Boehringer Ingelheim

Boehringer Ingelheim (Schweiz) GmbH

Prevexxion® RN

Prevexxion® RN + HVT + IBD

Documents for the involvement of federal offices and committees

IVI request dated 21.01.2022

Proprietary confidential information

Proprietary confidential information © 2022 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

Our ref : HEG/SK/CH.Bio22.D1010

© 2022 Boehringer Ingelheim International GmbH or one or more of its affiliated companies. All rights reserved. This document may not – in full or in part – be passed on, reproduced, published or otherwise used without prior written permission.

INTRODUCTION

On 11. June 2021, Boehringer Ingelheim (Schweiz) GmbH has submitted marketing authorization applications (MAA) for the poultry vaccines Prevexxion® RN and Prevexxion® RN+HVT+IBD to the Institute for Virology and Immunology (IVI).
These two products contain genetically modified organisms (GMO).

In accordance with Art 43 of the Ordinance on the Handling of Organisms in the Environment (Release Ordinance, RO, SR 814.911), legislation requires the involvement of federal offices and committees in the authorization of placing on the market of GMOs. The IVI, as the competent licensing authority, is responsible for organizing this consultation.

The consultation of the other specialist agencies can be organized as soon as the licensing authority (IVI) has received a complete application. Art. 28, para. 2 of the Release Ordinance regulates which information must be included in the application in order for it to be complete. IVI has assessed the two MAA with respect to the requirements according to Art 28 RO and has provided the applicant with a list of the required documents and their questions related to them.

The applicant is requested to submit the responses to these questions as well as a dossier containing all documents required according to art 28 RO until 21.04.2022

Proprietary confidential information © 2022 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

Our ref : HEG/SK/CH.Bio22.D1010

DOCUMENTS REQUIRED ACCORDING TO ART.28, RELEASE ORDINANCE, SR 814.911

a) Art 28, point a: a technical dossier containing the information in accordance with Annexes IIIA and IV of the Directive 2001/18/EC
→ dossier part 3.e.3

Question 1

Obtain the company's consent to forward part 3e for the consultation of the federal offices/specialist agencies and to compile the dossier for the office consultation.

Applicant's response

The applicant considers that part 3.e of this registration dossier is confidential and cannot be transmitted further. Instead, the applicant provides the EPAR (European Public Assessment Report) from EMA which contains on pages 21 to 22 the environmental risk assessment for products containing or consisting of genetically modified organisms.

b) Art 28, point b: the results of previous experiments using the same organisms concerning hazards to human beings or the environment, or impairments caused to the same, in particular, experiments in contained systems or, possibly, field trials
→ Expert statement: part 3e, critical summary page 14

Question 2

Obtain the company's consent to forward part 3e for the consultation of the federal offices/specialist agencies and to compile the dossier for the office consultation.

Applicant's response

The applicant considers that part 3.e of this registration dossier is confidential and cannot be transmitted further. Instead, the applicant provides the EPAR (European Public Assessment Report) from EMA which contains on pages 21 to 22 the environmental risk assessment for products containing or consisting of genetically modified organisms.

Proprietary confidential information © 2022 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

Our ref : HEG/SK/CH.Bio22.D1010

c) Art 28, point c: if available, any licences and evaluations from Swiss and foreign authorities for experimental releases and marketing of the same organisms

i. ANSES: EC-17-019 (PHN3257 (trial No. 16.0200.P)): 10.01.2017 -> PART CH 1a1, annex 5
ii. ANSES: EC-17-020 (PHN3257 (trial No. 16.0201.P)): 10.01.2017 -> PART CH 1a1, annex 5
iii. ANSES: EC-17-021 (PHN3257 (trial No. 16.0202.P)): 10.01.2017 -> PART CH 1a1, annex 5
iv. dossier Part 3.e.2: directorate general for research and innovation, dated 23.01.2013

Assessment of foreign authorities for placing on the market:
i. CVMP on the granting of a marketing authorization -> part CH 1a3, 4
ii. CVMP assessment report (20.05.2020) -> part CH 1a3, 3

Question 3

Obtain the company's consent to forward above-mentioned documents for the consultation of the federal offices/specialist agencies and to compile the dossier for the office consultation.

Applicant's response

The applicant agrees to the use of the above-mentioned documents for the consultation of the federal offices/specialist agencies and provides herewith a dossier containing all documents required for this consultation.

d) Art 28, point d: a risk determination and assessment in accordance with Annex 4
➔ Expert statement: part 3e, critical summary

Question 4

Clarify whether **Expert statement: part 3e, critical summary** can be used or whether risk identification and assessment must be recompiled.

