Committee for Risk Assessment (RAC)

Committee for Socio-economic Analysis (SEAC)

Opinion

on an Application for Authorisation for

4-(1,1,3,3-tetramethylbutyl)phenol, ethoxylated

(4-tert-OPnEO)

for

The use of 4-tert-OPnEO as a lysing agent for the permeabilization of the host cell membrane to release adenovirus particles used for the manufacture of vaccines. Its use allows the selective elimination of enveloped adventitious viruses and is compatible with the chemicals needed to control the host cell DNA precipitation in the next process step

Submitting applicant: Janssen Vaccines & Prevention BV

Co-applicant: Janssen Biologics B.V.

ECHA/RAC/SEAC: AFA-O-0000006710-79-01/D

Consolidated version

Date: 24/02/2020

Consolidated version of the Opinion of the Committee for Risk Assessment and Opinion of the Committee for Socio-economic Analysis on an Application for Authorisation

Having regard to Regulation (EC) No 1907/2006 of the European Parliament and of the Council 18 December 2006 concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals (the REACH Regulation), and in particular Chapter 2 of Title VII thereof, the Committee for Risk Assessment (RAC) and the Committee for Socio-economic Analysis (SEAC) have adopted their opinions in accordance with Article 64(4)(a) and (b) respectively of the REACH Regulation with regard to the following application for authorisation:

Applicant(s)[1]	**Janssen Vaccines & Prevention B.V.** (position in supply chain: downstream) **Janssen Biologics B.V.** (position in supply chain: downstream)
Substance ID EC No CAS No	**4-(1,1,3,3 - tetramethylbutyl) phenol, ethoxylated (4-tert-Octylphenol ethoxylates) (4-tert-OPnEO)** - -
Intrinsic properties referred to in Annex XIV	☐ Carcinogenic (Article 57(a)) ☐ Mutagenic (Article 57(b)) ☐ Toxic to reproduction (Article 57(c)) ☐ Persistent, bioaccumulative and toxic (Article 57(d)) ☐ Very persistent and very bioaccumulative (Article 57(e)) ☒ Other properties in accordance with Article 57(f) - effects to the environment
Use title	**4-tert-Octylphenol ethoxylate is used as a lysing agent for the permeabilization of the host cell membrane to release adenovirus particles used for the manufacture of vaccines. Its use allows the selective elimination of enveloped adventitious viruses and is compatible with the chemicals needed to control the host cell DNA precipitation in the next process step**
	Other connected uses:
	Same uses applied for:
Use performed by	☒ Applicant(s) ☐ Downstream User(s) of the applicant(s)

[1] 'Applicant(s)' - includes also 'Authorisation Holder(s)' in case of the review report

Use ID (ECHA website)	0169-01
Reference number	11-2120815841-57-0001 11-2120815841-57-0002
RAC Rapporteur RAC Co-rapporteur	DUNAUSKIENĖ Lina -
SEAC Rapporteur SEAC Co-rapporteur	LÜDEKE Andreas VASILIŪNĖ Žiedūna
ECHA Secretariat	REGIL Pablo NOGUEIRO Eugénia FIGUIERE Romain LUDBORŽS Arnis

PROCESS INFORMATION FOR ADOPTION OF THE OPINIONS

Date of submission of the application	30/05/2019
Date of payment, in accordance with Article 8 of Fee Regulation (EC) No 340/2008	25/07/2019
Application has been submitted by the Latest Application Date for the substance and applicant(s) [and their DUs] can benefit from the transitional arrangements described in Article 58(1)(c)(ii).	☒ Yes ☐ No
Public Consultation on use, in accordance with Article 64(2): https://echa.europa.eu/applications-for-authorisation-previous-consultations	14/08/2019-09/10/2019
Comments received	☐ Yes ☒ No Link:
Request for additional information in accordance with Article 64(3)	On 16/09/2019 Link: https://echa.europa.eu/applications-for-authorisation-previous-consultations/-/substance-rev/23848/del/200/col/synonymDynamicField_302/type/asc/pre/2/view
Trialogue meeting	21/10/2019
Extension of the time limit set in Article 64(1) for the sending of the draft opinions to the applicant(s)	☐ Yes ☒ No
The application included all the necessary information specified in Article 62 that is relevant to the Committees' remit.	☒ Yes ☐ No Comment:
Date of agreement of the draft opinion in accordance with Article 64(4)(a) and (b)	RAC: 05/12/2019, agreed by consensus
	SEAC: 05/12/2019, agreed by consensus.
Date of sending of the draft opinion to applicant(s)	07/02/2020

Date of decision of the applicants not to comment on the draft opinion, in accordance with Article 64(5)	24/02/2020
Date of receipt of comments in accordance with Article 64(5)	Not relevant
Date of adoption of the opinion in accordance with Article 64(5)	RAC: 24/02/2020, adopted by consensus.
	SEAC: 24/02/2020, adopted by consensus.
Minority positions	RAC: ☒ N/A
	SEAC: ☒ N/A

THE OPINION OF RAC

RAC has formulated its opinion on:

- the risks arising from the use applied for,
- the appropriateness and effectiveness of the risk management measures described,
- other available information.

In this application, the applicant did not derive PNEC(s). Therefore, RAC concluded, in accordance with Annex I of the REACH Regulation, that for the purposes of the assessment of this application it was not possible to determine PNEC(s) for the endocrine disrupting properties for the environment of the substance.

SEAC concluded that currently there are no technically and economically feasible alternatives available for the applicant(s) with the same function and similar level of performance. Therefore, RAC did not evaluate the potential risk of alternatives.

RAC concluded that the operational conditions and risk management measures described in the application are expected to be appropriate and effective in limiting the risk, provided that they are implemented and adhered to. The use applied for may result in emissions which will, in effect, be zero kg per year of the substance to the environment.

THE OPINION OF SEAC

SEAC has formulated its opinion on:

- the socio-economic factors, and
- the suitability and availability of alternatives associated with the use of the substance as documented in the application, as well as
- other available information.

SEAC took note of RAC's conclusion that it is not possible to determine a PNEC for the endocrine disrupting properties to the environment of the substance in accordance with Annex I of the REACH Regulation.

- The following alternatives are being assessed: Alkyl ethoxylates, Polysorbates, Alkyl glucosides.

SEAC concluded on the analysis of alternatives and the substitution plan that:

- By the Sunset date there are no alternatives available with the same function and similar level of performance that are safer and technically and/or economically feasible for the applicants.
- The substitution plan was credible and consistent with the analysis of alternatives and the socio-economic analysis.

SEAC concluded on the socio-economic analysis that:

- The expected socio-economic benefits of continued use to the applicant are at least €100-1 000 million per year and additional benefits to society have been assessed qualitatively but have not been monetized. These additional benefits comprise revenues for the applicant's suppliers of raw materials and services, as well as stable employment of the applicant's workers in R&D, production, and marketing. Some of the products (vaccines) provide for an unmet medical need which will benefit society.

- Considering
    - the endpoint relevant for listing the substance in Annex XIV of REACH
    - the monetised risk of continued use is €0 per year

Risks to the environment of alternatives have not been quantified. SEAC has no substantial reservations on the quantitative and qualitative elements of the applicant's assessment of the benefits and the monetised risks to the environment associated with the continued use of the substance.

SEAC considered that if an authorisation was refused, the use of the substance could:

- cease altogether

Furthermore, SEAC considered that, if an authorisation was refused, in the European Union

- 10 to 100 jobs could be lost

PROPOSED CONDITIONS AND MONITORING ARRANGEMENTS, AND RECOMMENDATIONS

No conditions or monitoring arrangements are proposed.

No recommendations for the review report are made.

