Adviesraad voor Bioveiligheid
Conseil consultatif de Biosécurité

Advice of the Belgian Biosafety Advisory Council on the notification B/BE/18/BVW4 of the company GlaxoSmithKline Biologicals SA for deliberate release in the environment of genetically modified organisms other than higher plants for research and development

01/10/2018
Ref. SC/1510/BAC/2018_0767

Context

The notification B/BE/18/BVW4 has been submitted by GlaxoSmithKline Biologicals SA to the Belgian Competent Authority in June 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 first-time-in human (FTIH), Phase I, randomized, multi-centric, single-blind, controlled dose-escalation study to evaluate the reactogenicity, safety immunogenicity and efficacy of GSK Biologicals' HBV viral vectored vaccines given in a prime-boost schedule with sequential or co-administration of adjuvanted proteins therapeutic vaccine (GSK3528869A) in chronic Hepatitis B patients (18-65 years old) well controlled under nucleo(s)tides analogues (NA) therapy".***
The proposed vaccination regimen comprises the use of two viral vaccines with hepatitis B surface antigens developed as a novel therapeutic Hepatitis B Virus (HBV) vaccination strategy to induce a robust T-cell response and/or antibody response against various HBV antigens (HBsAg). The aim is to restore the patients' immune control of HBV infection and to achieve functional cure, defined by loss and ultimate clearance of HBsAg, in order to allow patients to safely discontinue NA therapy. The investigational therapeutic HBV vaccines consist of a recombinant replication-defective Chimpanzee Adenovirus vector (ChAd155) encoding a fusion of sequences derived from two HBV proteins (ChAd155-hIi-HBV) and a highly attenuated orthopoxvirus Modified Vaccinia Virus Ankara (MVA), replication-deficient in humans and other mammals, with the same antigens-encoding transgene resulting in the viral vaccine MVA-HBV. The antigens-encoding transgene is a fusion of sequences encoding hepatitis B proteins HBc (core nucleocapsid protein) and HBs (small surface antigen) separated by a 2A self-cleaving region of the foot and mouth disease virus for processing of the HBc and HBs into separate proteins. In addition, the N-terminal part of the gene encoding the HBc protein has been fused to the gene encoding the human Major Histocompatibility Complex (MHC) class II-associated invariant chain p35 isoform (hIi) that is acting as a genetic adjuvant to the associated antigen and will help inducing a more robust HB antigen-specific immune response in the host.
Two separate doses of the investigational vaccines, administered by the intramuscular route (IM), will be evaluated in the Phase 1 clinical study: a higher potency dose ($5x10^{10}$ viral particles of ChAd155-

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hIi-HBV and 2 x 10^8 plaque forming unit of MVA-HBV) and a lower potency dose ($5x10^9$ viral particles of ChAd155-hIi-HBV and 2 x 10^8 plaque forming unit of MVA-HBV).

It is planned to conduct this first in human study in six clinical sites located in Brussels and the Flemish Region. A total of 148 patients will be enrolled in the study, which will last approximately 4.5 years.

The dossier has been officially acknowledged by the Competent Authority on 19 July 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. One 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 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 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 24 August 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 were received by the Competent Authority on 12 September 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 reactions 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 ChAd155 and ChAd155-hIi-HBV including phenotypic and genetic stability of the transgenes were found to be adequately described in the dossier.

