Bioveiligheidsraad
Conseil de Biosécurité

07-08-2012

Secretariaat
Secrétariat

O./ref.: WIV-ISP/41/BAC/2012_0721

Title: Advice of the Belgian Biosafety Advisory Council on the notification B/BE/11/BVW2 of the company BN ImmunoTherapeutics for deliberate release in the environment of genetically modified organisms other than higher plants for research and development

Context

The notification B/BE/11/BVW2 has been submitted by PPD on behalf of BN ImmunoTherapeutics to the Belgian Competent Authority in April 2012 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 Randomized, Double-blind, Phase 3 Efficacy Trial of PROSTVAC ± GM-CSF in Men With Asymptomatic or Minimally Symptomatic Metastatic, Castrate-Resistant Prostate Cancer "**.
The patients in this trial will be administered 2 study medications, PROSTVAC-V and PROSTVAC-F, which are two recombinant viral vectors derived from vaccine strains of *Vaccinia* and *Fowlpox*, respectively. Each recombinant vector co-expresses the human prostate-specific antigen (PSA) and human co-stimulatory molecules. This GM-therapy is developed for use as an immunotherapy in patients with asymptomatic or minimally symptomatic metastatic castration-resistant prostate cancer. The purpose of this large multicentric, multinational phase 3 study is to ascertain whether the survival of patients receiving PROSTVAC-V/F is superior of that of patients receiving placebo.

The product or matched placebo is administered sub-cutaneously and each subject in the study will receive 1 PROSTVAC-V vaccination followed by 6 PROSTVAC-F vaccinations at two week and monthly intervals. The two GM virus are deemed unable to replicate in human cells but virus can sometimes be found on the wound dressing covering the injection site. Given the dose schedule it is not possible for the subjects to remain within contained facilities for the duration of the study. As for Belgium the trial centres are located in Brussels and in Flanders and as the patients will be treated ambulatory, the national territory is considered as the wider potential release area of the GM *Vaccinia* and *Fowlpox* viruses.

The dossier has been officially acknowledged by the Competent Authority on 17 April 2012 and forwarded to the Biosafety Advisory Council for advice.
Within the framework of the evaluation procedure, the Biosafety Advisory Council, under the supervision of a coordinator and with the assistance of its Secretariat, contacted experts to evaluate the dossier. One expert from the common list of experts drawn up by the Biosafety Advisory Council and the Biosafety and Biotechnology Unit (SBB) answered positively to this request. The SBB also took part in the evaluation of the dossier while the Platform for Molecular Biology and Biotechnology of the Scientific Institute of Public Health evaluated the analytical procedure for the detection of PROSTVAC-V/F submitted by the notifier.

The expert 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 for its intended use, 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).

On 24 May 2012, based on a list of questions prepared by the Biosafety Advisory Council, the Competent Authority requested the notifier to provide additional information about the notification. The answers from the notifier to these questions were received by the Competent Authority on 10 July 2012 and transmitted to the secretariat of the Biosafety Council on the same day. This complementary information was reviewed by the coordinator and the experts.

For the purpose of this evaluation, the following legal basis has been considered:
- 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, economical or ethical considerations, are outside the scope of this evaluation.

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 didn't receive any reaction of the public relevant for the environmental and/or public health safety of the GMO.

Summary of the Scientific evaluation

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

No major risks were identified but the Biosafety Council asked to the notifier to complete the information regarding the attenuation of the parental *Fowlpox* strain.

The notifier who is not the owner of the attenuated *Fowlpox* strain could not find any data in scientific literature on its attenuation. However this parental *Fowlpox* strain is derived from an isolate of POXVAC-TC, a vaccine approved since 1961 in the US for the prevention of *Fowlpox* infection in poultry. To the applicant's knowledge, there have been no reports suggesting that treatment of poultry with POXVAC-TC resulted in *Fowlpox*-causing disease in treated animal or by transmission to non-vaccinated animals. In addition the notifier performed a rodent neurovirulence assay with PROSTVAC-F which results confirm the low virulence of the recombinant *Fowlpox* strain.