REVIEW PERIOD

Taking into account the information provided in the application for authorisation submitted by the applicants and the comments received on the broad information on use, a **12-year** review period is recommended for this use.

SUMMARY OF THE USE APPLIED FOR

Role of the applicants in the supply chain	Upstream ☐ [group of] manufacturer[s] ☐ [group of] importer[s] ☐ [group of] only representative[s] ☐ [group of] formulator[s] Downstream ☒ downstream users
Number and location of sites covered	One location. Janssen Vaccine Launch facility (VLF) in Leiden (the Netherlands).
Annual tonnage of Annex XIV substance used per site (or total for all sites)	0.27 tons/year. Future use.
Function(s) of the Annex XIV substance	*Primary function:* cell lysis. 4-tert-OPnEO is used as a selective lysing agent, which permeates the outer cell membranes of the cells but not the membranes around the cell nucleus. *Secondary function:* adventitious virus elimination, i.e. the presence of 4-tert-OPnEO eliminates viruses that have a lipidic envelope and reduces the chance of a harmful or undesirable adventitious virus being present in the vaccine. *Tertiary function:* complementary function with other essential chemicals such as detergent domiphen bromide that is used during DNA precipitation following the lysis step.
Type of products (e.g. articles or mixtures) made with Annex XIV substance and their market sectors	Production of vaccines based on adenoviruses (e.g. HIV, Ebola, Zika, HPV, RSV vaccines).
Shortlisted alternatives discussed in the application	Alternative substances considered: non-ionic surfactants of: Alkyl ethoxylates, Polysorbates, and Alkyl glucosides nature
Annex XIV substance present in concentrations above 0.1 % in the products (e.g. articles) made	☐ Yes ☒ No ☐ Unclear ☐ Not relevant

Releases to the environmental compartments	☐ Air ☐ Water ☐ Soil ☒ None
All endpoints listed in Annex XIV were addressed in the assessment	☒ Yes ☐ No if 'No' – which endpoints are not addressed
All relevant routes of exposure were considered	☐ Yes ☐ No ☒ Not relevant
Adequate control demonstrated by applicant(s) for the relevant endpoint(s)	☐ Yes ☐ No ☒ Not Applicable – non-threshold substance
Level of (combined, daily / shift-long) exposure/release used by applicant(s) for risk characterisation	<u>Environment:</u> No releases claimed by the applicants Air: 0 Water: 0 Soil: 0
Applicants are seeking authorisation for the period of time needed to finalise substitution ('*bridging application*')	☐ Yes ☐ No ☒ Unclear The applicants refer to this application as a "bridging application to allow the applicants to go through all the necessary qualification processes to implement the substitute. However, this is not considered to be a bridging application by RAC and SEAC as the applicants have not yet identified and started to test/implement a suitable alternative.
Review period argued for by the applicants (length)	15 years
Most likely Non-Use scenario	This application is for a future use, therefore such a use would not be viable until the implementation of a valid alternative. Therefore the non-use scenario considered is the delayed start of commercial production.
Applicants conclude that benefits of continued use outweigh the risks of continued use	☒ Yes ☐ No

	☐Not Applicable – threshold substance with adequate control
Applicants' benefits of continued use	€100-1 000 million (annualised) €1 billion-10 billion (for the review period argued)
Society's benefits of continued use	€1-10 million (annualised) €10-50 million (for the review period argued):
Distributional impacts if authorisation is not granted	€1 billion-10 billion (for the review period argued)
Job loss impacts if authorisation is not granted	10-100 loss

SUMMARY OF RAC AND SEAC CONCLUSIONS[2]

1. Operational Conditions and Risk Management Measures

1.1. Conclusions of RAC

Conclusion for environment

The use of 4-tert-OPnEO is reported to be handled in rigorous containment (closed system). All activities with the substance - except sample analysis and sample storage - are intended to be conducted in the BSL-2 area of the facility, which is completely separated from both the rest of the production facility and the outside environment.

RAC concludes that the operational conditions (OCs) and risk management measures (RMMs) in the exposure scenario (ES) for this future use are expected to be appropriate and effective in limiting the risk, provided they are implemented and adhered to.

Are the OCs/RMMs in the Exposure Scenario appropriate and effective in limiting the risk?

☒ Yes ☐ No

Are additional conditions related to the operational conditions and risk management measures proposed for the authorisation?

☐ Yes ☒ No

Does RAC recommend to the applicant(s) monitoring arrangements [and adjustment of RMMs] relevant to the potential review report?

☐ Yes ☒ No

2. Exposure Assessment

Releases to the environmental compartments

Air: No emissions
Water: No emissions
Soil: No emissions

Conclusions of RAC:

All solid and liquid waste and wastewater that may be contaminated with 4-tert-OPnEO is collected for incineration. The emissions to air are expected to be zero, considering the relatively low vapour pressure of 4-tert-OPnEO and the level of containment in the processes (largely in closed system).

RAC considers that the applicants have provided enough information to demonstrate that releases to environment would be prevented as far as technically and practically possible and in effect will be zero.

[2] The numbering of the sections below corresponds to the numbers of the relevant sections in the Justifications.

Conclusions of RAC:

Does RAC propose additional conditions[3] related to exposure assessment for the authorisation?

☐Yes ☒No

Does RAC recommend to the applicant(s) monitoring arrangements[4] relevant to the potential review report?

☐Yes ☒No

3. Risk Characterisation

Conclusions of RAC:

Based on the OCs & RMMs in the ES, notably the use of 4-tert-OPnEO in closed systems and collection and incineration of all process waste water and disposable solids, RAC is of the view that the applicants have demonstrated that releases to environmental compartments will be prevented after 2020 and in this case, it can be concluded that the likelihood of adverse effects caused by 4-tert-OPnEO will, in effect, be zero.

4. Analysis of alternatives and substitution plan[5]

What is the amount of substance that the applicant uses per year for the use applied for?

270 kg

Are there alternatives with the same function and similar level of performance that are technically and economically feasible to the applicant before the Sunset Date?

☐Yes ☒No

Has the applicant submitted a substitution plan?

☒Yes ☐No

[3] Conditions can be proposed where RCR is > 1, OCs and RMMs are not appropriate and effective, risk is not adequately controlled, minimisation of emissions is not demonstrated.

[4] Monitoring arrangements can be recommended where RCR is < 1, OCs and RMMs are appropriate and effective, risk is adequately controlled, minimisation of emissions is demonstrated – but minor concerns were identified.

[5] The judgment of the ECJ Case T-837/16 Sweden v Commission stated that the applicant has to submit a substitution plan if alternatives are available in general. The Commission is currently preparing the criteria, derived from the judgment for establishing when an alternative is available in general. Once these are prepared this opinion format will be amended accordingly. The European Commission informed the REACH Committee in 9-10 July 2019 of its preliminary views on the criteria. In that note that Commission considered that the criteria defining a 'suitable alternative' would imply that it was i) *safer* and ii) *suitable*. Suitability would not mean it to be *"in abstracto"* or "*in laboratory or exceptional conditions*" but it should be "*technically and economically feasible in the EU*" and "*available, from the point of view of production capacities of the substance or feasibility of the technology, and legal and factual conditions for placing on the market*".

If yes, is the substitution plan credible and consistent with the analysis of alternatives and the socio-economic analysis?

☒Yes ☐No

Conclusions of SEAC

By the Sunset date there are no alternatives available with the same function and similar level of performance that are safer and technically and/or economically feasible for the applicants.

SEAC finds the substitution plan presented by the applicants credible, with well described phases and timelines for completion. However, uncertainties on the successful execution of the relevant phases within the timelines envisaged in the applicants' AoA and substitution plan, exist.

