Committee for Risk Assessment (RAC)

Committee for Socio-economic Analysis (SEAC)

Opinion

on an Application for Authorisation for

Use of Octylphenolethoxylates as emulsifier in the siliconisation of glass containers used as primary packaging for two specific medicinal products (NutropinAq® and Lucentis®) of one pharmaceutical company

Submitting applicant: Vetter Pharma-Fertigung GmbH & Co. KG

ECHA/RAC/SEAC: AFA-O-0000006768-58-01/D

Consolidated version

Date: 08/06/2020

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]	**Vetter Pharma-Fertigung GmbH & Co. KG (in what follows referred to as Vetter)** (position in supply chain: downstream)
Substance ID EC No CAS No	**4-(1,1,3,3-Tetramethylbutyl)phenol, ethoxylated (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) - Endocrine disrupting properties - effects to the environment
Use title	**Use 1: Use of Octylphenolethoxylates as emulsifier in the siliconisation of glass containers used as primary packaging for two specific medicinal products (NutropinAq® and Lucentis®) of one pharmaceutical company**
	Other connected uses: **Use 2** - Use of Octylphenolethoxylates as emulsifier in the siliconisation of glass containers used as primary packaging material for medicinal products of several pharmaceutical companies listed in Appendix 1 to the AoA (this use has been submitted in a separate application for authorisation with a different timeline)

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

	Same uses applied for: -
Use performed by	☒ Applicant(s) ☐ Downstream User(s) of the applicant(s)
Use ID (ECHA website)	0161-01
Reference number	11-2120817567-47-0001
RAC Rapporteur RAC Co-rapporteur	VAN DER HAAR Rudolf BROVKINA Julija
SEAC Rapporteur SEAC Co-rapporteur	CAVALIERI Luisa ALEXANDRE João
ECHA Secretariat	HENRICHSON Sanna RODRIGUEZ UNAMUNO Virginia KVATCHADZE Giorgi

PROCESS INFORMATION FOR ADOPTION OF THE OPINIONS

Date of submission of the application	17/05/2019
Date of payment, in accordance with Article 8 of Fee Regulation (EC) No 340/2008	09/08/2019
Application has been submitted by the Latest Application Date for the substance and applicant(s) 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: https://echa.europa.eu/applications-for-authorisation-previous-consultations/-/substance-rev/23829/del/50/col/synonymDynamicField_302/type/asc/pre/6/view
Request for additional information in accordance with Article 64(3)	On 27/09/2019 and 06/10/2019 Link: https://echa.europa.eu/applications-for-authorisation-previous-consultations/-/substance-rev/23829/del/50/col/synonymDynamicField_302/type/asc/pre/6/view
Trialogue meeting	Not held – no need for additional information/discussion on any technical or scientific issues related to the application from the rapporteurs
Extension of the time limit set in Article 64(1) for the sending of the draft opinions to the applicant(s)	☐Yes, by [date] ☒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: 13/03/2020, agreed by consensus.
	SEAC: 05/12/2019, agreed by consensus.
Date of sending of the draft opinion to applicant(s)	11/05/2020
Date of decision of the applicant(s) not to comment on the draft opinion, in accordance with Article 64(5)	08/06/2020
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: 08/06/2020, adopted by consensus.
	SEAC: 08/06/2020, 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,
- as well as 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 appropriate and effective in limiting the risks, provided that they are adhered to.

The use applied for may result in up to approximately 1.0 g (0.932 g) per year emissions 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 of the substance in accordance with Annex I of the REACH Regulation.

The following alternative has been assessed: DOW CORNING® 366, 35% DIMETHICONE NF EMULSION (DC 366). (See Section 4 of the Justifications).

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 applicant.
- 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 are at least €1-10 million and additional benefits to society have been assessed qualitatively but have not been monetised.
- Risks to the environment of shortlisted alternatives have not been quantified. There may therefore be a risk arising due to the use of an alternative should the authorisation not be granted.

SEAC has no substantial reservations on the quantitative and qualitative elements of the applicant's assessment of the benefits and the risks to the environment associated with the continued use of the substance[2].

SEAC considered that if an authorisation was refused, the use of the substance could be taken up by market actors operating outside of the EU.

SEAC considered that, if an authorisation was refused, it was likely that in the European Union[3] no jobs would 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 applicant(s) and the comments received on the broad information on use, a **5-year** review period is recommended for this use.

[2] The formulation of this conclusion may be adapted in future versions of this format.
[3] Wherever reference is made to the European Union, this shall apply also to EEA countries.

SUMMARY OF THE USE APPLIED FOR

Role of the applicant(s) in the supply chain	Upstream ☐ [group of] manufacturer[s] ☐ [group of] importer[s] ☐ [group of] only representative[s] ☐ [group of] formulator[s] Downstream ☒ downstream user
Number and location of sites covered	Two sites: - Langenargen (Germany) and - Ravensburg (Germany)
Annual tonnage of Annex XIV substance used per site (or total for all sites)	- 0.0254 kg/year in Langenargen (Germany) and - 0.281 kg/year in Ravensburg (Germany) Total: 0.306 kg/year
Function(s) of the Annex XIV substance.	4-tert-OPnEO is used as emulsifier in the siliconisation of glass containers used as primary packaging material for medicinal products.
Type of products (e.g. articles or mixtures) made with Annex XIV substance and their market sectors	Two medicinal products: NutropinAq® and Lucentis® produced for F. Hoffmann-La Roche Ltd. NutropinAq® is a solution for injection in a cartridge. Each cartridge contains the active substance somatropin (i.e. human growth hormone) and it is indicated for long-term treatment of children with growth failure. It is also used to treat adults with a deficiency (low levels) of growth hormone. Lucentis® is a medicinal product used to treat adults with certain sight problems caused by damage to the retina (the light-sensing layer at the back of the eye), and more specifically its central region, known as the macula.
Shortlisted alternatives discussed in the application	Alternative substances considered: DOW CORNING® 366, 35% DIMETHICONE NF EMULSION (DC 366) Alternative technologies considered: none Others: none
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
The applicant has PNEC recommended by RAC	☐Yes ☐No ☒Not relevant
All endpoints listed in Annex XIV were addressed in the assessment	☒Yes ☐No if 'No' – which endpoints are not addressed
Adequate control demonstrated by applicant(s) for the relevant endpoint(s)	☐Yes ☐No ☒Not Applicable – non-threshold substance
Level of release used by applicant for risk characterisation	<u>Release to Environment:</u> *In Langenargen (Germany):* **Water:** 0.177 g/year (release to wastewater, based on maximum theoretical production capacity). The release factor is 0.70%. **Air**: 0 g/year (emissions to air are considered negligible due the low vapour pressure of 4-tert-OPnEO and presence of the HEPA filter). **Soil**: 0 g/year (the substance is handled indoor; sludge from STP is incinerated). *In Ravensburg (Germany):* **Water**: 0.755 g/year (release to wastewater, based on maximum theoretical production capacity). The release factor is 0.27%. **Air**: 0 g/year (emissions to air are considered negligible due the low vapour pressure of 4-tert-OPnEO and presence of the HEPA filter during the depyrogenation step in the dry-heat tunnel treatment). **Soil**: 0 g/year Total release in water: 0.932 g/year 4-tert-OPnEO. Release of 4-tert-OPnEO to wastewater occurs from the cleaning/sanitizing of the spray nozzles and distribution lines inside the equipment performed after drainage of the equipment as well as from the cleaning of the compounding equipment which is used for manufacturing of the diluted silicone oil emulsion.