2. Information related to the characteristics of the GMO

The notifier was asked to clarify the methods employed to ensure and to verify the genetic stability of both PROSTVAC-V and PROSTVAC-F during the production.
The notifier has adequately answered this question: the genetic stability of PROSTVAC-V and F is demonstrated by the restriction site analysis of the whole genome and the analysis of a PCR-amplicon encompassing the whole insert sequence for each production lot. The notifier provided the precise descriptions of these procedures.

The notifier was also asked to react on a recent article referring to studies that have shown replication of *Fowlpox* in mammalian cell cultures which could change the statement made in the application on the unlikely shedding of the GM *Fowlpox* when administered to humans.

In his answer the notifier refers to the results of a biodistribution study in mice showing that, when administered subcutaneously, there is no general or systemic *Fowlpox virus* DNA detection at other sites other than the administration site and draining lymphnodes. In addition they performed in vitro studies with mammalian cells including the same mammalian cell for which replication of *Fowlpox* replication was observed in a recent article mentioned above. No cell to cell virus propagation occurred during the culture time, no infectious progeny virion was released by PROSTVAC-F infected cells. Based on those results the BAC agrees with the notifier that shedding of recombinant *Fowlpox* is unlikely when administered in humans.

However, from available results of clinical trials performed with canarypox based vaccines it is known that viral particles have been recovered from the vaccination site but it is not known if it were life viruses or not.
The BAC takes note of the fact that the notifier has no plan to evaluate the putative shedding of *Fowlpox* virus during the planned clinical trial but that the possibility of such evaluation will however be explored in a separate study.

3. The condition of release

The experts expressed many critics on the Study staff instructions (SSI) prepared by the notifier for the people who will handle the product. The BAC made suggestions for proper management measures and asked to the notifier to submit amended SSI and correct translations in Dutch and French.

The notifier submitted an amended SSI which integrates all of the BAC suggestions for proper management measures assuring the protection of the workers and preventing unnecessary release of the vector into the environment. The new document has been correctly translated in Dutch and French.

Regarding the information for the patient, the BAC asked to the notifier to better inform the patient that a wound plaster or bandage used to cover the injection site can be contaminated with the study product and is finally biological risk material that needs appropriate waste management procedures.
The notifier submitted an amended patient informed consent form that has taken into account the above remark.

4. The risks for the environment and human health

No major risks were identified neither from PROSTVAC-V or from PROSTVAC-F but the BAC requested to the notifier to complete the environmental risk assessment by considering also the risk, if any, of the recombinant *Fowlpox* for animals other than birds.

This assessment was received and judged satisfactory. Knowing that shedding of recombinant *Fowlpox* is unlikely when administered in humans (see above), the BAC agrees that with the proposed management measures environmental release of PROSTVAC-F is highly unlikely, and that the impact of any such release is expected to be minimal because *Fowlpox virus* has a highly restricted host range, limited *in vivo* to chickens, turkeys, and pigeons.

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

The notifier was asked to give more details on the follow-up they foresee in case suspected vaccinia lesions appear in patients treated with the study drug.

This point was partially addressed by the notifier in the clinical trial protocol. In addition the notifier will provide to each patient included into the study a wallet-size card that would identify him as study participant. The card specifies the trial number and a name and contact number of the investigator. The card also specifies the date of primary vaccination with PROSTVAC-V and notifies the reader that special precautions should be taken not to come in direct contact with the injection site for 3 weeks after the date of the injection. Subjects will be instructed to inform any medical practitioner they are going to see that they are study participants.

6. The analytical procedure proposed by the notifier to accompany the control samples that will be send to the Scientific Institute of Public Health after the start of the clinical trial

The notifier was questioned about the specificity of the detection method and requested to precise the position of the primers in the DNA sequence for both PROSTVAC-V and PROSTVAC-F.
The additional information and documentation provided by the notifier adequately completes the analytical method.

