Adviesraad voor Bioveiligheid
Conseil consultatif de Biosécurité

Advice of the Belgian Biosafety Advisory Council on the notification B/BE/18/BVW9 of the company GlaxoSmithKline Biologicals for deliberate release in the environment of genetically modified organisms other than higher plants for research and development

22/01/2019
Ref. SC/1510/BAC/2019_0078

Context

The notification B/BE/18/BVW9 has been submitted by GlaxoSmithKline Biologicals to the Belgian Competent Authority in October 2018 for a request of deliberate release in the environment of genetically modified organisms (GMO) 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 1/2, randomized, observer-blind, controlled, multi-center study to evaluate safety, reactogenicity and immunogenicity of GSK Biologicals' respiratory syncytial virus (RSV) investigational vaccine based on the RSV viral proteins F, N and M2-1 encoded by chimpanzee-derived adenovector (ChAd155-RSV) (GSK3389245A), when administered intramuscularly as a single dose or as two doses according to a 0, 1-month schedule, to infants aged 6 and 7 months".***

The GMO ChAd155-RSV has been developed as a preventive vaccine candidate for active immunization of infants for the prevention of any lower respiratory tract infections (LRTI; bronchiolitis and [broncho] pneumonia) associated with RSV [subtypes A and B]. The GMO is a viral suspension of a live recombinant, replication-defective simian (chimpanzee-derived) group C adenovirus serotype 155 (ChAd155) viral vector construct engineered to express three proteins from the Respiratory Syncytial Virus (RSV): the fusion F protein (deleted of the transmembrane region, named F0ΔTM), the nucleocapsid protein N and the transcription antitermination protein M2-1. The expected biological activity of the GMO is the induction of an immune response against the RSV proteins that constitute the transgene.
The GMO will be administrated using a vaccination regimen based on one intramuscular injection of $1{,}5x10^{10}$ viral particles of the ChAd155-RSV vaccine or two intramuscular injections of $5x10^{10}$ viral particles of the ChAd155-RSV vaccine, administered with a 4-week interval between vaccinations.

It is planned to conduct this study in two clinical sites located in Brussels and the Flemish Region. Fifty patients per dose group will receive the GMO.

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The dossier has been officially acknowledged by the Competent Authority on 21 November 2018 and forwarded to the Biosafety Advisory Council (BAC) for advice.
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. Three 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. 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.

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 several reactions from the public, one of them being related to biosafety. The comment has been considered by the BAC in the preparation of the current advice.

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 ChAd155 and ChAd155-RSV including phenotypic and genetic stability of the transgenes were found to be adequately described in the dossier.

3. The conditions of the release

Measures to avoid exposure of the personnel during manipulations potentially giving rise to aerosols containing virus vectors are adequately described in the the ‘Biosafety Instructions for site staff’. Study staff are required to wear appropriate personal protective equipment (PPE) including protective gloves, lab coats at any time and additional safety glasses and facial mask while performing manipulations that

may create aerosols. The document also specifies that any bandages will be discarded as biohazard waste before the patient leaves the hospital.

4. The risks for the environment or human health

The notifier states there is a theoretical possibility of shedding of infectious particles into the environment and potentially to the public during the release. He argues however that defective recombinant adenoviruses have been used extensively in clinical trials, either through direct administration or cell therapy strategies (contained in the cells). The majority of the studies have not detected viral release in biological samples (sputum, saliva, urine, feces) and whenever detected through urine or saliva, it disappears in few days from administration. With respect to the persistence or survivability of the ChAd155-RSV vector in the environment, the BAC could not agree with the notifier stating there is only minimal risk of persistence or survivability. Adenoviruses are unusually resistant to chemical or physical agents and adverse pH conditions, allowing for prolonged survival outside of the body. Adenovirus has been shown to be resistant to both tertiary treatment and UV radiation of urban wastewater (Thompson et al. 2003[1]; Thurston-Enriquez et al. 2003[2]). With respect to the probability for recombination with wild-type adenovirus, the BAC acknowledges Wold and Toth, 2013[3] concluding that recombination events between replication-deficient adenoviral vectors have not been reported and if these were to occur, these would not lead to replication-competent viruses expressing the transgene.