Risk Characterisation	Environmental compartments: The applicant did not attempt to derive PNECs or RCRs. The applicant has treated 4-tert-OPnEO as a non-threshold substance. The CSR describes how the Operation Conditions (OCs) and Risk Management Measures (RMMs) in the Exposure Scenario (ES) minimise releases to the environment as far as technically and practically possible (with the view to minimising the likelihood of adverse effects).
Applicant is seeking authorisation for the period of time needed to finalise substitution ('*bridging application*')	☒Yes ☐No ☐Unclear The applicant's supplier has proposed an alternative silicone oil emulsion, which the applicant has done preliminary experiments on. Further testing and the generation of stability data of each medicinal product is required, in addition to change notifications and approvals from all concerned health authorities.
Review period argued for by the applicant(s) (length)	5 years
Most likely Non-Use scenario	Temporary interruption of production while the applicant substitutes to the identified alternative
Applicant concludes that benefits of continued use outweigh the risks of continued use	☒Yes ☐No ☐Not Applicable – threshold substance with adequate control
Applicant's benefits of continued use	€1-10 million EBITA losses for one year (most likely non-use scenario) €10-100 million EBITA losses over the 5-year review period (worst-case scenario)
Society's benefits of continued use	100 000-1 000 000 patients will continue to benefit from health services offered by NutropinAq® and Lucentis®
Monetised health impact on workers	Not relevant
Distributional impacts if authorisation is not granted	Pharmaceutical companies operating outside the EEA are expected to take over the applicant's market share. Patients benefitting from the medicinal products may be affected.
Job loss impacts if authorisation is not granted	Marginal

SUMMARY OF RAC AND SEAC CONCLUSIONS

1. Operational Conditions and Risk Management Measures

1.1. Conclusions of RAC

Conclusion for environment

The main risk management measures (RMMs) are to collect any surplus or rests of silicone oil emulsion, as well as to collect any cleaning cloths/materials or single use equipment, which had been in contact with 4-tert-OPnEO and no relevant shortcomings to the operational conditions (OCs) and RMMs have been identified.

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

☒Yes ☐No

Does RAC propose additional conditions related to the operational conditions and risk management measures for the authorisation?

☐Yes ☒No

Does RAC propose monitoring arrangements related to the operational conditions and risk management measures for the authorisation?

☐Yes ☒No

Does RAC make recommendations related to the operational conditions and risk management measures for the review report?

☐Yes ☒No

2. Exposure Assessment

Releases to the environmental compartments:

Air: No emissions

Soil: No emissions

Water: 0.932 g/year (release to wastewater)

RAC considers that the release estimates provided by the Applicant are acceptable. RAC did not identify any shortcomings in the methodology used by the Applicant.

Does RAC propose additional conditions[4] related to exposure assessment for the authorisation?

[4] Conditions can be proposed where RCR is > 1, OCs and RMMs are not appropriate and effective, risk is

☐Yes ☒No

Does RAC recommend to the applicant(s) monitoring arrangements[5] relevant to the potential review report?

☐Yes ☒No

3. Risk Characterisation

The applicant has 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[6] and RAC's conclusion on this issue at RAC-50 meeting that it is currently not possible to determine a threshold for the endocrine disrupted properties of this substance.

Based on the OCs & RMMs described in the exposure assessment, the total amount of 4-tert-OPnEO used per year, release in water and the collection for incineration of all solid and main liquid wastes, RAC is of the view that the applicant has demonstrated that releases to environmental compartments have been minimised as far as technically and practically possible (with the view to minimising the likelihood of adverse effects).

The use applied for may result in up to approximately 1 g (0.932 g) per year emissions of 4-tert-OPnEO to the environment.

4. Analysis of alternatives and substitution plan

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

0.306 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

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

☒Yes ☐No

not adequately controlled, minimisation of emissions is not demonstrated.

[5] 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.

[6] https://echa.europa.eu/documents/10162/13637/npneo_and_opneo_for_agreement_final_en.pdf/026cbafc-6580-1726-27f3-476d05fbeef0

Conclusions of SEAC

The alternatives identified by the applicant are not suitable by the sunset date. The substitution plan was credible and consistent with the analysis of alternatives and the socio-economic analysis.

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 applicant(s) related to the content of the potential review report?

☐Yes ☒No

5. Benefits and risks of continued use

Has the applicant 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 applicant's 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,
- SEAC's assessment of the availability, technical feasibility and economic viability of alternatives,
- any additional information provided by the applicant or its downstream users,
- RAC's assessment of the risks to the environment.