7. Additional points considered by the experts of the Belgian Biosafety Advisory Council

Although out of the scope of the Directive 2001/18, the Biosafety Advisory Council drew the attention of the notifier on one point concerning the safety of the product.
The question of the Council and the answer received from the notifier are given in annex 1.

Conclusion

Based on the scientific assessment of the notification made by the Belgian experts, the Biosafety Advisory Council concludes that it is unlikely that the genetically modified *Vaccinia* and *Fowlpox* viruses (PROSTVAC-V/F) genetically modified to express the genes of the human prostate-specific antigen (PSA) and of human co-stimulatory molecules. and developed as a therapeutic vaccination for the treatment of prostate cancer, will have any adverse effects on human health or on the environment in the context of the intended clinical trial.

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, as described in the dossier.
- 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 authorisations 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 2 weeks when the first patient starts the treatment and the last subject 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 the recombinant *Vaccinia* or *Fowlpox virus*.

i.o. Dr. Ph. Herman

Prof. D. Reheul
President of the Belgian Biosafety Advisory Council

Annex 1: Additional comments related to the safety and efficacy of the product and answers given by the applicant.
Annex 2: Compilation of comments of experts in charge of assessing the dossier B/BE/11/BVW2 (ref: BAC_2012_0505)

Annex 1: Additional comment related to the safety of the product and answer given by the applicant.

Although out of the scope of the Directive 2001/18/EC, the Biosafety Advisory Council would like to draw the attention of the notifier on the following point :

MVA production may contain traces of egg antigens. As allergy against egg antigens is quite frequent in the human population, the applicant should make sure that anti-choc treatments are available when the drug is administered.

Response:

BNIT will ensure that the investigational sites follow the appropriate institutional procedures for emergency care.

Bioveiligheidsraad
Conseil de Biosécurité

24-05-2012

Secretariaat
Secrétariat

O./ref.: WIV-ISP/41/BAC_2012_0505
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Compilation of Comments of Experts in charge of assessing the dossier B/BE/11/BVW2

Mandate for the Group of Experts: mandate of the Biosafety Advisory Council (BAC) of 8 December 2011
Coordinator: Prof. Philippe Hermans
Experts: Katia Pauwels (WIV/ISP), Nicolas Willemarck (WIV/ISP), Willy Zorzi (ULg)
Domains of expertise of experts involved: Human medicine, oncology, virology, gene therapy, therapeutic vaccination, biosafety viral vectors, risk assessment
Secretariat (SBB): Didier Breyer, Martine Goossens, Philippe Herman, Katia Pauwels

INTRODUCTION

Dossier **B/BE/11/BVW2** concerns a notification of the company BN Immunoyherapeutics 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 17 April 2012 and concerns a clinical trial with PROSTVAC-V and PROSTVAC-F, two recombinant viral vectors derived from vaccine strains of vaccinia and fowlpox, respectively. Each recombinant vector co-express human prostate-specific antigen (PSA) and human co-stimulatory molecules. This GM-medication is developed for use as an immunotherapy in patients with asymptomatic or minimally symptomatic metastatic castration-resistant prostate cancer.

♦ 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 23-05-2012 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.

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

Even if the parental fowlpox strain is considered a safe vaccine, from the data in the dossier it is not clear how it is attenuated. More information regarding the attenuation should be appreciated and will certainly be needed for a later application for marketing authorisation.

Comment 3

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 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 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

What are the methods employed to ensure and to verify the genetic stability of both ProstVac-V and ProstVac-F during the production ? Point 64 on page 47 of the notification form does not answer this question and is rather related to the environmental survivability of the GMO.

Comment 3

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

See comment under point 5.1.