Does SEAC propose any additional conditions or monitoring arrangements related to the assessment of alternatives for the authorisation?

☐Yes ☒No

Does SEAC make any recommendations to the applicants related to the content of the potential review report?

☐Yes ☒No

5. Benefits and risks of continued use

Have the applicants adequately assessed the benefits and the risks of continued use?

Conclusions of SEAC:

☒Yes ☐No

SEAC has no substantial reservations on the quantitative and qualitative elements of the applicants' assessment of the benefits and the risks to the environment associated with the continued use of the substance. This conclusion is made on the basis of:

- the application for authorisation,
- SEAC's assessment of the benefits of continued use,
- any additional information provided by the applicants,
- RAC's assessment of the risks to the environment

6. Proposed review period for the use

☐ 4 years

☐ 7 years

☒ 12 years

☐ Other – … years

7. Proposed additional conditions for the authorisation

RAC

Additional conditions:

For workers	☐ Yes	☒ No
For Humans via Environment	☐ Yes	☒ No
For consumers	☐ Yes	☒ No
For the environment	☐ Yes	☒ No

SEAC

Additional conditions: ☐ Yes ☒ No

8. Proposed monitoring arrangements for the authorisation

RAC

Monitoring arrangements:

For workers	☐ Yes	☒ No
For Humans via Environment	☐ Yes	☒ No
For consumers	☐ Yes	☒ No
For the environment	☐ Yes	☒ No

SEAC

Monitoring arrangements	☐ Yes	☒ No

9. Recommendations for the review report

RAC

For workers	☐ Yes	☒ No
For consumers	☐ Yes	☒ No
For the environment / HvE	☐ Yes	☒ No

SEAC

AoA	☐ Yes	☒ No
SP	☐ Yes	☒ No
SEA	☐ Yes	☒ No

10. Applicant(s) comments on the draft opinion

Have the applicants commented the draft opinion?

☐Yes ☒No

Have actions been taken resulting from the analysis of the applicants' comments?

☐Yes ☐No ☒ Not applicable

JUSTIFICATIONS

0. Short description of use

Janssen Vaccines & Prevention B.V. and Janssen Biologics B.V. applied for the future use of 4-tert-OPnEO as a lysing agent for the 'permeabilization' of the host cell membrane to release adenovirus particles used for the manufacture of vaccines. Its use allows the selective elimination of enveloped adventitious viruses and is compatible with the chemicals needed to control the host cell DNA precipitation in the next process step. The substance will be used in a newly built Janssen Vaccine Launch facility (VLF) in Leiden (the Netherlands). The total anticipated maximum usage of 4-tert-OPnEO in the facility is envisaged to be 270 kg/year.

0.1 Description of the process in which Annex XIV substance is used

4-tert-OPnEO is used as a processing agent in the production of the adenovirus-based vaccines. The overall vaccine production process involves 10 stages; the process starts with the growth of the required cells (stage 1 and 2). Subsequently the cells are infected in order to produce the vaccine-specific adenovirus (stage 3). When this process is completed, the virus particles are extracted. This extraction takes place through a process called cell lysis, which requires the use of 4-tert-OPnEO. Following a development program, as well as the production of clinical trial materials, the applicants will start the commercial production in a closed system. Although the Adenovirus particles produced in Janssen's facility are replication incompetent and do not pose health risks, the adenovirus drug substance produced is considered a biosafety level 2 biological agent (BSL-2). The BSL-2 part of the manufacturing plant where OPnEO is used in the process, is completely segregated from the outside environment with a dedicated sewage system, which contains an obligatory heat treatment (Biokill) system. Therefore, requirements set in Directive 2009/41/EC on the contained use of genetically modified micro-organisms (BSL-2 regulations) are followed in the design and operation of the facility. All activities with 4-tert-OPnEO - except for sample analysis and sample storage - are conducted in the BSL-2 area of the facility. 4-tert-OPnEO is used in closed processes in accordance with the use conditions set out in the CSR. 4-tert-OPnEO is not present in the final products, unless it is an impurity. Typically, this value is orders of magnitude below 0.1 %, which does not exert a function in the final product.

Supply and storage

The substance is received from the supplier at the main warehouse where it is stored before distribution to the site.

Addition of 4-tert-OPnEO to the process

For the lysis step, 4-tert-OPnEO is introduced to the process by coupling containers with 10 % w/v 4-tert-OPnEO in water (WFI) to the fill line. 4-tert-OPnEO is added to a bioreactor (which contains the solution with cells containing the viral particles) via a closed connection (flexible plastic tubing) by means of a pump which has no contact with the liquid. Prior to disconnecting the (partially) emptied 4-tert-OPnEO container, the flexible plastic tubing is heat sealed and disconnected by cutting through the sealed portion. Both the emptied closed container and closed tubing which have been in contact with 4-tert-OPnEO are collected in hard walled containers and shipped to a certified waste handler for incineration. The applicant stated that all 4-tert-OPnEO is removed from the process during subsequent DNA precipitation, clarification, chromatography and polishing and buffer exchange steps and does not end up in

the final product. All disposable materials used in the BSL-2 area of the facility, are carefully disconnected/sealed, collected in separate waste containers and shipped to a certified incinerator.

Sampling

Samples are taken in 50 mL bags attached to the sampling line, via gravity flow. Once measured and/or aliquoted, all bags, sample tubes and cryovials are labelled, double contained and packaged in a labelled bag. All samples from BSL-2 rooms need also a biohazard label. All BSL-2 samples are double bagged (or placed in a sample box) and the outside of the bag (or box) is decontaminated before transport with a NaOH solution. Samples with potential residues of 4-tert-OPnEO are marked as hazardous waste and are handled and incinerated in a similar way as solid materials used in the production process.

All samples from the BSL-2 area to other parts of the Leiden facility are transferred in a leak-proof outer and inner packaging according to UN3245 requirements. Liquid and solid waste from sampling generated outside the BSL-2 facility is collected separately, disinfected, packaged and shipped to a certified waste handler for incineration.

0.2 Key functions and properties provided by the Annex XIV substance

The primary function of 4-tert-OPnEO is cell lysis. 4-tert-OPnEO is used as the selective lysing agent which permeates the outer cell membranes of the cells but not the membranes around the cell nucleus.

The secondary function of 4-tert-OPnEO is adventitious virus elimination, i.e. its presence eliminates viruses that have a lipidic envelope and reduces the chance of a harmful or undesirable adventitious virus being present in the vaccine.

The tertiary function of 4-tert-OPnEO is ability to complementary function with other essential chemicals such as detergent domiphen bromide that is used during DNA precipitation following the lysis step.

0.3 Type(s) of product(s) made with Annex XIV substance and market sector(s) likely to be affected by the authorisation

The use of 4-tert-OPnEO under the use applied for, concerns the following types of products: Ebola monovalent vaccine, RSV (respiratory syncytial virus) senior preventive vaccine, HIV-1 preventive vaccine, Zika virus preventive vaccine, RSV junior preventive vaccine, Filovirus multivalent preventative vaccine, HIV therapeutic vaccine and HPV (human papilloma virus) therapeutic vaccine.

1. Operational Conditions and Risk Management Measures

1.1 Environment

The applicants presented one exposure scenario (ES1 Pharmaceutical use of 4-tert-OPnEO as a non-reactive processing aid in vaccine production) with one environmental contributing scenario (ECS) that includes receipt and storage, addition to the process, sampling and handling of waste - ERC4
A summary of the OCs & RMMs in the environmental contributing scenarios is provided below. The detailed conditions of use are available from section 9.2.1 through 9.2.6 of the CSR. Four worker contributing scenarios are presented in the succinct summary but are not

discussed in detail, as the scope of the CSR is limited on the environmental risk of 4-tert-OPnEO.
No contributing scenario for the service life is provided because 4-tert-OPnEO is not present in the final products (unless it is an impurity, typically, below 0.1 %).