6. Proposed review period for the use

☐ 4 years

☐ 7 years

☐ 12 years

☒ Other – 5 years

7. Proposed additional conditions for the authorisation

RAC

Additional conditions:

For the environment	☐Yes	☒No

SEAC

Additional conditions:	☐Yes	☒No

8. Proposed monitoring arrangements for the authorisation

RAC

Monitoring arrangements:

For the environment	☐Yes	☒No

SEAC

Monitoring arrangements	☐Yes	☒No

9. Recommendations for the review report

RAC

For the environment	☐Yes	☒No

SEAC

AoA	☐Yes	☒No
SP	☐Yes	☒No
SEA	☐Yes	☒No

10. Applicant(s) comments on the draft opinion

Has the applicant commented on the draft opinion?

☐Yes ☒No

Has action been taken resulting from the analysis of the applicant's comments?

☐Yes ☐No ☒Not applicable

JUSTIFICATIONS

0. Short description of use

The applicant, Vetter, uses the silicone oil emulsion DOW CORNING® 365, 35% DIMETHICONE NF EMULSION (DC 365), which contains 4-tert-OPnEO as an emulsifier, for the siliconisation of glass containers for two medicinal products. The products, NutropinAq® and Lucentis®, are used in cartridges for injection pens and pre-filled syringes. The applicant, which is a contract development and manufacturing organisation, produces these two medicinal products for F. Hoffmann-La Roche Ltd. (Roche). The applicant receives the active substance for these medicinal products from Roche and then, in accordance with the supply agreement and agreed specifications, it produces the agreed quantity of final medicinal product. The production of the medicinal product includes the preparation of the glass container (including the siliconisation), its filling and packaging for shipment.

The silicone layer improves the glass containers' ability to drain and prevents adsorption of ingredients on the glass surface. The siliconisation is achieved by spraying diluted silicone oil emulsion onto the inner surface of the glass container. Afterwards, the sprayed glass containers are moved into a dry-heat tunnel where water and other components of the emulsion evaporate and a thin silicone oil layer remains on the inner glass surface. The emulsifiers and preservatives are destroyed or reduced to a residual amount during the dry-heat treatment. After siliconisation and sterilisation, the glass containers are filled with the drug solution.

It should be noted that other applications for authorisation have been submitted, by Nuova Ompi S.r.l. unipersonale (Ompi) and by Roche for the use of DC 365 in the siliconisation of glass containers of other medicinal products.

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

Supply and dilution

The 18.9 L high density polyethylene containers of silicone oil emulsion containing 4-tert-OPnEO at a concentration of ≤ 2.6% w/w are received from the distributor by the Vetter warehouse and undergo a quality control test prior to release. Based on the supplier's certificate of analysis, the applicant performs at least an identification test. In performing the test solid and liquid waste is generated. All wastes are collected in relevant containers, transferred to the waste disposal site and finally disposed of by incineration.

The containers are transferred manually to a ventilated hood to be semi-automatically diluted into flasks. These flasks are then transferred manually to the conveyer belt of the washing and siliconisation compartment of the production line, where washing and siliconisation occurs.

During this dilution step, large spills are not expected. In case of small spills, 4-tert-OPnEO solution is wiped up with single-use cloths. These cloths are disposed of in ASP-containers (from German: *Abfall-Sammler-Pastös*, container for collecting hazardous, paste-like material).

At both sites the compounding equipment, which is used for manufacturing of the diluted silicone oil emulsion (stirrer, vessels, funnels), are cleaned by means of washing machines. The cleaning program consumes per washing cycle 271 L of purified water and 77 L of Water for Injection. One washing cycle is needed for cleaning the equipment. Rinsing waters are released to the respective municipal sewage systems.

Siliconisation of the primary packaging materials

The packaged sets of the primary glass containers are manually loaded into a machine and transferred to the conveyor belt. The conveyer belt distributes the primary glass containers and transports them to the washing and siliconising steps occurring in a closed compartment. Each primary glass container is flushed from below via a nozzle with pressurized purified water. Following the washing step, the primary glass containers are dried by using sterile filtered air. After drying, the primary glass containers are moved to the siliconisation compartment of the machine. In the siliconisation area, they are sprayed via nozzles from below with the diluted silicone oil emulsion. For spraying, the needles are moved into the glass barrels which minimizes the probability that sprayed emulsion can escape into the machine compartment. The amount of diluted silicone oil emulsion is properly adjusted to ensure a correct spraying rate and to avoid any surplus dripping from the barrels. Nevertheless, in case sprayed emulsion escapes into the machine interior, due to the laminar air flow most of the spray is deposited on the machine bed or is extracted by the exhaust system.

The remaining diluted silicone oil emulsion in the delivery container is collected in an IBC container, which is finally disposed via incineration. The delivery container is cleaned. The cleaning water is drained into respective municipal sewage.

The machine is cleaned with disposable cloths, which are afterwards collected as contaminated waste and disposed of for incineration with other waste such as the single use silicone tubings.

The surplus of the diluted silicone oil emulsion as well as the remaining emulsion in the delivery container is collected and disposed of for incineration.

Line cleaning is performed after each manufacturing batch. The siliconisation equipment (spraying needles and teflon tubing) are sanitized (using clean water steam) or cleaned (using purified water). The resulting, wastewater is released into the respective municipal sewage system.

Sterilising and depyrogenation unit (dry heat tunnel)

In the dry-heat tunnel, the primary glass containers are sterilised and depyrogenated for ≥ 5 min at ≥ 300 °C. It has been shown, that under these conditions 4-tert-OPnEO completely decomposes and no traces can be detected on the siliconised glass surface during this treatment[7].

There is no wastewater or solid waste generated during this step. The only liquid present may be condensation water in the air filter. The air filter is checked during the yearly maintenance phase. If necessary, the filter is replaced. The used filter is disposed of in ASP-containers (container for collecting hazardous, paste-like material) and finally destructed in an incineration plant.