Comment 2

In the notification form (see pages 16, 17, 37) and the ERA (see page 27) it is repeated that Fowlpox only replicates in avian cells. In a recent article (Weli and Tryland, 2011) the authors refer to studies that have shown replication of fowlpox in mammalian cell cultures and challenge the hypothesis that avipoxviruses cannot undergo a full replication cycle in mammalian cells. Has the applicant taken this information under consideration ? Does it change the applicants position on the unlikely shedding of the GM fowlpox when administered to humans ?
In addition, the applicant did not check if the fowlpox particles recovered from the vaccination site are life viruses or not (see page 18-19 ERA). Why ?

Comment 3

It is known that vaccinia virus vaccination can lead to serious adverse events/complications of vaccinia infections (such as eczema vaccinatum or postvaccinal encephalitis). Although those complications are rare events, I'm wondering if those complications can be linked with an enhanced replication of the virus and an elevated risk of spreading?

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

Several remarks concerning the study staff instruction (SSI):
In the SSI it is recommended to wear goggles, gloves and labcoat when manipulating the study drugs. In addition the staff should also wear a mask to avoid any contamination by aerosolisation.
For the staff handling the study drug it is important to avoid any needlestick injury. It is therefore out of question to allow to cap the needle as instructed on page 2 of the SSI. If the hospital does not have safety syringes this material should be provided by the sponsor of the trial or the sponsor should propose handling measures where the risk of needle stick injury is mitigated.
In the SSI regarding instructions in case of accidental spill (see page 4) additional instructions should be given about the handling of the waste generated.
In general in the SSI the instructions regarding waste and biohazard signs are not enough detailed.

Comment 3

In app. 1 staff instruction is written to use always when handling PROSTVAC-V a hood or a biological safety cabinet if one is available. A hood is not the right containment to prevent unintentional release of the GMO in the environment. *Please delete the word "hood" that may confuse the staff and use only biological safety cabinet (BSC) and notify that only BSC minimal of class 2 is mandatory.*

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

PROSTVAC-V is able to cause a transient infection and to replicate in the cytoplasm of infected cells and the patient in treatment could excrete viral material by this way(p 8 and 9 of Part 1 and p 9 of Part A4).
Apparently, no detectable trace (in the limits of the employed PCR technique) of PROSTVAC-V nor PROSTVAC-F are found in the urine when the treated patients have a normal kidney function. But, in case of kidney filtration disorder, it is strongly plausible to find non-negligible amounts of viral material in the urine … with the risk for the patient to contaminate his home and consecutively, the environment.

Additional comment SBB:
Even if the parental Vaccinia virus is an attenuated replication defective strain unable to produce virus progeny it is potentially able to reach target issues other than the site of administration. But a rapid viral clearance (max. 48h) is expected (Gomez et al, 2007; Sittelaar et al., 2001) and shedding via urine should be minimal. Even if the GM Vaccinia virus can survive in the environment this replicative deficient virus will be unable to produce new viral progeny and to propagate in most mammalian cells (Verheust et al, 2011)

Note from the coordinator:
Renal insufficiency is not frequent in patients suffering prostate cancer. It can however be associated with other pathologies (hypertension and diabetes…) but the protocol of the clinical trial foresees that patients "with significant medical abnormality" are excluded.

Comment 2

See question under point 3.3

Comment 3

There are no safety measurements described about the use of PROSTVAC_FOWL when the receiving host (patient) (can) comes in close contact with permissive host organisms; birds/ poultry (chickens, turkeys, and pigeons, but not in quail, ducks, or canaries). Keeping chickens or pigeons is a common habit in Belgium!

The same concern about the use of PROSTVAC_VACCINIA when the receiving host/patient (can) come(s) in close contact with permissive host organism other than human, such as warm-blooded vertebrates such as cattle, cats, rodents, rabbits and pigs? Keeping cats and or rabbits as a pet is a common habit in Belgium! (cattle&pigs are farm animals)

Both situation should be stressed as risks in at least the informed consent form (ICF)**,** because, although the risk is low when patient are following the prescribed containment measures (covering the injection site, changing clothes & bed linen and washing hands), an accidental release of the IMP to e.g. chickens, pigeons, rabbit, cat or cattle, will be difficult to detect (the IMP is subclinical without really symptoms) and to control. In those situations there is a risk of possible long-term survival outside of receiving host/patient.