Broadly speaking the risks associated to shedding are poorly analyzed in the dossier. However, a detailed assessment has been provided by the notifier, and considered by the BAC, in the framework of the evaluation of the dossier B/BE/18/BVW4, in which a GMO developed using the same ChAd155 vector was used (see BAC advice of 01/10/2018, ref. SC/1510/BAC/2018_0767).
Given the replication-defective properties of the vector, its low probability of shedding especially when administered by the intramuscular injection route, the fact that no recombination events have been reported so far with E1/E4-deleted replication-defective vector, and the absence of indication that the RSV transgene could influence the shedding behavior of recombinant ChAd vectors, the BAC concludes that the risk for the environment and human health associated to possible shedding of the ChAd155-RSV vector, if it were to occur, is low.

With regards to the 'Biosafety Instructions for site staff' the BAC notes that the description of the procedures for the management of accidental spills still leaves room for improvement and proposes to add the following procedure:
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/she should close the area and post "DO NOT ENTER". After 30 min, he/she must wear a clean lab coat and wear gloves, glasses, over-shoes 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/she must remove the paper towels

[1] Thompson, S. S., J. L. Jackson, M. Suva-Castillo, W. A. Yanko, Z. E. Jack, J. Kuo, C.-L. Chen, F. P. Williams, and D. P. Schnurr. 2003. Detection of infectious human adenovirus in tertiary-treated and ultraviolet-disinfected wastewater. Water Environ. Res. 75:163-170.
[2] Thurston-Enriquez, J. A., C. N. Haas, J. Jacangelo, K. Riley, and C. P. Gerba. 2003. Inactivation of feline calicivirus and adenovirus type 40 by UV irradiation. Appl. Environ. Microbiol. 69:577-582.
[3] Wold, W. S. and K. Toth (2013). "Adenovirus vectors for gene therapy, vaccination and cancer gene therapy." Curr Gene Ther 13(6): 421-433.

and broken vials with tongs or forceps and discard in a biohazard waste bag. This procedure with absorbent materials and disinfectant should be performed twice. The PPE should be discard in the biohazard bag. The lab coat should be decontaminated before disposal. The medical staff should report the incident to the responsible of the site.
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, over-shoes), tongs or forceps in order to take broken vials, absorbent paper towels, biohazard waste bags.

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

The Biosafety Advisory Council is of the opinion that the information provided is sufficient and does not raise safety concerns.

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 investigational therapeutic ChAd155-RSV vaccine will have any adverse effects on human health or on the environment in the context of the intended clinical trial 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.

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

- 'Biosafety Instructions for site staff' should be more explitely described and updated as mentioned under section 4 above.

- 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 ChAd155-RSV.

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/BVW9 (ref. SC/1510/BAC/2019_0050)

Compilation of comments of experts in charge of evaluating the dossier B/BE/18/BVW9

15 January 2019
Ref. SC/1510/BAC/2019_0050

Mandate for the Group of Experts: Mandate of the Biosafety Advisory Council (BAC) of 19 November 2018.
Coordinator: Jozef Anné (KUL)
Experts: Aline Baldo (Sciensano, SBB), Anton Roebroek (KUL), Viggo Van Tendeloo (UZA), Willy Zorzi (ULiège)
SBB: Didier Breyer

INTRODUCTION

Dossier **B/BE/18/BVW9** concerns a notification from Glaxo SmithKline Biologicals for the 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 21 November 2018 and concerns a clinical trial entitled "*A Phase 1/2, randomized, observer-blind, controlled, multi-center study to evaluate safety, reactogenicity and immunogenicity of GSK Biologicals' respiratory syncytial virus (RSV) investigational vaccine based on the RSV viral proteins F, N and M2-1 encoded by chimpanzee-derived adenovector (ChAd155-RSV) (GSK3389245A), when administered intramuscularly as a single dose or as two doses according to a 0, 1-month schedule, to infants aged 6 and 7 months.*"

♦ 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.

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

Has not evaluated this item.

Comment 3

Has evaluated this item and has no questions/comments.

Comment 4

Has evaluated this item and has no questions/comments.