Final products

The primary glass containers are automatically closed with sterilised stoppers or closure parts. Afterwards, the primary glass containers are aseptically filled with the required amount of medicinal product and sealed with sterilised crimp cramps (cartridges) or plugged with sterilised stoppers (syringes), both under sterile conditions. The filled primary glass containers

[7] Tobias Mundry: Einbrennsilikonisierung bei pharmazeutischen Glaspackmitteln – Analytische Studien eines Produktionsprozesses – Dissertation zur Erlangung des akademischen Grades doctor rerum naturalium im Fach Pharmazie eingeriehct an der Mathematisch- Natuwissenschaftlichen Fakultät I der Humboldt-Universität zu Berlin. (1999) Page 308.

are packaged for shipment.

0.2 Key functions and properties provided by the Annex XIV substance

The technical function of 4-tert-OPnEO is as an emulsifier. The pre-filled syringes and cartridges are siliconised to allow the movement of a plunger stopper along the inner side of the glass containers, while at the same time allowing for a tight connection between the glass container and the plunger stopper.

For an alternative silicone oil emulsion to be considered as an appropriate replacement of the 4-tert-OPnEO-containing emulsion, the following conditions should be fulfilled:

- The physicochemical behaviour of the silicone oil emulsion must be appropriate for the manufacturing process. This behaviour determines if the content and distribution of the silicone oil on the glass container can be achieved within the specified ranges.
- The closing as well as the gliding properties of the plunger stopper must be within the specified ranges.
- The components of the silicone oil emulsion must be compatible with the medicinal product, i.e. stability studies have to demonstrate that the medicinal product meets the specified requirements at the end of shelf life.

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

NutropinAq® is commercialised by Roche in cartridges for injection pens, although production of the cartridges is conducted by Vetter at the Ravensburg site. The active substance in NutropinAq®, somatropin, is identical to the human growth hormone. It is used for the treatment of children who fail to grow because of a lack of the growth hormone, long-lasting kidney disease or Turner syndrome, as well as for adults with a deficiency of growth hormone. The medicinal product is distributed in the United States and Canada by Roche and in other parts of the world (including Europe) by Ipsen Pharma, which has supply contracts in place with Roche.

Lucentis® is commercialised by Roche in pre-filled syringes of two dosage strengths produced by Vetter at the Langenargen site. Lucentis® is used to treat adults with certain conditions that impair their sight by damaging the retina, and more specifically its central region, known as the macula. The macula provides the vision needed to see detail for everyday tasks such as driving, reading, and recognising faces. Lucentis® is used specifically to treat adults with a "wet" form of age-related macular degeneration (AMD). It is also used to treat other sight problems associated with choroidal neovascularisation (i.e. abnormal growth of blood vessels beneath the retina), macular oedema (swelling of the macula) caused by diabetes, or macular oedema caused by occlusion (blockage) of the veins behind the retina.

1. Operational Conditions and Risk Management Measures

A summary of the OCs and RMMs in the environmental contributing scenarios is provided below. The detailed conditions of use are available in Section 9.3 of the CSR.

No working contributing scenarios are presented, as the scope of the CSR is limited to the environmental risk of 4-tert-OPnEO.

No contributing scenario for the service life is provided because it is not relevant.

1.1 Environment

The applicant presented one exposure scenario (ES1 – use of 4-tert-OPnEO as emulsifier in the siliconisation of glass containers) for both sites (ERC4 - Use of non-reactive processing aid at industrial site (no inclusion into or onto article)).

Table 1: Summary of operational conditions (sunset date 2021 and until the end of the review period)

Site	**Langenargen**	**Ravensburg**
Annual amount	0.0254 kg/year	0.281 kg/year
Maximal number of emission days per year	50	50
Maximum daily site tonnage	0.002 kg/day	0.0104 kg/day
Maximum daily release of 4-tert-OPnEO[8]	0.014 g/day	0.028 g/day
Concentration of 4-tert-OPnEO	≤ 2.6% raw material < 0.1% w/w in end product (glass container)	≤ 2.6% raw material < 0.1% w/w in end product (glass container)
Temperature	All process are carried out at 19-25 °C, except of dry heat tunnel treatment (≥ 300 °C) and cold room storage (2-8 °C)	

Water:

Cleaning of compounding equipment which is used for manufacturing of the diluted silicone oil emulsion (stirrer, vessels and funnels) and of the siliconisation equipment (delivery container, siliconisation needles and tubings) is conducted automatically by using washing machines or sanitised by using clean steam. The wastewater streams are drained into the sewage system and discharged in the respective municipal STPs.

Soil:

There are no direct releases to soil from the Vetter production sites since the process takes place in a well-controlled clean room environment where large spilling is not expected to occur. In case of small spills, spilled drops of OPnEO solution would be absorbed with binding material that is sent to the waste disposal station for incineration.

Air:

Direct releases to the air from the manufacturing process are not expected due to the very low vapour pressure of 4-tert-OPnEO. As well, air is filtered through a high efficiency particulate air (HEPA) filter before being released to the environment.

Waste management

The surplus is collected in a separate IBC container and stored until finally shipped to an incineration plant. At the end of the batch manufacturing, the remaining silicone oil emulsion in the delivery container is collected separately and incinerated. The silicone tubings are single

[8] Rinsing waters

use equipment. After use they are collected in ASP-containers and disposed of by incineration. Before or after sanitisation, the inside of the washing and siliconisation compartment is manually cleaned by using disposable cloths. The used cloths are also disposed of in ASP-container which is finally destructed by incineration. Air filter is checked during maintenance phase and in case a filter change has to be conducted, the used filter is disposed of in ASP-containers and finally destructed in an incineration plant.

Both sites have contracted a certified disposal company for handling solid and liquid waste. The liquid / solid waste is incinerated in an industrial waste incinerator.