3. The conditions of the release

Upon request of additional information of the BAC on measures to avoid exposure of the personnel during manipulations potentially giving rise to aerosols containing virus vecors, the notifier adapted the site staff instruction document so as to recommend study staff 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 notifier also further specified 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 very low risk of shedding of ChAd155-hIi-HBV into the environment. Because no shedding data are currently available associated to the administration of this vector in humans, the notifier refer to the shedding data obtained with another E1/E4-deleted replication-defective chimpanzee-derived adenoviral vector (ChAd3) carrying a transgene encoding a hepatitis C virus protein (NSmut) given the homology between the ChAd3-NSmut and ChAd155. The BAC is of the opinion that the relevance of the shedding study with ChAd3 based on a claimed 99% homology with ChAd155 has not been sufficiently substantiated given (1) the provided homology study (alignment ChAd3 >< ChAd155) does not cover a full-length alignment; (2) the rationale to limit the alignment to some of the adenoviral proteins has not been further discussed; (3) the identified regions of non-homology and their biological relevance have not been further discussed and (4) the lack of information concerning the design of the shedding study. On the other hand the BAC acknowledges that on the basis of a review of biodistribution studies of several adenovirus vector backbones administered via the intramuscular route, it can be anticipated the vector may have a similar shedding profile.
Since the probability of shedding of ChAd155-hIi-HBV vaccine cannot be excluded, the notifier was also asked to elaborate on the probability of shedding and the risks associated to the consequences of shedding should it occur. With respect to the persistence or survivability of the ChAd155-hIi-HBV vector in the environment, the BAC could not agree with the notifier stating there is only minimal risk of persistance 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; Thurston-Enriquez *et al*. 2003). With respect to the probability for recombination with wild-type adenovirus, the BAC acknowledges Wold and Toth, 2013 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.

Given the replication-defective properties of the vector, the low probability of shedding, and the fact that no recombination events have been reported so far with E1/E4-deleted replication-defective vector, the BAC concludes that the risk for the environment and human health associated to possible shedding of the vector, if it were to occur, is low.

The environmental risk assessment associated to the intended use of MVA-HBV was found to be adequately described in the dossier. Taking into account that i) wild type vaccinia virus and the parental MVA are not naturally found in the environment ii) the MVA vector has lost about 15% of its parental genome, precluding the ability of poxviruses to complement MVA iii) MVA is a non-integrative vector unable to produce vector particles in human cells iv) the lack of viral shedding observed from subjects vaccinated with MVA vectors, the BAC concludes that it is unlikely that the proposed intended use of MVA-HBV would confer risks to the human health or the environment.

The notifier was also requested by the BAC to update the 'Biosafety Instructions for site staff' with respect to the use of effective disinfectant (with particular attention for effective disinfectants for non-enveloped adenoviral vectors) and to further specify the use of personal protective equipment. These remarks were adequately implemented in the updated document. After having received the updated document the Biosafety Advisory Council further remarked 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 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

Upon request of the Biosafety Advisory Council the notifier further specified instructions for the patient in regards the removal and disposal of bandages at home as appropriate.
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 HBV vaccines ChAd155-hIi-HBV and MVA-HBV 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. The notifier is recommended to further improve the description of procedures for study staff in regards the management of accidental spills or breakage of a vial containing the GMO by means of the 'Biosafety instructions for site staff".

- 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, ChAd155-hIi-HBV and MVA-HBV.

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/BVW4 (ref. SC/1510/BAC/18_0748)

Compilation of comments of experts in charge of evaluating the dossier B/BE/18/BVW4 And comments submitted to the notifier

24 August 2018
Ref. SC/1510/BAC/2018_0748

Mandate for the Group of Experts: Mandate of the Biosafety Advisory Council (BAC) of 18 July 2018.
Coordinator: Jozef Anné (KUL)
Experts: Anton Roebroek (KUL), Aline Baldo (Sciensano, SBB), Amaya Leunda (Sciensano, SBB)
SBB: Katia Pauwels.

INTRODUCTION

Dossier **B/BE/18/BVW4** concerns a notification of the company GSK Biologicals SA 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 19 July 2018 and concerns a first-time-in human phase I clinical trial involving the administration of HBV viral vectored vaccines to chronic Hepatitis B patients.

♦ 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 24-08-2018 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

Have not evaluated this item.

2. INFORMATION RELATED TO THE VECTOR

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

Comment 1

Has evaluated this item and has no questions/comments.

Comment 2

Have not evaluated this item.

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

Have not evaluated this item.

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 processing of the HBc-HBs fusion into separate protein antigens. Does this protease cleave other host proteins?