Operational Conditions and Risk Management Measures in place for control of emissions to:

All activities with 4-tert-OPnEO -except for sample analysis and sample storage- are conducted in the BSL-2 area of the facility. The BSL-2 area is completely separated from both, the rest of the production facility and the outside environment.

Air

- Product used in closed system.
- The air inside the BSL-2 area is mechanically ventilated using dedicated air handling systems.
- All in-streams pass a HEPA filter. The BSL-2 area is under a slight overpressure.
- All transfer of liquid waste water is performed at ambient temperatures using methods which minimise aerosol formation.
- Filter on exhaust of dedicated liquid waste storage.

Water

- All surfaces in the BSL-2 area are impermeable.
- Product used in workrooms with no connection to external drainage system.
- Dedicated drains system connect to dedicated liquid waste storage.
- Spent fluid collected in closed storage facility and transported to incinerator.

Soil

- Impervious floor in storage, operating rooms, waste collection and incineration.

Waste

The site has contracted certified waste disposal companies for handling solid and liquid waste that could have been in contact with the 4-tert-OPnEO.

All liquid waste streams from the BSL-2 area are led through dedicated piping to a buffer tank and are subsequently thermally treated to deactivate active virus components ('biokill-system'). From this system the liquid waste is led by means of dedicated piping to tanker trucks and shipped to a certified waste handler for incineration. In response to RAC questions, the applicants clarified that all the piping inside the plant was in place as designed and built because of biological safety requirements (BSL-2) and therefore also dedicated to all 4-tert-OPnEO-containing liquid waste streams. The piping outside the building and the collection into tanker trucks is to be built in the first half of 2020. The system will be operational by October 2020. In response to RAC questions, the applicant provided detailed step by step timelines for engineering, construction and commissioning of the new collection system.

Solid waste containing 4-tert-OPnEO residues generated:

- after adding of the 4-tert-OPnEO to the reactor vessel (e.g. disposables, lining, containers of samples and emptied packaging) is collected in hard-walled containers (e.g. hospital bins). Afterwards these containers are shipped to a certified waste handler for incineration.

- during the lysis step itself (e.g. plastic tubing) is collected, stored in hard-walled containers (hospital bins), decontaminated and shipped to a certified waste handler for incineration.

Solid waste such as work clothes (in case of contamination) are collected and shipped to a certified waste handler for incineration.

Waste management in case of incidents (e.g. after loss of containment):

- all liquids are absorbed, collected, stored in hard-walled containers (hospital bins), decontaminated (if the materials have been in contact with bio hazard materials) and shipped to a certified waste handler for incineration);

- excess liquid and liquid used for cleaning is led to the bio-kill system by dedicated piping for decontamination and further led by means of dedicated piping to tanker trucks and shipped to a certified waste handler for incineration.

Table 3: Environmental RMMs - summary

Compartment	RMM	Stated Effectiveness
Air	Closed system	Not applicable (closed systems and relatively low volatility)
Water	Incineration of solid and liquid waste	No residual releases from waste water that is collected for incineration
Soil	Incineration of solid and liquid waste	No residual releases from solid or liquid waste which is all collected for incineration

Additional technical and organisational conditions and measures that are not mentioned above:

- Production and transfer of fluids containing 4-tert-OPnEO takes place under rigorous containment in the BSL-2 area in closed equipment.
- The BSL-2 area is completely separated from both the rest of the production facility and the outside world environment.
- Fully disposable (internal) containers, bioreactors and tubing are used during the process.
- Specific sampling procedures, 4-tert-OPnEO contaminated samples are labelled and treated as hazardous material or waste.
- An emergency plan is available for spill incidents, all waste after a spill event will be disposed of and incinerated by a certified contractor.
- A preventive maintenance program is in place, all waste generated during maintenance is collected (decontaminated if needed) and incinerated by a certified contractor.
- Maintenance on the Biokill system, which is the only foreseeable maintenance with 4-tert-OPnEO relevance, will be performed when the facility is not producing.
- Emission from maintenance activities will not occur from the manufacturing process steps, because the process is based on disposable technology.
- Access to the laboratories and BSL-2 area is restricted to authorized, trained personnel.

1.2 Discussion on OCs and RMMs and relevant shortcomings or uncertainties

Since all solid and liquid waste, which has been in contact with 4-tert-OPnEO, is collected and disposed of for incineration and the all relevant wastewater is collected for incineration as well, no relevant shortcomings to the operational conditions (OCs) and risk management measures (RMMs) have been identified.

1.3 Conclusions on OCs and RMMs

Overall conclusion: OCs and RMMs in the exposure scenario (ES) are expected to be appropriate and effective in limiting the risk, provided they are implemented and adhered to.

Are the operational conditions and risk management measures appropriate[6] and effective[7] in limiting the risk for workers, consumers, humans via environment and / or environment?

Workers	☐Yes	☐No	☒Not relevant
Consumers	☐Yes	☐No	☒Not relevant
Humans via Environment	☐Yes	☐No	☒Not relevant
Environment	☒Yes	☐No	☐Not relevant

2. Exposure assessment

2.1. Environmental emissions

Water

Since all solid and liquid waste and wastewater that could be contaminated with 4-tert-OPnEO is collected for incineration, no emissions to the water compartment are foreseen.

Air

As a result of the relatively low vapour pressure of 4-tert-OPnEO and the level of containment in the processes (largely in a closed system), RAC concurs that releases to air are expected to be zero.

Soil

Since all solid and liquid waste and wastewater that could be contaminated with 4-tert-OPnEO is collected for incineration RAC agrees that direct releases to soil are not likely. Similarly RAC agrees that indirect releases to soil are not expected.

Table 5: Summary of environmental emissions

Release route	**Release factor**	**Anticipated release per year** (kilograms)	**Release estimation method and details**
Water	0%	0	All generated waste is sent for incineration
Air	0%	0	Product applied in aqueous process solution with relatively low volatility potential in closed system
Soil	0%	0	All generated waste is sent for incineration

[6] 'Appropriateness' – relates to the following of the principles of the hierarchy of controls in application of RMMs and compliance with the relevant legislation.
[7] 'Effectiveness' – evaluation of the degree to which the RMM is successful in producing the desired effect – exposure / emissions reduction, taking into account for example proper installation, maintenance, procedures and relevant training provided.

2.2. Discussion of the information provided and any relevant shortcomings or uncertainties related to exposure assessment

Environment

RAC notes that the potential for release of 4-tert-OPnEO into the environment is non-existent as a result of the use of 4-tert-OPnEO in closed systems and incineration of all solid and liquid wastewater generated. RAC notes that no shortcomings were identified in the applicants' exposure assessment.

2.3. Conclusions on exposure assessment

RAC considers that the applicants have provided enough information to demonstrate that releases to environmental compartments are prevented as far as technically and practically possible.

3. Risk characterisation

3.1. Environment

The applicants have treated 4-tert-OPnEO as a non-threshold substance and did not attempt to derive PNECs or RCRs. This approach is in line with RAC's paper "Risk-related considerations in applications for authorisation for endocrine disrupting substances for the environment, specifically OPnEO and NPnEO", adopted at RAC-43 and RAC's conclusion at its 50th meeting that it is currently not possible to determine a threshold for the ED properties of this substance.