Technical and organisational conditions

- Vetter has established an Environmental, Health and Safety system. The management system introduced in accordance with the standards of DIN EN ISO 14001 and 50001 and BS OHSAS 18001 includes identifying those plants, processes, activities and products that have a significant impact on the environment (environmental aspect assessment), energy consumption (energy aspects) and on the occupational safety and health of employees (risk assessment). All personnel who is allowed to handle 4-tert-OPnEO are trained regarding EHS issues by the Vetter-course CRS 100064 "Handling hazardous substances and medicine";
- The entire siliconisation, sterilisation, depyrogenation and aseptically filling processes of the glass containers take place in a highly-controlled environment, corresponding to EudraLex - Volume 4 - Good Manufacturing Practice Guidelines[9], in isolated and closed compartments without manual handling of the glass containers during the process;
- Line cleaning is performed after each manufacturing batch;
- An emergency plan is available for spill incidents (liquid is absorbed and all wastes after spill event are collected and disposed by incineration);
- The staff members involved in the disposal process have been trained regarding the handling of hazardous waste and are equipped with appropriate protective equipment. The transportation of production wastes is accompanied by a security guard to prevent any unauthorized access to the material to be destroyed and to ensure that the entire content of the container ends up in the waste bunker of the incineration plant.

Table 2: Summary of main environmental RMMs

Compartment	RMM	Stated effectiveness
Water	The main RMM is to drain the system after each batch and to collect any surplus or rests of (diluted / non-diluted) silicone oil emulsion and incinerate them. Additional RMMs include the collection and subsequent disposal into solid waste of any cleaning cloths/materials used for regular wiping of all equipment surfaces. Solid wastes are subject for incineration.	For incineration of solid and liquid wastes a 100% efficacy is assumed. Residual release of 4-tert-OPnEO to wastewater occurs from the cleaning/sanitising of the spray needles and tubing, as well as from the cleaning of the compounding equipment which is used for manufacturing of the diluted silicone oil emulsion.
Air	Low volatility / Air is filtered through a high efficiency particulate air (HEPA) filter	No direct release

[9] EudraLex - Good Manufacturing Practice (GMP) guidelines - Volume 4: Human & Veterinary, European Commission, Brussels, December 2010, ISBN 92-828-2029-7

	before being released to the environment. The filter is exchanged regularly and incinerated.	
Soil	Well-controlled clean room environment. Binding material used for the cleaning of potential spills are sent to the waste disposal station for incineration.	No direct release

1.2 Discussion on OCs and RMMs and relevant shortcomings or uncertainties

Since the main RMMs are to collect any surplus or remains of silicone oil emulsion, as cleaning cloths/materials or single use equipment, which had been in contact with 4-tert-OPnEO, no relevant shortcomings to the operational conditions (OCs) and risk management measures (RMMs) have been identified.

The only residual amount of 4-tert-OPnEO (~ 1.0 g/year) is released to wastewater during cleaning/sanitising of the compounding equipment, siliconisation and filling equipment. Cleaning is performed by employing washing machines which are not only used for cleaning of 4-tert-OPnEO-contaminated equipment of Use 1, but also for cleaning of 4-tert-OPnEO-contaminated equipment used for the manufacturing of products covered by the connected Use 2 (submitted in a separate application) as well as for the cleaning of equipment which was not in contact with 4-tert-OPnEO.

The corresponding volume of wastewater produced per day is 29-36 m^3. According to the applicant to collect this wastewater a large tank at the sites would be required which cannot be installed without substantial interventions in the facilities. Furthermore, there is currently no space available. This would require an evaluation project and full reconstruction of the material preparation areas that could not be done during ongoing manufacturing activities. The shut-down of the manufacturing activities would not only affect the manufacturing of Lucentis® and NutropinAq®, but also all drugs manufactured at these sites. In addition, the applicant stated that the transportation of the separated wastewater to the incineration plant would require a great deal of organisational effort and installations would be operated only during the 5-year period applied for.

The applicant confirmed that the substitution plan will be implemented before the end of the review period.

RAC takes note of the technical constraints mentioned by the applicant for collecting the rinsing water and the fact that within the 5-year review period all 4-tert-OPnEO will be substituted. The economic restraints are discussed by SEAC in section 5.1.

1.3 Conclusions on OCs and RMMs

Overall conclusion: OCs and RMMs in the ES are appropriate and effective in limiting the risk.

Are the operational conditions and risk management measures appropriate and effective 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

For the exposure assessment a total annual tonnage of 0.0254 kg/year and 0.281 kg/year at the Langenargen and Ravensburg site, respectively, was taken forward which corresponds to the maximum production capacity at the sunset date and could potentially be maintained until the end of the review period (end of 2025).

Solid and liquid wastes, with the exception of the release to water during the sanitising/cleaning process step, is collected for incineration. Therefore, the environmental exposure assessment presented by the applicant is based on the residual release from this washing water.

The applicant determined the release factor to wastewater (i.e. release to the municipal STP) of 0.70% and 0.27% at the Langenargen and Ravensburg site, respectively by using the mass balance of 4-tert-OPnEO during production process, corresponding to the maximum amounts of 4-tert-OPnEO used at sunset date (see Table 3).

Table 3: Mass balance for 4-tert-OPnEO based on amounts used at Vetter sites at the sunset date 2021 assuming production for maximum expected orders

Site	**Langenargen**		**Ravensburg**	
	kg/year	% (w/w)	kg/year	% (w/w)
Annual amount	0.0254	100	0.281	100
Total amount removed during depyrogenation step	0.00702	27.7	0.0374	13.33
Total amount incinerated	0.0182	71.6	0.243	86.40
Total release to wastewater	**0.000177**	**0.70**	**0.000755**	**0.27**

To estimate the total releases of 4-tert-OPnEO to the wastewater, data was obtained by weighing the respective equipment parts before and after the sanitising/cleaning process step. Considering the number of batches per year and the concentration of 4-tert-OPnEO, the total amount of 4-tert-OPnEO drained into the sewage system per year was calculated. The amount incinerated is calculated by subtracting the amount removed during sanitisation/washing of the siliconisation equipment and the amount removed during depyrogenation[10] (100% of the

[10] Tobias Mundry: Einbrennsilikonisierung bei pharmazeutischen Glaspackmitteln – Analytische Studien eines Produktionsprozesses – Dissertation zur Erlangung des akademischen Grades doctor rerum naturalium im Fach Pharmazie eingeriehct an der Mathematisch-Natuwissenschaftlichen Fakultät I der Humboldt-Universität zu Berlin. (1999) Page 308.

initially sprayed amount) from the total amount prepared for processing.

In Table 4 the annual release estimates of 4-tert-OPnEO for both sites are presented.