This issue is not discussed in Protocol BNIT-PRV-301: Part A1 point 62 (p54) and informed consent form (ICF)? At least the ICF should detail how to prevent this accidental contact transmission.

Although the likelihood that the IMP would result in the establishment and persistence of the virus (prostvac_V or prostvac_F) in wild or domestic animals is remote, I'm wondering if it is not better to exclude those people from this study? Or are the well prescribed containment measurements appropriate enough to prevent accidental contact transmission? In case of the latter, an highlighting of those containment measurements and the recommendation to prevent close contact with permissive host is a minimal requirement that has to be included in the CFS? Can the notifier comment this?

Additional comment SBB:
See comment above. The GM viruses are replication defective strains unable to produce virus progeny. In case of accidental transmission to an animal it will not propagate.
The hygienic measures prescribed to the patient should be sufficient to mitigate the accidental transmission to domestic animals.

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

See comment under point 5.1.

Comment 2

Has evaluated this item and has no questions/comments.

Comment 3

The spill and incident procedures are not described into details and sometimes it misses some crucial points.

For skin and eye contamination with/without injury it is prescribed to wash immediately and abundantly with tap water. Although there are waste and decontamination measures taken in general, there is no specific procedure in case of incident. For example the first step in case of skin contamination has to be soaking up all liquid with absorbent paper or other material (with appropriate inactivation afterwards), then decontaminate the skin (which product, contact time?) and then rinse with water. This to minimize the release of GMOs into the public. Contaminated clothes and used paper to absorb the most concentrated IMP must be disposed or inactivated as infectious material!

In case of eye contamination the washing product has to be collected and inactivated before disposing.

In addition, the staff instruction should detail how to deal with an incident involving an aerosol incident, needle stick injury and the prevention of accidental exposure of other people than the patient and care keeper (the person administering the injection) during injection (*Family, friends and other personnel can be asked to leave the room for this short intervention e.g.).*

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

Comment 1

The notifier explains that there is a potential risk to have recombination between PROSTVAC-V (classified as BSL-2 GMO) with a wild-type vaccinia which could infect certain host organisms. Recombination between PROSTVAC-F and a wild or vaccine strain of fowlpox would require release of PROSTVAC-F into an environment containing poultry.

Comment 2

See question under point 3.3. If fowlpox is really capable to replicate in mammalian cell cultures should the risk for animals other than birds also not be considered ?

Comment 3

Given the medium persistence of the IMP under normal environmental conditions is days to weeks depending of the conditions (dry – humid), I'm concerned about possible accidental release/ contact transmission of the IMP in a permissive host (such as birds, warm-blooded animals) in which the infected host become a long-term latent reservoir in nature without any (further) control (with possible further spread via e.g. mosquitoes).

Additional comment SBB
See comment under point 5.1

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.

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 evaluated this item and has no questions/comments.

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.

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.

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

See comment under 5.1.
If the patient at home develops a disorder of the kidney function (kidney filtration disorder) such as pyelonephritis, associated with proteinury and hematury, which kind of follow-up is proposed by the notifier ?

Comment 2

Has evaluated this item and has no questions/comments.