Based on the OCs & RMMs in the ES, notably the use of 4-tert-OPnEO in closed systems and collection and incineration of all process waste water and disposable solids, RAC is of the view that the applicants have demonstrated that releases to environmental compartments will be prevented after 2020 and in this case, it can be concluded that the likelihood of adverse effects caused by 4-tert-OPnEO will, in effect, be zero.

3.2. Shortcomings or uncertainties in the risk characterisation

No shortcomings were identified in the risk characterisation, however it must be noted that it is a future use and the plant has yet to be commissioned and the OCs and RMMs implemented.

3.3. Conclusions on risk characterisation

Based on information provided in the application, it can be concluded that the releases of 4-tert-OPnEO will be prevented as far as technically and practically possible, and in this case will, in effect, be zero.

4. Analysis of Alternatives and substitution plan[8]

There are two applicants for the authorisation: both are daughter companies of Johnson & Johnson. Janssen Vaccines & Prevention B.V. and Janssen Biologics B.V. applied for the future use of 4-tert-OPnEO as a lysing agent for the 'permeabilisation' of the host cell membrane to release adenovirus particles used for the manufacture of vaccines. Janssen Vaccines & Prevention B.V. develops, conducts clinical trials and tests the vaccines. Janssen Biologics B.V. operates a vaccine manufacturing site in Leiden (the Netherlands).

What is the amount of substance that the applicant uses per year for the use applied for?

270 kg

4.1. Summary of the Analysis of Alternatives and substitution plan by the applicants and of the comments received during the public consultation and other information available

Janssen uses a unique platform concept, whereby a multiplicity of vaccines can be produced in the same place, by the same personnel, on the same equipment. Any alternative will, therefore, have to fulfil the many functionalities that 4-tert-OPnEO has. This unique platform approach is specific to the applicants and, as far as they know, it is not used by any manufacturer of vaccines in the market.

In the answers to SEAC questions, the applicants stated that they are convinced that there are alternatives to 4-tert-OPnEO. Thus, the applicants launched an initiative phase of substitution program to phase out OPnEO in 2017 and this program is fully underway since the beginning of 2018. The applicants explained that, originally, an assessment has been performed on 55 commercially available non-ionic detergents that are used in life sciences. The applicants expect that from this research not more than six detergents will prove theoretically applicable at this stage. The criteria which will be taken into consideration are: physico-chemical characteristics similar to 4-tert-OPnEO, and regulatory and manufacturing aspects. At this time, the applicants have completed the analysis of two possible non-ionic surfactants and are in the process of examining two additional ones. The applicants explained in their AoA the three main steps to the substitution of the 4-tert-OPnEO by another compound: 1) identification of an alternative, 2) Development phase and 3) Implementation phase.

The applicants also stated that a shortlist of detergents, identified as potential replacers on the basis of predefined selection criteria, amongst which "Risk of future environmental ban" is one of them, will be scrutinized in a next round. The list contains surfactants with either one of three possible chemical groups:

- Alkyl ethoxylates
- Polysorbates

[8] The judgment of the ECJ Case T-837/16 Sweden v Commission stated that the applicant has to submit a substitution plan if alternatives are available in general. The Commission is currently preparing the criteria, derived from the judgment for establishing when an alternative is available in general. Once these are prepared this opinion format will be amended accordingly. The European Commission informed the REACH Committee in 9-10 July 2019 of its preliminary views on the criteria. In that note that Commission considered that the criteria defining a 'suitable alternative' would imply that it was i) *safer* and ii) *suitable*. Suitability would not mean it to be *"in abstracto"* or "*in laboratory or exceptional conditions*" but it should be "*technically and economically feasible in the EU*" and "*available, from the point of view of production capacities of the substance or feasibility of the technology, and legal and factual conditions for placing on the market*".

- Alkyl glucosides

For these chemical families, an environmental risk assessment has been made.

All chemical groups identified are considered as safer compounds than 4-tert-OPnEO. The applicants underlined that they are convinced to substitute 4-tert-OPnEO in their process and consider this application as bridging. They will have to go through all the necessary steps (including qualification) in order to substitute 4-tert-OPnEO with an alternative substance.

SEAC concludes that the analysis of alternatives is clear in its description and scope, and sufficiently detailed to conclude on the short-list derivation of alternatives as well as their suitability in the context of the use applied for. The applicants described the use applied for in detail, as well as the requirements associated with a viable alternative.

4.2. Risk reduction capacity of the alternatives

Would the implementation of the short-listed alternative(s) lead to an overall reduction of risks?

☐ Yes

☐ No

☒ Not applicable

SEAC has concluded that currently there are no technically and economically feasible alternatives available for the applicants with the same function and similar level of performance. Therefore, RAC did not evaluate the potential risk of alternatives.

4.3. Availability and technical and economic feasibility of alternatives for the applicant

Are there alternatives with the same function and similar level of performance that are technically and economically feasible to the applicant before the Sunset Date?

☐ Yes ☒ No

The applicants expect that alternatives may be technically and economically feasible in the future, but not before the Sunset Date.

The applicants explained that chemical lysis methods can be potentially carried out with detergents. Generally speaking, these can be grouped within 4 different categories: non-ionic, anionic, cationic and zwitterionic (charge dependent on pH). The cationic detergents were ruled out on the basis of a theoretical and experimentally proven electrostatic interaction with the adenovirus virus particles and HC-DNA. A feasibility study was carried out with candidates of the remaining detergent groups (nonionic, anionic, zwitterionic). The zwitterionic candidate was removed from further assessment on the basis of safety considerations; the anionic candidate showed too high protein destabilization (denaturing of adenovirus particles). Furthermore, anionic detergents are known for their denaturing effects and, due to the basis of the feasibility study results and literature, are now also excluded. Therefore, the non-ionic detergents are the only viable option.

Moreover, according to the applicants, the process of substitution is complicated for three main reasons:

- The vaccines are in the process of being tested on humans, with some of them in the final

stages of that process;

- The vaccines and, consequently, their manufacturing process have a high degree of complexity. The multiplicity of vaccines output from a single platform requires rigour and testing far above the norm, even for pharmaceutical manufacturing;

- There is an unknown timing aspect related to regulatory requirements from authorities such as the European Medicines Agency.

The applicants also stated that the price of the potential alternative substance is a minor consideration due to the low volume and therefore economic considerations are purely linked to the feasibility of technically using the alternative in the current platform of production. For example, a tenfold price increase would be less problematic than uncertainty around the availability and quality of the material delivered.

No comments on alternative substances or techniques were submitted during the public consultation.

SEAC's evaluation/view on the availability and technical and economic feasibility of alternatives for the applicant

SEAC reviewed the information provided by the applicants on the alternatives, regarding the following points:

- Technical function requirements
- Requirements for overall virus production process
- Credibility of timelines for substitution

SEAC considers that the applicants' approach to identify and assess alternatives for the use applied for allows to make conclusions on the suitability of alternatives. SEAC concludes that the applicant's assessment is sufficient and clear.

SEAC is of the opinion that the applicants convincingly demonstrate that technically feasible alternatives will not become available to the applicants before the Sunset Date.

4.4. Substitution activities/plan

The applicants are committed to substitute the substance in 15 years and are confident that substitution will be possible despite the absence of currently available alternatives. The applicants are working on a substitution initiative consisting of three different phases as illustrated in Figure 1 below.