Comment coordinator :

See Donnelly *et al*., 2001. The P2 portion in the picornavirus genome encodes three mature viral proteins, namely 2A, 2B, and 2C (Fig. 1). 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 $3C^{pro}$ or $3CD^{pro}$.
Hence the question raised in comment 2 must not be retained.

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?

SBB comment :

Indeed, on p17 of annex IIIA the notifier states 'The ChAd155 vector is replication-deficient and only whereas in section II.2 of Annex II it is mentioned that GLP toxicology studies were performed in animals evaluating the ChAd155-hIi-HBV candidate. It is not clear whether these studies were indicative to conclude on lack of replication in animal species. The applicant is requested to comment on the studies that could substantiate the lack of replication in other animal species.

Comment coordinator :

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

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

Two questions:
- the dilution and retrieve of vaccine from the vial are manipulations that could create aerosols. How does the applicant limit the personal exposition to these aerosols potentially containing the GMO vaccine, as he does not use a biosafety cabinet for vaccine preparation?
- the bandage is removed from the administration site of the patient after 30 minutes in the hospital centre and is disposed of as a biohazard waste. Then, patient will discard the bandage as a normal waste at home. Is the applicant sure that no more GMO will be present in the bandage at that time?

SBB comment :

The notifier indicated that local inflammatory reaction is the most likely reaction to occur following intramuscular injection of the MVA- vectored GMO. Hence further instructions for the patients in regards removal and disposal of bandages may be considered.

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 very low risk of shedding of ChAd155-hli-HBV into the environment. We cannot consider that there is no shedding because this vector has never been use in human clinical trials (one clinical trial was performed but we do not have any results concerning the shedding).
Could the applicant consider the risk of shedding?
The applicant says that there is no shedding after administration of another recombinant vector ChAd3) expressing HCV transgene NSmut. The applicant says that ChAd155 is closely related to ChAd3 but he does not justify by sequencing or by a reference.

SBB suggestion:

For rephrasing ‘risk of shedding’: could the applicant elaborate on the probability of shedding and the risks associated to the consequences of shedding should it occur.

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

Page 38/39 of document ‘2017-001452-55_Annex IIIA_Th HBV_ChAd155-hIi-HBV_V1 (May-2018)’ states that adenoviruses are endemic in the pediatric population; epidemics and outbreaks with higher morbidity and mortality can also occur. Clinical manifestations in immunocompromised patients include pneumonia, hepatitis, hemorrhagic cystitis, colitis, pancreatitis, meningoencephalitis, and disseminated disease, depending on the underlying disease, affected organ system, patient age, and virus serotype. However the GMO recipient is a simian-derived adenovirus backbone, and the GMO itself is not expected to be pathogenic in immunocompetent or immunocompromised humans since the encoded transgene is not pathogenic.

The argument in the previous, last sentence, that the GMO itself is not expected to be pathogenic in immunocompetent or immunocompromised humans, because the transgene(s) are not pathogenic, is not correct or insufficiently worked out. The fact, that the GMO recipient has an engineered replication-defective simian-derived adenoviral backbone prevails the establishment of a propagative infection both in immunocompetent and immunocompromised humans. This is of course a very important argument next to the transgene(s) themselves not being pathogenic to expect the GMO to be non-pathogenic.

Comment 2

Have not evaluated this item.

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

Have not evaluated this item.

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

Have not evaluated this item.

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

Have 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

Have 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

Have 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

Have not evaluated this item.

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

Same questions as point 4 : no BSC and discard of bandage as normal waste.