Applicant's response

The applicant considers that part 3.e and the critical summary of this registration dossier are confidential and cannot be transmitted further. Instead, the applicant provides the EPAR (European Public Assessment Report) from EMA.

Proprietary confidential information © 2022 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

Our ref : HEG/SK/CH.Bio22.D1010

e) Art 28, point e: a monitoring plan to show how the applicant will examine whether the assumptions of the risk determination and assessment in accordance with Annex 4 are correct and whether the measures to adhere to the principles of Article 6 paragraphs 1 and 3 and Art. 7 GTA are sufficient, and which contains at least the following details:
1. the type, specificity, sensitivity and reliability of the methods,
2. the duration and frequency of the monitoring

Question 5
Establish a monitoring plan in accordance with Art 28, point e

Applicant's response

Information on the monitoring plan in accordance with Art.28 point e is described in part 3e.3.V.A (page 33-34).

V. INFORMATION ON MONITORING, CONTROL, WASTE TREATMENT AND EMERGENCY RESPONSE PLANS

A. MONITORING TECHNIQUES

1. METHODS FOR TRACING THE GMOS, AND FOR MONITORING THEIR EFFECTS

As a veterinary vaccine, PHN3257 is subject to the regulations for medicinal products for veterinary use. It must be prescribed by a veterinary surgeon only.

In the field, the GMOs may be detected and/or quantified by the following methods:

- Polymerase chain reaction (PCR): a classical and/or real time PCR can be used to detect specifically vHVT013 (Lemière *et al.*, 2009) and RN1250 (technique No. 200815). These tests are the methods of choice to detect specifically the two GMOs. These tests can be done on total DNA extracted from feather follicles or from blood or spleen leucocytes from suspected animals. It may also be done from poultry house dust (Islam *et al.*, 2006).
- Antibody detection by ELISA: vHVT013 is inducing antibodies against IBDV VP2 that can be detected by a commercial ELISA (Synbiotics Proflok plus IBD) or by seroneutralisation; it can also induce antibodies detected by the classical IBDV ELISA commercial kit but the antibody titer is lower since this kit detects mainly anti-VP3 IBDV antibodies (see below, section 3.E.3.V.A.2. and Prandini *et al.*, 2008). Antibodies against RN1250 are not easily detectable.
- vHVT013 and RN1250 may be isolated by culture on chicken embryo fibroblasts (according to techniques No. 15007 and 200831). Moreover vHVT013 can be specifically identified by immunofluorescence (according to techniques No. 200832 and 002154). The last method is carried out using a monospecific anti-HVT chicken serum, a specific monoclonal anti-VP2 antibody, and their respective immunoconjugate with two different fluorescent stainings (producing respectively a red and green fluorescence). PCR and sequencing can be further applied on isolated virus samples to confirm the identity of both viruses.

2. SPECIFICITY (TO IDENTIFY THE GMOS AND TO DISTINGUISH THEM FROM THE DONOR, RECIPIENT OR, WHERE APPROPRIATE, THE PARENTAL ORGANISMS) SENSITIVITY AND RELIABILITY OF THE MONITORING TECHNIQUES

The classical PCR used as the RN1250 identity test is specific for LTR insertion into RN1250; it can also detect the presence of the parental virus at a concentration as low as 1% compared to RN1250 (technique No. 200815). To further confirm that the virus is RN1250 and not a wild type MDV virus into which the LTR insert was transferred by homologous recombination, sequencing data will have to be obtained from the UL region in these genomic area known to be different between the vaccine CVI988 strain and the wild type MDV strains (Spatz and Silva, 2007).

A real time PCR specific of vHVT013 has been developed by Merial (Lemière *et al.*, 2009). It can be applied on different samples. Feathers are samples that can be easily collected; vHVT013 virus load peaks at 28 days post-vaccination in the feathers follicles (Cupillard *et al.*, 2008).

Another real time PCR specific of RN1250 has been developed (technique No. 200867) and can be used on different samples as well.