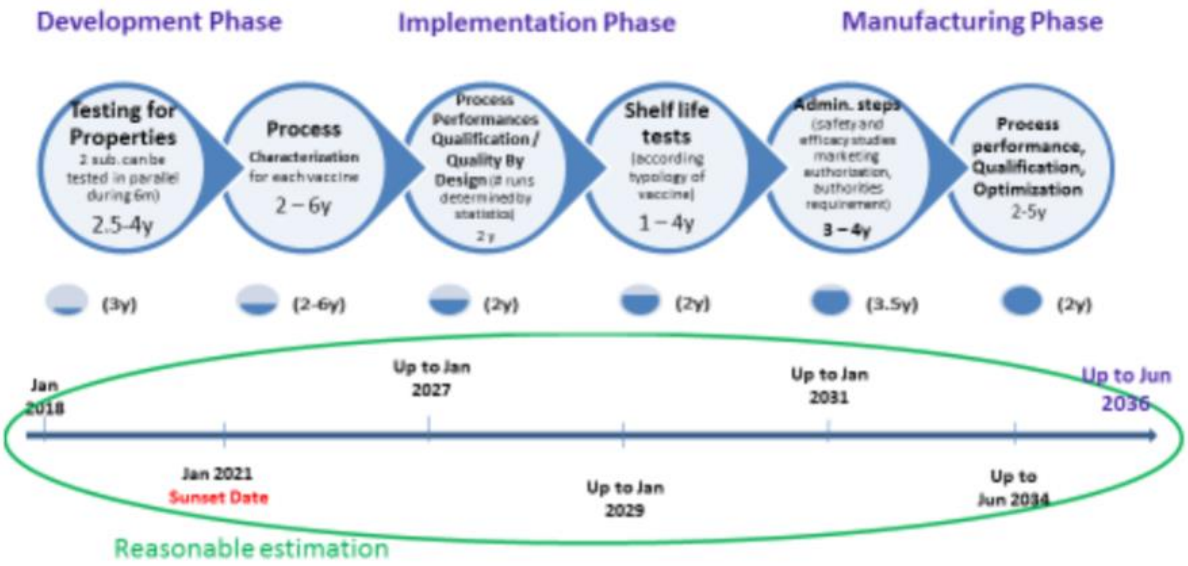

Figure 1. Substitution timeline

As depicted in the figure above, the overall duration of the substitution is conditioned by several steps. Some of those steps are also conditioned, in turn, by key external factors such as the regulatory compliance that has to be carried out before the finalisation of the substitution of 4-tert-OPnEO. The applicants presented, as an example, a detailed (confidential) listing of clinical trials already performed (and also being currently performed) for the HIV vaccine. The applicants added that this is when the time estimates become the most uncertain as the marketing authorisation agencies must be informed; If one of the authorities decides that any phase of the clinical trials need to be repeated, the process can be further delayed.

The applicants elaborated further on the complexities of the substitution process in the AoA; in particular, arguing that Janssen intends to market the drugs concerned with the use applied for in several markets, not just the EU. A target product profile is agreed with the relevant authorities (EMA in Europe and the FDA in USA) but the applicants negotiate with dozens of authorities worldwide and the information needs are not harmonised. Regulatory approval is dictated by complex and time consuming requirements outside of the applicants' control and this could have an impact on the proposed timelines. In the trialogue with the applicants, they expanded on the relationship between regulatory timelines and planning leading up to the requested review period. This relationship can be summarised as follows:

1) Janssen's late phase vaccines (Ebola/RSV/HIV) are being prepared for licensure. Complex process changes can no longer be implemented before licensure.

2) The majority of tests/changes must be implemented for all vaccines before changes can be notified.

3) OPnEO-removal is best implemented after 2028 in post-approval filings. Global implementation will take 4 additional years in a realistic best case (without additional clinical studies).

4) Janssen's earlier stage phase vaccines (Zika, Influenza, HPV,) are in variable stages of development, for these vaccines it makes more sense to implement changes before licensure process starts.

5) A shorter review period could force halt in development until an alternative identification is complete.

The applicants concluded that a 15-year review period will be needed to attain the full substitution of 4-tert-OPnEO for the applied use, when all the required steps that comprise the development, implementation and manufacturing phases are added up.

Has the applicant submitted a substitution plan?

☒Yes ☐No

If yes, is the substitution plan credible and consistent with the analysis of alternatives and the socio-economic analysis?

☒Yes ☐No

SEAC's evaluation/view on the substitution activities/plan

Overall, SEAC finds the substitution plan presented by the applicants credible, with well described phases and timelines for completion.

The applicants are already engaged in a substitution programme and structured it as a stepwise activity. R&D activities are currently underway, however, the required feasibility testing has not yet started in practice on all shortlisted alternatives. The applicants hope that further testing in the development phase will confirm the technical validity of the possible alternative substance and will enable them to enter the phase of implementation, during which all the actions necessary for vaccine production will be defined and taken.

The applicants provided stepwise timelines for achieving the most crucial steps in their substitution plan with the overall goal to finish all activities in 15 years. They added that all the phases envisioned in the substitution plan (including regulatory approval) cannot be completed in 12 years or even earlier if considering that reapplication has to be submitted 18 month before the expiring date of the 12 year review period. SEAC notes that the substitution plan provided by the applicants is well elaborated and appears credible, however there is a lack of certainty that the substitution plan timelines (including regulatory approvals) for all the utilisations under the scope of use can be met as the applicants expect them to be. The applicants implied in their AoA that the most reasonable estimate shows an overall substitution period of 20 years (counting from the year 2017), therefore it seems conceivable, judging by this indication, that even the requested review period of 15 years (counting from the Sunset Date i.e. year 2021) would not be met, and that the applicants would need to reapply for a review period extension.

The applicants stated that, in case of a recommendation by SEAC of a shorter than 15 years review period, they would be encouraged to favour the substitution of the 4-tert-OPnEO over the launch of the vaccines and that, in practice, they would be delaying the testing, production up-scale and marketing authorisation of the vaccines until the substitute was found and proven to work. In response to SEAC's questions, the applicants stated that *"the financial and resource burden for a reapplication in the midst of a substitution process is substantial and would delay the substitution process itself"*. The applicants also acknowledged the impossibility to give a precise indication of the delay to market caused by a refused or shorter authorisation review period and claimed that even a small uncertainty around review-extension would make the management and legal teams decide to avoid risks as there might be an incentive to prioritise other processes over substitution. SEAC is of the opinion that these arguments, about the financial and resource burden for a reapplication potentially delaying the substitution process, as well as the uncertainty about the submission of a review report, might be questionable, as, in principle, the reapplication should not be too resource-consuming. Indeed, it could primarily focus on whether the substitution process is on track and the implementation of a valid

alternative is ongoing, showing how the milestones in the substitution plan are being executed and how they measure up against the predicted timelines.

4.5. Conclusions on the analysis of alternatives and the substitution plan

By the Sunset date there are no alternatives available with the same function and similar level of performance that are safer and technically and/or economically feasible for the applicants.

SEAC finds the substitution plan presented by the applicants credible, with well described phases and timelines for completion. However, uncertainties on the successful execution of the relevant phases, within the timelines envisaged in the applicants' AoA and substitution plan, exist.

5. Benefits and risks of continued use

Have the applicants adequately assessed the benefits and the risks of continued use?

☒ Yes

☐ No

5.1. Human health and environmental impacts of continued use

According to the applicants, the risk management measures currently implemented at the applicants' site eliminate potential releases of 4-tert-OPnEO into the environment and, therefore, prevent endocrine disrupting effects on any species potentially exposed to it in their natural habitat to occur.

5.2. Benefits of continued use

Non-use scenario

The applicants apply for the use of 4-tert-OPnEO in the production of newly developed vaccines. The applicants has assessed one non-use scenario: Substitution with an alternative substance. As was shown in the Analysis of Alternatives, no technically suitable alternatives will be available before the sunset date. Therefore, in case of non-authorisation production and market-introduction of the vaccines will be delayed, and the newly developed vaccines will not be available for the patients, until an alternative can be identified, and re-validation of production process and market approvals from national and EU health authorities are obtained. According to the applicants, overall, this could take up to 15 years.

