appropriate disinfectant before being released into the sewer system.

SBB comment :

Similar comments regarding instructions in case of accidental spill were raised in the context of the dossier B/BE/14/BVW1 involving the use of recombinant HSV-1 (Talimogene laherparepvec). If a list of questions will be sent out, the BAC may consider to ask the notifier to amend the Investigational product instruction manual and the Information for health care personnel accordingly.

Comment coordinator:

In my opinion procedures are clearly described.

Comment 4

Has not evaluated this item.

6.5 Information related to the identification of the GMO and the detection techniques

(e.g. identification methods and detection techniques, sensitivity, reliability and specificity of the proposed tests ..)

Comment 1

Has evaluated this item and has no questions/comments.

Comment 2

Has evaluated this item and has no questions/comments.

Comment 3

Has not evaluated this item.

Comment 4
Has not evaluated this item.

Comment 5
In regards the detection method for TG6002:
-Part 2.2.3 test sample : IMP is missing in the list of abbreviation. The applicant is requested to add IMP in the list of abbreviations

-It is not mentioned whether particular biosafety precautions need to be taken when carrying out the protocol. If no particular biosafety precautions are to be taken when handling the test sample prior and during to extraction, the applicant is asked to clearly mention this in the detection method. Conditions to perform the PCR (use of pre-PCR, PCR and post PCR rooms) have been adequately explained.

-Tabel 1
If primers are delivered with the control sample, the applicant is asked to complement table 1 (components of the PCR-mix) with concentrations of the stock (in nM or µM for the primers) and final concentration in the mix.

Comment coordinator
As there is no list of abbreviations for this chapter the full name could be given investigational medicinal product, with between brackets (IMP)

7. OTHER INFORMATION

7.1 Do you have any other questions/comments concerning this notification that are not covered under the previous items?

Comment 1
None

Comment 2
None

Comment 3
None

Comment 4
None

References

Erbs *et al*., 2000. *In Vivo* Cancer Gene Therapy by Adenovirus-mediated Transfer of a Bifunctional Yeast Cytosine Deaminase/Uracil Phosphoribosyltransferase Fusion Gene. *Cancer Res* 60 (14); 3813-3822.

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Silva de Oliveira *et al*., 2017. Vaccinia Virus Natural Infections in Brazil : The Good, the Bad, and the Ugly. *Viruses,* 9(11), 340

Walsh *et al*., 2016. A Randomized Placebo Controlled Trial of Ibuprofen for Respiratory Syncytial Virus Infection in a Bovine Model. Plos One 11(4) e0152913.