2. INFORMATION RELATED TO THE VECTOR

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

Comment 1

The document '02_2018-000431-27_Annex III (27-AUG-2018)' shows on page 24 of 58 a map of BAC ChAd155 RSV. The accompanying legend, however corresponds to another BAC ChAd155 construct.

Comment 2

Has not evaluated this item.

Comment 3

Has evaluated this item and has no questions/comments.

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 not evaluated this item.

Comment 3

Has evaluated this item and has no questions/comments.

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

The insert contains the self-cleaving 2A region of foot-and-mouth disease virus (FMDV), that allows separating the soluble F protein and the other two RSV antigens. Does this protease cleave other host proteins?

***Comment SBB and coordinator**:*

The same comment was formulated in the framework of the evaluation of dossier B/BE/18/BVW4 in which a GMO developed using the same ChAd155 vector was used. It was not retained with the following justification:

See Donnelly et al., 2001. The P2 portion in the picornavirus genome encodes three mature viral proteins, namely 2A, 2B, and 2C. FMDV 2B and 2C are partially homologous to other picornavirus, whereas FMDV 2A is only an 18 aa peptide and is much shorter than the other picornavirus members but highly conserved with cardiovirus at the 2A/2B junction. The FMDV 2A protein lacks any protease motifs and only contains the characteristic C-terminal motif "-Glu(x)AsnProGly(2A)/Pro(2B)-" In addition, the conserved cleavage site is located between 2A and 2B Gly(2A)/Pro(2B). Mutation research confirmed that Gly (2A) is the most important amino acid for cleavage activity at the 2A/2B junction, whereas recombinant FMDV sequence containing mutation in the 2A peptide can produce uncleaved

proteins. Moreover, cleavage between 2A and 2B only occurs as a co-translational event. Thus, the 2A cleavage event occurs only during polypeptide synthesis , such that the 2A peptide remains connected to the P1 structural protein precursor (P1-2A) following primary cleavage of the polyprotein. 2A is cleaved from the P1-2A precursor either by 3Cpro or 3CDpro.

Comment 3

Has evaluated this item and has no questions/comments.

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

Has evaluated this item and has no questions/comments.

Comment 2

The applicant does not demonstrate that the vector is not able to replicate in other animal species. Is the replication of ChAd155 species specific?

***Comment SBB and coordinator**:*

The same comment was formulated in the framework of the evaluation of dossier B/BE/18/BVW4 in which case a GMO developed using the same ChAd155 vector was used. It was not retained with the following justification:

In case the "ChAd155 vector" means ChAd155 with deleted E1, then ChAd155 vector cannot replicate, since E1 is essential for Ad viral replication.

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

Adenoviruses are transmitted effectively by direct contact via contaminated aerosols and water droplets and indirectly via contact with objects contaminated with respiratory secretions from an infected person. As the release will take place during a clinical study held under Good clinical practices, precautions will be taken to minimize the production of aerosols during the handling, preparation and administration of the GMO. Also any contaminated surfaces or objects will be disinfected immediately with appropriate adenoviral-active disinfectants and standard institutional procedures for decontamination of biohazard waste. Strict adherence to the safety measures to be taken during the handling, preparation and administration of the GMO during the clinical trial as specified in the clinical protocol will adequately control any potential spread of the GMO.
Due to the context of the proposed GMO release, where the GMO is administered to subjects in an enclosed hospital or clinical examination room, it is unlikely the GMO will come into contact with any non-target organisms in the ecosystem.
In the event of inadvertent administration to non-target organisms, further dissemination is unlikely because GMO is unable to complete a viral replication cycle and as such is non-virulent and unable to disseminate in target or non-target organisms. Even if the administration of the vaccine will be performed by dedicated and trained medical personnel, the possibility that hospital staff may be injected by accident or be exposed indirectly (ex: by negligence) may occur. Please describe precisely the workers protection measures and equipment, specifically used to limit the exposure to contaminated aerosols, droplets… during the administration of the vaccine: 1. Type of mask (type 2 earloop mask or FFP1 or FFP2 or FFP3); 2. Goggles or not…
In the SNIF dossier, it is written that ChAd155-RSV vaccine is supplied in a glass vial. There is clearly a risk of glass vial breakage during the handling of vaccine. Please consider the necessity to adopt unbreakable containers for the doses of vaccine in the context of this dossier.
***Comment SBB and coordinator**:*
The same type of comment is formulated under 6.4.
For the sake of consistency with the advice adopted for the clinical trial B/BE/18/BVW4 (in which a GMO developed using the same ChAd155 vector was used) a recommendation to update the "Biosafety Instructions for site staff"will be included in the advice of the Council for the dossier B/BE/18/BVW9.