No further non-use scenarios, like outsourcing of the single production step of lysing, in which 4-tert-OPnEO is involved or relocation of the complete production process of vaccines was discussed by the applicants. The applicants clarified, in response to a SEAC question, that relocation was excluded since the production site was especially chosen with regard to the unique technology and the specific human resources and level of know-how which is available at that production site. SEAC considers this plausible due to the significant expertise and high level of know-how that is required.

SEAC finds the non-use scenario adequate with a focus on duration and consequences of disruption of supply of newly developed vaccines for the patients.

What is likely to happen to the use of the substance if an authorisation was not granted?

- the use would cease altogether

What is likely to happen to jobs in the European Union if an authorisation was refused?

- up to 10-100 jobs would be lost in the European Union

Economic impacts of continued use

The applicants are developing different vaccines by using the AdVac® technology. This technology allows producing different vaccines against infection diseases for example respiratory syncytial virus (RSV), HIV, ZIKA Virus, Ebola monovalent, Filo Multi, and Influenza. Some of the vaccines are in an early R&D stage, and some close to efficacy clinical trials such as the HIV vaccine. Janssen has developed a specific platform on which to produce vaccines based on adenoviruses. This platform is unique and allows the applicants to manufacture, efficiently, high volumes of several vaccines (single production line for multiple vaccines). Some of the vaccines are already provided by other competitors, but by using a different production process. For some viruses, like HIV, only a few competitors are active in searching for a vaccine (market introduction within the review period of the authorisation recommended by SEAC).

Profit losses and producer surplus

The applicants have assessed the economic benefits of authorisation by calculation of the economic surplus of future production of the vaccines (EBIT, net-present value, with 4 % discount rate) over the time-period 2021-2028 which would be at least in the range €1-10 billion. The applicants assume that in case of a refused authorisation, the market introduction would be shifted at least for seven years, from 2021 to 2028. These figures are conservatively used to present economic impacts over the assessment period of 15-years, as it is likely that up to 15 years are needed for substitution, revalidation of the production process, and re-approval of market authorisations which are time consuming and also costly processes. Also, negative impacts for the applicants´ competitiveness are mentioned since competitors in Non-EEA may increase their market shares in the applicants´ vaccine markets.

The applicants also mentioned impacts for the suppliers of raw materials and services although they were not quantified.

Health impacts of continued use

Patients in EEA and Non-EEA will benefit from the planned launch of newly developed preventive and therapeutic vaccines by a better health status (e.g. Ebola monovalent vaccine; RSV senior preventive vaccine, HIV-1). In a case study, the applicants have quantified the health benefits of availability of HIV vaccine in terms of reduced mortality, a better quality of life and lower health care costs (mainly for antiretroviral therapy) compared to a 7 year delayed market introduction. The health status of an HIV-infected person is valued with the concept of Quality of Adjusted Life Years (QALY), and the WHO monetary reference for a QALY is applied to transfer the QALY loss into monetary terms (WHO Guidance value adapted to 2021). Given the estimation of not avoided HIV-cases due to a refused authorisation, the monetised health impacts (including treatment costs) amount to about €10-50 million (exact figure claimed

confidential but provided to SEAC) over 7 years. The applicants mention different sources of underestimation of health impacts, e.g. not taking into account loss of productivity of infected persons, benefit of herd immunity, and costs of hospitalisation. In addition, the benefits of launch of other vaccines were not quantified. Therefore, the case study can only be considered to provide some minimum costs of refusing authorisation.

Unemployment impacts

As social benefits, the applicants have included the employment of 10-100 employees which would become redundant if commercial production does not start in 2021. Most of the workers are high-skilled. For these workers, an unemployment duration of 50 % of the arithmetic mean of unemployment for The Netherlands in the age-group 25-64 (ca. 18 months) was assumed, and for the low-skilled workers the arithmetic mean duration of temporal unemployment. The social costs of employment are calculated to be in the range €1-10 million.

The applicants also mention business risks for their long-term financial plan due to the revenue losses of the delayed market introduction of the HIV and other vaccines. Since substitution would not be possible during a short period of time, employment of workers in R&D, production, and marketing (figure confidential but provided to SEAC) are at risk. As a worst-case scenario, the social costs from the unemployment of these workers were quantified (figure confidential but provided to SEAC). The applicants have provided these additional monetisation values only for the sake of completeness of the analysis, but did not add them up with the other monetised impacts to be taken forward, therefore SEAC will not consider them either in its calculations.

Table 10: Socio-economic benefits of continued use

Description of major impacts	**Quantification of impacts**
1. Benefits to the applicant(s) and/or their supply chain	
1.1 Avoided profit loss due to investment and/or production costs related to the adoption of an alternative	N/A
1.2 Avoided profit loss due to ceasing the use applied for	€1-10 billion over a 15-year assessment period. This results in lost profits of approximately €100-1 000 million per average year.
1.3 Avoided relocation or closure cost	N/A
1.4 Avoided residual value of capital	N/A
1.5 Avoided additional cost for transportation, quality testing, etc.	N/A
Sum of benefits to the applicants and/or their supply chain	100-1 000
2. Quantified impacts of the continuation of the SVHC use applied for on other actors	
2.1 Avoided net job loss in the affected industry[9]	€1-10 million over a 15-year assessment period.

[9] Job losses to be accounted for only for the arithmetic mean period of unemployment in the concerned region/country as outlined in the SEAC paper on the valuation of job losses (See The social cost of unemployment and Valuing the social costs of job losses in applications for authorisation).

2.2 Foregone spill-over impact on surplus of alternative producers	N/A
2.3 Avoided consumer surplus loss (e.g. because of inferior quality, higher price, reduced quantity, etc.)	N/A
2.4 Avoided other societal impacts	> €10-50 million human health cost over a 15-year assessment period (based on a delay of 7-year in introduction HIV vaccine).
Sum of impacts of continuation of the use applied for	10-60 million over 15-year assessment period
3. Aggregated socio-economic benefits (1+2)	€100-1 000 million over 15-year assessment period (based on 1 year profit loss, social cost of unemployment and HH benefits)

N/A; not applicable

5.3. Combined assessment of impacts

The applicants assess that the monetised costs of the non-use scenario would be in the range €1-10 billion over the requested review period taking into account losses of EBIT as well as the costs of unemployment. These costs include also the monetised health impacts which would arise due to a delayed market introduction of 7-years.

Environmental impacts are considered zero since all releases are prevented by the manufacturing process and risk management measures implemented.

Table 11: Socio-economic benefits and risks of continued use

Socio-economic benefits of continued use		**Excess risks associated with continued use**	
Benefits	€100-1 000 million over 15-years (based on 1 year profit loss)	Monetised excess risks to workers directly exposed in the use applied for annualised to € million per year	N/A
Quantified impacts of the continuation of the SVHC use applied for on other actors	€10-60 million over 15-year assessment period	Monetised excess risks to the general population and indirectly exposed workers annualised to € million per year	N/A
Additional qualitatively assessed impacts	Revenues for applicants´ suppliers of raw materials and services Stable employment of applicants´ workers in R&D, production, and marketing	Additional qualitatively assessed risks	N/A
Aggregated socio-economic benefits	**€100-1 000 million over 15-years and Revenues for applicants´ suppliers of raw materials and services Stable employment of applicants´ workers in R&D, production, and marketing**	**Aggregated excess risk [annualised to € million per year and main qualitatively assessed risks]**	N/A

Table 12: Cost of non-use per kg and year

	Per year
Total cost (€)	€100-1 000 million over 15-years (based on 1 year profit loss, social cost of unemployment and HH benefits)
Total emissions (kg)	No emissions
Ratio (€/kg)	Not applicable as no emissions are expected

Notes:

1. "Total cost" (of non-authorisation) = Benefit of authorisation
2. "Total emissions" (if authorisation is granted) = Estimated emissions to the environment, kg per year, based on Table 5
3. "Ratio" = Total cost/Total emissions

Annualised to a typical year based on the time horizon used in the analysis

5.4. SEAC's view on Socio-economic analysis

The applicants have considered the delayed start of commercial production and selling of the vaccines as non-use scenario. Relocation of the part of the production process in which 4-tert-OPnEO is used to Non-EEA, and complete relocation to Jansen´s production facilities e.g. in the USA was not considered, since the production site was especially chosen with regard to the unique technology and the specific human resources and level of know-how which is available at that production site. SEAC considers that this plausible, due to the significant expertise and high level of know-how that is required.