Table 4: Summary of environmental emissions of 4-tert-OPnEO

Release route	Release factor	Release per year	Release estimation method
Water	Langenargen site: 0.70% Ravensburg site: 0.27%	0.177 g/year 0.755 g/year	Based on the mass balance during production process
Air	0	0 g/year	Emissions to air are considered negligible.
Soil	0	0 g/year	Direct releases to soil are not possible. Sewage sludge from STPs is not applied to soil.

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

RAC considers that the methodology for assessing the exposure from residual releases to water is appropriate. The release factors and release estimates are based on site-specific parameters. All parameters are transparently reported and adequately justified. The estimates can be considered to be representative and are not likely to underestimate exposure.

As a result of the relatively low vapour pressure of 4-tert-OPnEO, the type of production process and the OCs and RMMs in place, RAC concludes that releases to air are expected to be negligible. Similarly, RAC agrees that direct release to soil are not likely.

RAC did not evaluate the predicted environmental concentrations (PECs) provided by the applicants since 4-tert-OPnEO is treated as a non-threshold substance with regard to its endocrine disrupting properties for the environment and therefore no appropriate PNECs or other benchmark values such as EQSs are available for comparison.

RAC takes note that the applicant will, while the plant is in operation and the substance is used, perform a monitoring campaign to measure 4-tert-OPnEO and its degradation products in the wastewater from the site prior to release to the general sewage system. The applicant pointed out that emissions from the use covered by this application (Use 1) cannot be distinguished from emissions from Use 2 which takes place at the same site. Therefore, the monitoring data will inevitably include the overall 4-tert-OPnEO resulting from the siliconisation related to the products covered by the presented use and the connected Use 2.

RAC takes note that within the 5-year review period all 4-tert-OPnEO will be substituted.

2.6. Conclusions on exposure assessment

RAC considers that the release estimates provided by the applicant are appropriate. RAC did not identify shortcoming in the methodology used by the applicant to estimate exposure (mass balance approach), that would invalidate the conclusion.

3. Risk characterisation

3.1. Environment

The applicant compared the predicted environmental concentrations (PECs) with available background concentration in surface water (River Schussen, Ravensburg site) and with the Environmental Quality Standards (EQS) for 4-tert-OP of the Water Framework Directive (Directive 2000/60/EC). RAC has not assessed this comparison as the applicant had clearly chosen a non-threshold approach in which minimisation of emissions is central and a quantitative risk assessment cannot be carried out for 4-tert-OPnEO. 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. Furthermore at RAC 50, the Committee decided, based on industry submissions contained in several applications for authorisation, that the current state of knowledge of the endocrine disrupting properties, mode(s) of action and effects of 4-tert-OPnEO in the environment is insufficient to determine a threshold.

The use applied for may result in up to approximately 1 g per year of emissions of 4-tert-OPnEO to the environment (this value represents release to wastewater before the municipal STP).

3.2. Conclusions on risk characterisation

Based on the OCs and RMMs in the ES, notably the use of 4-tert-OPnEO in mainly closed systems and incineration of solid and main liquid wastes the total amount of 4-tert-OPnEO used per year and release in water, RAC is of the view that the applicant has demonstrated that releases to environmental compartments have been minimised as far as technically and practically possible (with the view to minimising the likelihood of adverse effects).

4. Analysis of Alternatives and substitution plan[11]

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

0.306 kg

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

According to the applicant, DC 365 is a standard silicone oil emulsion available on the market that fulfils the stringent requirements of the pharmaceutical industry. An alternative silicone

[11] 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*".

oil emulsion without 4-tert-OPnEO has been developed by the supplier: DOW CORNING® 366, 35% DIMETHICONE NF EMULSION (DC 366). This alternative has similar properties to DC 365 but contains Polyethylene Glycol Monoundecyl Ether (CAS 34398-01-1) instead of 4-tert-OPnEO. It is a high temperature volatile surfactant, which is soluble in water, biodegradable and does not have endocrine disrupting properties.

First experiments regarding physicochemical properties as well as machinability behaviour of the alternative were promising. While DC 366 is considered very likely to be a suitable replacement, the process required for the substitution of the 4-tert-OPnEO containing silicone oil emulsion requires extensive testing and the generation of stability data for each medicinal product.

Since medicinal products are subject to extensive regulation by the health authorities all over the world, change notifications have to be submitted to competent health authorities when any change is introduced in their production process. As substitution with an alternative silicone oil emulsion is a change in manufacturing process, the substitution can only be completed after approvals from health authorities have been received. The change of the silicone oil emulsion requires extensive testing and the generation of stability data demonstrating that the resulting medicinal product complies with the specification at the end of the shelf life and that the change has no adverse impact on the quality of the medicinal product. Some countries update their marketing authorisations based on the approval of other countries so that not all updates can be made in parallel. It should be noted that Roche is the holder of the marketing authorisation of the two medicinal products covered by this application. Therefore, Roche is responsible for determining what tests need to be done and the data needs to be collected, analysed and submitted to the health authorities.

The applicant outlines the steps required to substitute, including pre-selection and evaluation of alternatives, feasibility testing, stability testing of the medicinal products, update of marketing authorisation/regulatory approval of health authorities, implementation of the change and introduction to all markets. The applicant is currently in the stability-testing phase.

The applicant expects the substitution to be completed between the end of 2021 (most likely case) and the end of 2025 (worst case). Under very favourable conditions, the applicant states that it may even be possible to complete the change in the production before the sunset date but that would require implementation and introduction to the market immediately after the first possible date for the regulatory approval and there is a high risk that this will not be possible for the affected products. Possible reasons for delays would, according to the applicant, include technical difficulties or results concluding that the alternative silicone oil emulsion is not suitable, limited availability of personnel resources and/or additional time required to obtain the necessary change approvals of marketing authorisations. The applicant is therefore applying for an authorisation to implement DC 366, while accounting for any possible delays.

Apart from changing the silicone oil emulsion, the applicant also assessed other managerial alternatives. These are discussed further in section 5.2.

No comments were received in the consultation.

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

Not applicable as no technically and economically feasible alternatives are available before the Sunset Date.