Comment 4

Has evaluated this item and has no questions/comments.

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

The applicant says that there is a theoretical possibility of shedding of ChAd155-RSV into the environment. Could the applicant consider the risk of shedding?

***Comment coordinator**:*

The probability of shedding and the risks associated to this shedding have already been extensively considered in the frame of the evaluation of dossier B/BE/18/BVW4, in which a GMO developed using the same ChAd155 vector was used. In that context the notifier provided, upon request of the BAC, a detailed assessment.

Although this detailed assessment was not provided in dossier B/BE/18/BVW9, the conclusions of the BAC for dossier B/BE/18/BVW4 also appplies here, and one can conclude that the risk for the environment and human health associated to possible shedding of the vector, if it were to occur, is low.

Comment 3

Has evaluated this item and has no questions/comments.

Comment 4

Has evaluated this item and has no questions/comments.

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

Could the applicant evaluate the possible effects if an immunocompromised people comes into contact with the GMO?

Comment 3

The expert refers to its comment under point 4.

Comment 4

Has evaluated this item and has no questions/comments.

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 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.

5.4. 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 evaluated this item and has no questions/comments.

Comment 4

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.

Comment 4

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.

Comment 4

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

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

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

Has evaluated this item and has no questions/comments

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

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

Comment 1

In '06_2018-000431-27_Biosafety Instructions for Site Staff_version-1 (04-Oct-2018)' it is suggested under 'Room Set Up' and 'Accidental Spill' that 70% ethyl alcohol can be used to effectively inactivate the GMO upon contamination or spill. Since the adenoviral GMO is non-enveloped, this is questionable.
***Comment coordinator**:*
Adenovirus type 5 is usually inactivated by ethanol between 70% and 90% in 30 s (J Hosp Infect. 2018 Apr;98(4):331-338. doi: 10.1016/j.jhin.2017.08.025.).

Comment 2

Have 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.

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

Comment 1

Has evaluated this item and has no questions/comments.

Comment 2

Strict procedures should be provided for medical staff and persons in contact with the patient during the injection of the vaccine candidate ChAd155-RSV. These procedures should be posted in the hospital room where the vaccination 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 must wear a clean lab coat and wear gloves, glasses and a mask. He must cover the spill with towels and other absorbent material starting from the edge toward the centre. He 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. The medical staff should report the incident to the responsible of the site.
***Comment SBB and coordinator**:*
The same type of comment is formulated under 4.
For the sake of consistency with the advice adopted for the clinical trial B/BE/18/BVW4 (in which a GMO developed using the same ChAd155 vector was used) a recommendation to update the "Biosafety Instructions for site staff"will be included in the advice of the Council for the dossier B/BE/18/BVW9.

Comment 3

Has evaluated this item and has no questions/comments.

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 not evaluated this item.

Comment 3

Has evaluated this item and has no questions/comments.

Comment 4

Has evaluated this item and has no questions/comments.

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

The document '02_2018-000431-27_Annex III (27-AUG-2018)' mentions on page 19 of 58 under '(c) parental organisms' that adenoviruses are susceptible to heat and disinfectants active against enveloped viruses. This should be 'disinfectants active against non-enveloped viruses'.
In the document '10_2018-000431-27_ICF BE NL, version 1 (24-JUL-2018)' '(zie rubriek "Korte beschrijving en verloop van de studie?")' should be corrected in '(zie rubriek "Korte beschrijving van het verloop van de studie en de behandeling")'.

Comment 2

None

Comment 3

None

Comment 4

In the SNIF document on page 22 second paragraph there is a reference missing on the use of ChAd3 vector for hep C vaccination ("Error! Reference source not found, 2011").

References

None.