Comment 3

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

See comment under 5.1.
On one side, the medical follow-up controls described in the dossier seem adapted to classical check-up of the patient. Also, in case of problems such as described here above, there is certainly an emergency follow-up of the suffering patients through a specific medical assistance. But little is known about the specific management of potentially contaminated urine from those patients. In this case, while, under normal environmental conditions, PROSTVAC-V and PROSTVAC-F are expected to survive for considerable periods in dried spill material adhering on surfaces of the lavatories or bathroom.
Through the information sheet and the informed consent form, the patient could be sensitized to this hazard by a clear and detailed protocol explaining which kind of risk could occur in such a case. The furniture of an adapted decontamination biohazard/spill kit could also be necessary. While the frontier between the site where the patient is living during the ambulatory phases of the treatment and the

environment is not well secured, it is necessary to propose solutions to avoid a potential contamination of the environment. We invite the notifier to add this topic to the risk assessment plan, with a new adapted management protocol in order to prevent this hazard. Otherwise, to preserve the biosafety of the environment, it is better to keep these patients at the hospital during the Period 2 of this study.

Comment 2

Has evaluated this item and has no questions/comments.

Comment 3

See comment 5.1.

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

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

Comment 1

See comment under 5.1.

Comment 2

Has evaluated this item and has no questions/comments.

Comment 3

App. 1 staff instruction p4 is written “All materials and devices (vials, stoppers, needles, gauze etc.) that come into contact with vaccine should be discarded in leak-proof containers to be disposed of according to the institution’s policy”.

Waste management has to comply with the Belgian law by the **Royal Decree of 21 February 2005 “**on the deliberate release of GMOs into the environment” and with the Belgian regional regulations on contained use of GMO's and/or pathogen organisms (biological contaminated waste has to be inactivated before disposing (incinerated as RMA, autoclaved, chemically inactivated,…). (see also p 43,46&65 **Protocol BNIT-PRV-301: Part A1)**

In addition, please emphasize in ICF that a wound plaster or bandages used to cover the injection site can be contaminated with IMP and is finally biological risk material that needs a appropriate waste management procedure.

The notifier has to include/complete those omissions.

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

Comment 1

See comment under point 6.2..

Comment 2

Please specify the instruction for countries outside the united states when there is an onset of suspected vaccinia lesions in patients treated with the IMP (BNIT-PRV-301: Staff Instructions p 5).
Is there a procedure described about how to supervise patients with vaccinia-related complications? How are the (external) medical practitioners not involved in the clinical study informed about how to treat patients with complication, e.g. general practitioner?

IV-VIG and Cidofovir have to be sufficiently available on all investigational site during the clinical trial to prevent the elevated risk of spreading when there are complications (especially for IV-VIG therapy, since IV-VIG may work better if given early).

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

The detection methods for ProstVac-V and ProstVac-F are clearly detailed (see identity release tests) but are these really specific? Could the applicant indicate for each recombinant virus the precise position of the primers in the sequence ?

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

I have many criticisms concerning the staff instructions. It lacks critical details and the translation is not always well done, which can lead to misinterpretations.

[Concerning TRANSPORT] App. 1 staff instruction p2/3. The notifier distinguishes short and long IMP transport. All transport the vial or syringe containing the GMO-IMP must be performed in a sealed double leak-proof container/bag displaying a appropriate biohazard sign also if it is in the same building (except if IMP reconstitution and filling of the needle is possible in the patient's room).
For transport on the public highways/roads, the reference to the European Agreement concerning the International Carriage of Dangerous Goods by Road is missing.

[Concerning translation // Contradiction] in app. 1 staff instruction p2 "Draw up the vaccine or placebo after wiping the rubber stopper with an alcohol-soaked gauze pad, keeping the pad covering the

stopper to the extent possible" in **Dutch** is written not cleaning/disinfecting the rubber stopper but open the rubber stopper with a alcohol-soaked gauze pad. This sentence in Dutch is very confusing and needs to be rewritten. Please, emphasize in instruction the fact that the staff have to avoid the creation, spreading and release of infectious aerosols by only drawing up the IMP without opening the vial (by perforating the rubber stopper with the needle itself without opening the vial). Then only, in closed situation, it is indeed allowed to eject air out the needle in the vial.

(French translation is OK at least for this sentence, the document in French not fully checked)

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