The economic impacts are monetised by calculation of the applicants´ losses due to a delayed market introduction of the first newly developed vaccines. The losses are assessed by use of the economic measure Earnings Before Interest and Tax (EBIT). The measure is considered adequate by SEAC.

SEAC considers that changes in profits are a relevant measure of changes in producer surplus and appropriate to monetising the welfare implications of continued use. However, changes in profits made by the applicants do not necessarily reflect net changes in economic surplus across the EU economy. Considering the profit losses of the applicants over a long time period does not take into account the possibility of mitigating actions that could reduce the economic impacts (e.g. resources being redeployed by the applicants or by other companies) and may overstate the long-term impacts. Therefore, SEAC does not consider it appropriate to use the profit loss incurred by the applicants over 15 years and uses the single year of lost profits (approximately in the €100-1 000 million range) to account for the net changes in producer surplus.

SEAC notes the applicants' reasoning on challenges in redeploying the resources to alternative uses and recognises that SEAC's approach may underestimate the net changes in economic surplus.

Regarding the profit losses from vaccine for the prevention of RSV in older adults, which is near to market entry, the applicants expect market introduction of competitors very soon after the applicants. For SEAC it is not clear whether the competitors' market entry is based on a different production technology. For this vaccine, the EBIT losses calculated over 7 years may represent an overestimate of the net impacts to the society even though this might be still valid for the applicants themselves.

No further economic impacts were quantified.

The calculation of social impacts regarding the employees linked to the future production follows the approach outlined in the SEAC paper on the Social Cost of Unemployment (ECHA 2016). The assumed average unemployment duration, and the adaption of this duration according to high-skilled and low-skilled workers is plausible. It is recognised by SEAC that the financial risks of a refused authorisation may spill over to other parts of the business and to the staff employed there. Because of the uncertainties of estimating the employment dynamics, the assumed worst-case scenario is not taken into account for concluding on quantification and monetisation of the magnitude of the economic impacts.

The applicants have provided an approach for monetising the health benefits for a not delayed market introduction of a HIV preventive vaccine, however SEAC is not able to fully scrutinise all the assumptions taken. The approach is plausible, and the conservative assumption e.g. regarding effectiveness of HIV-vaccines is recognised. SEAC also recognises that the main benefits will arise outside EEA, since the vaccine is mainly produced for export (e.g. sub-Saharan countries).

5.5. Conclusion on the socio-economic analysis

SEAC has no substantial reservations on the quantitative and qualitative elements of the applicants' assessment of the benefits and the risks to the environment associated with the continued use of the substance. This conclusion is made on the basis of:

- the application for authorisation,
- SEAC's assessment of the benefits of continued use,
- any additional information provided by the applicants,
- RAC's assessment of the risks to the environment.

6. Proposed review period

☐ Normal (7 years)

☒ Long (12 years)

☐ Short (…. years)

☐ Other: _____ years

When recommending the review period SEAC took note of the following considerations:

6.1 RAC's advice

RAC has no advice concerning the length of the review period.

6.2. Substitution and socio-economic considerations

The applicants consider that their AoA provides sufficient justification for a longer than 12 year review period, and requests a review period of 15 years in order to develop, implement and validate alternatives for the use applied for.

In identifying the proposed review period SEAC took note of the following considerations:

- No emission expected to the environment from 4-tert-OPnEO will take place since the production process is a closed system and all waste streams containing 4-tert-OPnEO will be collected and incinerated.
- SEAC has no substantial reservations on the quantitative and qualitative elements of the applicants' assessment of the benefits and the risks to the environment associated with the continued use of the substance. The applicants' impact assessment was considered by SEAC to provide robust conclusions in this respect.
- SEAC concurs with the applicants that there is currently no technically feasible alternative.
- Due to high performance requirements and the regulatory approval process, SEAC finds it credible that it would not be possible for the applicants to substitute within a normal (seven year) review period.
- SEAC, however, does not see sufficient basis to grant a 15-year review period. Following the guidelines set out on the CARACAL paper on the criteria to consider for a longer than 12 years review period, SEAC considers that the applicants have not demonstrated, without any significant uncertainties, that there are no suitable alternatives for any of the utilisations under the scope of the use applied for and that it is highly unlikely that suitable alternatives can be implemented for the use concerned within a requested review period (that is 15 years).
- Furthermore, this case does not fall within any of the examples laid out in the CARACAL's paper non exhaustive list, since the substance is not a source of a biologically essential inorganic micronutrient for human, plant, animal or microbial cells and neither is the substance irreplaceable due its atomic properties. The substance is neither used in the production of spare parts, nor is it used in the defence sector, nor has the substance been authorised in accordance with other EU legislation.
- Finally, SEAC does not find credible the applicants' argument that the preparation of a potential review report would be resource consuming in a way such that market introduction of some vaccines would be delayed, since, in principle, the review report could primarily focus on whether the substitution process is ongoing and in line with the defined milestones and timelines.

Taking into account these points, **SEAC recommends 12-year review period**.

7. Proposed additional conditions for the authorisation

Were additional conditions[10] proposed for the authorisation?

☐ Yes

☒ No

[10] Conditions are to be proposed where RCR is > 1, OCs and RMMs are not appropriate and effective, risk is not adequately controlled, minimisation of emissions is not demonstrated.

7.1 Description

RAC

Proposed additional conditions

None

SEAC

Proposed additional conditions

None

7.2. Justification

RAC is of the view that:

- the applicants have demonstrated that releases to environmental compartments are prevented; and
- the likelihood of adverse effects can be considered to be effectively zero.

8. Proposed monitoring arrangements for the authorisation

Were monitoring arrangements[11] proposed for the authorisation?

☐ Yes

☒ No

8.1 Description

N/A

8.2 Justification

RAC is of the view that:

- the applicants have demonstrated, on paper, that releases to environmental compartments will be prevented; and
- the likelihood of adverse effects can be considered to be effectively zero.

9. Recommendations for the review report

Were recommendations for the review report made?

☐ Yes

☒ No

[11] Monitoring arrangements for the authorisation are to be proposed where RCR is < 1, OCs and RMMs are appropriate and effective, risk is adequately controlled, minimisation of emissions is demonstrated – but there are some moderate concerns.

9.1 Description

N/A

9.2 Justifications

RAC is of the view that:

- the applicants have demonstrated, on paper, that releases to environmental compartments will be prevented; and
- the likelihood of adverse effects can be considered to be effectively zero.

10. Comments on the draft final opinion

Did the applicant(s) provide comments on the draft final opinion?

☐ Yes

☒ No

Comments of the applicant(s)

Was action taken resulting from the analysis of the comments of the applicant(s)?

☐ Yes

☐ No

☒ Not applicable – the applicant(s) did not comment