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

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

Comment 1

Of the two GMOs to be used as a vaccine, the recombinant vaccine vector Modified Vaccinia Ankara-HBV is an enveloped replication-defective virus, of which it indeed can be expected to be become efficiently inactivated by treatment with 70% ethanol in case of accidental spilling (Rabenau *et al*., 2010) For the recombinant vaccine vector ChAd155-hIi-HBV being a non-enveloped adenoviral vector this is questionable, although the document 'Biosafety instructions for site staff' suggests to use 70% ethanol in case of spilling ("In case of spilling of the vaccine/sample, the area should be decontaminated with 70% ethanol-soaked cloth with a minimal contact time of 1 min."). 70% ethanol has virucidal acivity against adenoviruses, but is probably only efficient after prolonged exposure times (see e.g. https://digitalcommons.usu.edu/biology_posters/140/). Furthermore, there might be strain-related differences with respect to sensitivity (Iwasawa *et al*., 2012). Anyhow, laboratory protocols and biosafety guides for using adenoviral vectors state clearly that ethanol is not suitable to inactivate adenoviruses adequately (https://ehs.research.uiowa.edu/adenovirus-and-adenoviral-vectors, https://www.addgene.org/biosafety/). The document 'Biosafety instructions for site staff' should be updated and state clearly that in case of ChAd155-hIi-HBV suitable disinfectants like Virkon S, Umonium spray or a 1% solution of sodium hypochlorite should be used.

Comment coordinator :

Ethanol is not considered an effective agent to disinfect adenovirus

Adenovirus susceptible to: 0.5% Sodium hypochlorite, 2% Glutaraldehyde, 5% Phenol, or Autoclave for 30 minutes at 121°C under 15 lbs. Biosafety instructions should preferentially be adapted

Comment 2

Have 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

Have evaluated this item and has no questions/comments.

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

Have not evaluated this item.

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

Document "2017-001452-55_Annex II_Th HBV_ChAd155-hIi-HBV_V1"

Page 7, table 1: high and low dose mistakenly swapped

Document "2017-001452-55_Annex IIIA_Th HBV_ChAd155-hIi-HBV_V1 (May-2018)"

Page 36: safety concerns (Baerlecken et al, 2014; Barliakos et al, 2014)**Error! Reference source not found.**.: refer correctly to two different papers by Baerlecken *et al.*, 2014

Page 49: With regard the techniques for detecting transfer of the donated genetic material to other organisms, would it not be more relevant to carry out a PCR detection, as described on p23 ?

Page 40, table 1: high and low dose mistakenly swapped

Page 46: first sentence: 'replication' should be 'replication-defective'

Page 47: Significance of the asterisk in “Chronically Hepatitis B infected subjects* adherent to entecavir or tenofovir treatment given as per approved label/dosage as a first course of HBV oral therapy for least 30 months”?

Page 50: With regard the methods for decontamination of the areas affected ‘ *the GMO is replication-defective and susceptible to most common disinfectants. All surfaces will be disinfected using appropriate means’*. It might be more appropriate to be more specific based on tests for inactivation

Page 51: information is missing (“The safety holding rules which will be assessed by the iSRC are defined in **Error! Reference source not found..**”)

Document “2017-001452-55_Annex IIIA_Th HBV_MVA-HBV_ V1 (May-2018)”

Page 41: Does the asterisk in “Chronically Hepatitis B infected subjects* adherent to entecavir or tenofovir treatment given as per approved label/dosage as a first course of HBV oral therapy for least 30 months” refer to the next sentence in italics?

Page 48: information is missing (“The safety holding rules which will be assessed by the iSRC are defined in .”)

Comment 2
None

References

Donnelly, M. L., G. Luke, A. Mehrotra, X. Li, L. E. Hughes, D. Gani and M. D. Ryan (2001). Analysis of the aphthovirus 2A/2B polyprotein 'cleavage' mechanism indicates not a proteolytic reaction, but a novel translational effect: a putative ribosomal 'skip'. Journal of General Virology, 82, 1013-1025.

Iwasawa A, Niwano Y, Kohno M, Ayaki M (2012). Virucidal activity of alcohol-based hand rub desinfectants. Biocontrol Sci. 12(1): 45-49.

Rabenau HF, Rapp I and Steinmann J (2010). *Can Vaccinia virus be replaced by MVA virus for testing virucidal activity of chemical desinfectants ?* BMC Infectious Diseases 2010, 10:185.