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

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

SEAC considers that the approach by the applicant to identifying and assessing alternatives allows for conclusions on the availability and suitability of alternatives. The shortlisted alternative was developed by the supplier of the silicone oil emulsion, Dow Corning, as a 4-tert-OPnEO-free alternative with similar properties to DC 365. In response to SEAC's questions, the applicant clarified that it also conducted its own market evaluation of emulsions provided by alternative suppliers. However, the composition of these alternative emulsions differed too much from the composition of DC 365.

In SEAC's opinion, the applicant convincingly demonstrates that technically feasible alternatives will not become available to the applicant before the sunset date because of the required stability testing of the medicinal products and the update of marketing authorisations/regulatory approval of health authorities.

4.4. Substitution activities/plan

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

Physicochemical and machinability tests on DC 366 have been performed by the applicant with positive results. The applicant is currently undertaking stability testing and, if the results are positive, the proposed marketing authorisation variations could be submitted to authorities in Q4 of 2019 at the earliest. Based on a regulatory pre-assessment by Roche and Ipsen Pharma, the approval for both medicinal products in all affected markets is expected to take approximately one year. When including a buffer period for possible delays from the best-case

assumption, the most realistic date for implementing DC 365 in the production of both medicinal products is Q4 of 2021. Nevertheless, some of the steps might take longer due to unexpected problems, technical difficulties or results concluding that the alternative is not suitable. The applicant therefore also presents the required timetables to substitute under different risk scenarios. In the worst-case scenario, there would be a failure of the stability study at the end of the medicinal product shelf life, with the consequence that the whole replacement procedure would need to be re-started. In this case, the complete replacement of DC 365 would take until the end of 2025, i.e. five years after the sunset date.

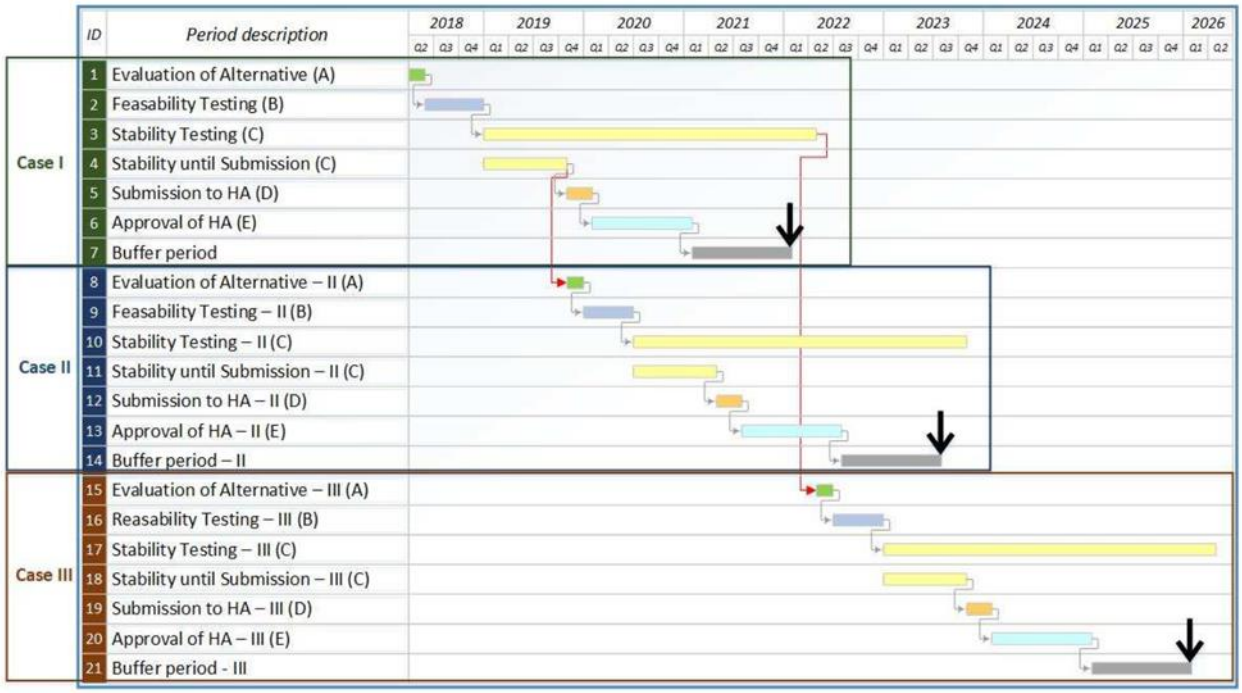

Figure 1 - Expected substitution timelines based on different scenarios, depending mainly on stability testing.

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

The applicant's substitution plan clearly outlines the actions needed to complete substitution, the timetable for implementing the changes and the current status of the substitution schedule. Upon request, the applicant provided additional information on the stability-testing, clarifying that the first task in that step is to assess what regulatory requirements in all relevant countries are for the change of the silicone oil emulsion, while the second task in that step is to define the scope of the stability studies (e.g. how many batches need to be tested, whether all or only selected dosage strengths need to be tested). The applicant also confirmed that the substitution timeline cannot be reduced by hiring additional personnel, as the current personnel itself is not a limiting factor to the substitution. The substitution plan also includes a clearly defined organisational structure and monitoring system to ensure the success of the substitution project.

In SEAC's view the substitution plan convincingly demonstrates that the substitution is likely to be completed by the end of 2021. A delay until 2025 would according to the applicant be the worst-case scenario, where failure is observed at the end of the stability study and the applicant would thereby need to re-start the process by evaluating alternatives, undertaking feasibility testing and undertaking stability testing, before submitting the proposed marketing

authorisation variations to health authorities.

The applicant clearly outlines the steps and timelines needed to substitute. The applicant has based the timelines on the required changes in marketing authorisations and associated stability testing, while including an extra time buffer for any testing issues and marketing authorisation delays. SEAC finds this approach reasonable.

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

The alternatives identified by the applicant are not suitable by the sunset date. The substitution plan is credible and consistent with the analysis of alternatives and the socio-economic analysis.