In addition, the control technique No. 200027 is based on a real time PCR that can specifically detect the three serotypes of Marek's disease virus (serotype 1 or Gallid herpesvirus 2; serotype 2 or Gallid herpesvirus 3; serotype 3 or Meleagrid herpesvirus 1 (or HVT)). vHVT013 as well as its parent HVT will be positive for serotype 3 PCR only and RN1250 as well as its parent CVI988 will be positive for serotype 1 PCR only. Additional more specific PCR described above can be then applied to make the difference between the parental viruses and the GMOs.

The already described technique No. 002154 is specific, sensitive, and reliable (see section 3.E.3.II.C.2). It is based on a double immunofluorescence assay using a monospecific anti-HVT chicken serum and an IBD VP2 specific monoclonal antibody, and it enables to distinguish vHVT013 from the parental organism. From the field, serological techniques enable to distinguish between IBDV antibodies induced by classical vaccination, and VP2 specific antibodies induced by vHVT013. Indeed, vHVT013 administration induces a strong positive response with VP2 specific ELISA test, and a reduced, if not absent, response with classical IBDV ELISA commercial kits (they are not related specifically to VP2, but also to other proteins such as VP3; VP2 is well known for its neutralising properties). Results obtained with VP2 ELISA kit are significantly related to those obtained with seroneutralisation technique (report 99.111.R). Another study has shown that the combined use of two ELISA kits (PROFLOK IBD Ab test and an "improved" kit, PROFLOK Plus IBD Ab test, which allows a more accurate detection of IBDV protective VP2 antibodies) enables differentiation between chickens vaccinated with VAXXITEK HVT+IBD from birds naturally infected or vaccinated with IBD modified-live vaccines (MLVs) (intermediate and intermediate plus): VAXXITEK HVT+IBD vaccinated chickens had low antibody titres using PROFLOCK IBD Ab test and high antibody titres (usually >4000) using PROFLOCK Plus IBD Ab test after 3 to 4 weeks of age. In contrast, chickens infected by IBDV or vaccinated with MLVs had high antibody titres with both tests after 6 weeks of age (Prandini *et al.*, 2008).

3. TECHNIQUES FOR DETECTING TRANSFER OF THE DONATED GENETIC MATERIAL TO OTHER ORGANISMS

The methods of choice for detecting potential transfer of the donated genetic material from the GMO to other organisms will be PCR. As mentioned above, several techniques are available. To differentiate between RN1250 and a wild type MDV virus with the transferred LTR, sequencing data will have to be obtained from the UL region in these genomic areas known to be different between the vaccine CVI988 strain and the wild type MDV strains (Spatz and Silva, 2007).

The transfer of vHVT013 insert into a wild type HVT by homologous recombination could potentially be detected by sequencing the genome of the suspect virus and compare its sequence to vHVT013 and other HVT sequences.

4. DURATION AND FREQUENCY OF THE MONITORING

The follow-up will be done through the Merial Pharmacovigilance department who will collect and analyse the reports of unexpected events linked to the use of this vaccine. Regular assessments will be performed and periodic safety update reports written, in accordance with the regulation in force.

Proprietary confidential information © 2022 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

Our ref : HEG/SK/CH.Bio22.D1010

f) Art 28, point f: an evaluation of interests in accordance with Article 8 GTA that shows that the genetic modification of the genetic material of animals or plants has not failed to respect the dignity of living beings

Question 6

Establish an evaluation of interests in accordance with Art 28, point f.

Applicant's response

According to the applicant's understanding, point f is applicable only to genetic modifications in animals or plants. The current application concerns the genetic modification of a virus and point f is therefore not applicable.

g) Art 28, point g: a proposal for the labelling (Art. 10), informing the recipients (Art. 5), and for any packaging of the organisms

Question 7

Art 27, VAM: add the corresponding declaration to the packaging elements and the information for professionals and re-submit these elements.

Applicant's response

GMO declaration has been added to the information for professionals and the updated text is provided with this response in pdf and word format.
On the vial label, however, there is not enough space for adding any text, we apply for a "blister-version" for the vial label.

Proprietary confidential information © 2022 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

Our ref : HEG/SK/CH.Bio22.D1010

h) Art 28, point h: proof that the liability guarantee has been fulfilled

Question 8
h) proof that the liability guarantee has been fulfilled must be provided

Applicant's response

According to the applicant's understanding, extra liability guarantees are usually required in the context of clinical trials. In Switzerland, no studies have been carried out with Prevexxion RN or Prevexxion RN+HVT+IBD and the product will not be used in Switzerland before obtention of the marketing authorizations. However, any damages due to an approved product would then fall under normal corporate liability.