5. Benefits and risks of continued use

Has the applicant 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 applicant, release factors to wastewater have been reduced to 0.27% in Ravensburg and 0.70% in Langenargen, due to risk management measures (e.g. collection and incineration of surplus, minimisation of releases to wastewater during cleaning). Based on the highest expected usage, the applicant estimates that the maximum releases to wastewater will be 0.932 grams per year for both sites. RAC agrees with this estimate.

In response to RAC's question regarding whether the releases could be further reduced or eliminated, the applicant stated that separation of the wastewater resulting of the washing and siliconisation process as well as of the cleaning/sanitising process of the compounding and siliconisation equipment is currently not possible at either site. For this reason, an appropriate modification would need to be carried out, requiring an internal change process of 3-6 months and then shut down of manufacturing activities for several weeks. This shut-down would affect the entire production sites, not only the manufacturing activities related to relevant clean rooms. All in all, the applicant estimates that the cost of the reconstruction work would be approx. €1.3 million for Langenargen and approx. €1.1 million for Ravensburg. Furthermore, there would be additional disposal costs, land costs, potential penalties and costs for dismantling after the expiry of the review period. SEAC finds the estimated costs credible considering in particular the need to temporarily shut down the entire production sites. Furthermore, SEAC recognises that the benefits of this reconstruction would only be relevant until the applicant's ongoing substitution efforts were completed. The substitution is likely to be completed one year after the sunset date, and in the worst-case scenario five years after the sunset date.

5.2. Benefits of continued use

Non-use scenario

In the non-use scenario, the applicant would stop siliconising the glass containers of the affected medicinal products until the necessary steps to switch to the alternative emulsifier based on the alternative silicone oil emulsion DC 366 are completed. The supply of NutropinAq® and Lucentis® is expected to be temporarily interrupted. The applicant expects patients to switch to biosimilar products offered by competitors or to Lucentis® vials, as long as they are available in sufficient quantities on the market. The applicant notes that its competitors may also be affected by a non- authorisation. Due to the common usage of DC 365 in the pharmaceutical industry, pharmaceutical companies with manufacturing facilities outside the EEA are overall expected to gain.

The applicant also assessed other options from the perspectives of itself and Roche, including using pre-siliconised glass containers obtained from external sources and producing the medicinal product outside the EU. However, these changes would still require extensive testing and stability data generation, as well as a more complex change in the marketing authorisation in comparison to the change of the silicone oil emulsion. Moreover, the Vetter Group´s production facility outside of the European Economic Area (EEA) is only a development site where no production activities for commercial market supply is conducted. Stock-building of unfilled pre-siliconised glass containers is not an option as the siliconisation is part of the production process. Building a stock of the final product is also not possible, because NutropinAq® has a shelf life of 2 years while Lucentis® has a shelf life of 3 years. Finally, the commercialisation of the medicinal products in alternative dosage forms is also not feasible, as the distribution would require marketing authorisation from the health authorities.

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

- the use would be taken up by market actors operating outside the EU

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

- no jobs would be lost in the European Union

Socio-economic impacts of continued use

Considering the limited possibility of stock building for the medicinal products and their shelf life, the applicant estimates that NutropinAq® and Lucentis® will not be available on the market for the treatment of patients after an estimated 6 months and 11 months, respectively. A total of 100 000-1 000 000 patients use NutropinAq® and Lucentis® every year (50 000-500 000 for each of the products).

As there are alternative products available on the market for NutropinAq®, the applicant considers a severe lack of supply unlikely. For the purpose of the impact assessment, it assumes that competitors outside the EEA would be able to supply alternative medicinal products.

Patients using Lucentis® pre-filled syringes are also expected to be able to switch to biosimilar

products. However, Lucentis® is the only product available as pre-filled syringes in the United States. The possible alternatives on the market in the United States are not administered with pre-filled syringes. Furthermore, the applicant states that the competitors do not have approval to treat Myopic Choroidal Neovascularisation in the United States. The only equivalent approved alternative treatment in the United States would be Lucentis® vial (an alternative dosage form). Therefore, patients are expected to be switched either to Lucentis® vial or to non-pre-filled syringe biosimilars offered by competitors. According to the applicant, pre-filled syringes make the injection process easier and therefore help to avoid mistakes and ensure safety of patients. The applicant highlights that this is supported by the fact that once Lucentis® pre-filled syringes first became available as the first pre-filled syringe for its indication areas, physicians almost completely switched from vials to pre-filled syringes within a short time period.

The applicant notes that in general the change to another medicinal product can lead to unpredictable reactions triggered by the disposition of the individual patient. Moreover, different excipients in an alternative medicinal product increase the likelihood that the patient may be intolerant or allergic to the medicinal product.

In estimating the economic impacts of the non-use scenario, the applicant presents both a most likely scenario where substitution is completed in one year after the sunset date, and a worst-case scenario where substitution is completed five years after the sunset date. The most likely scenario would result in EBITA losses of €1-10 million to the applicant, while the worst-case scenario would result in EBITA losses of €10-100 million to the applicant.

Additionally, Roche would also be directly affected in the non-use scenario. For NutropinAq® the market losses are expected to be permanent, as it is considered unlikely that patients would switch back after the substitution. For Lucentis®, some patients are expected to switch to Roche's alternative dosage form of vials. Roche would also be affected in terms of a loss in reputation as well as potentially business-critical customer claims for breach of contracts.

While 20-50 jobs are expected to be re-allocated at the applicant's site, and some additional jobs are expected to be re-allocated at Roche, net impacts would be marginal. According to the applicant, the main employment-related risk is an "accelerated redundancy", i.e. that there are more than the needed number of employees with a specific skill in the same department. The associated social cost of unemployment were not estimated by the applicant.

Table 5: 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	Not applicable
1.2 Avoided profit loss due to ceasing the use applied for	€1-10 million
1.3 Avoided relocation or closure cost	Not applicable
1.4 Avoided residual value of capital	Not applicable
1.5 Avoided additional cost for transportation, quality testing, etc.	Not applicable
Sum of benefits to the applicant(s) and / or their supply chain	€1-10 million Described qualitatively

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[12]	Not applicable
2.2 Foregone spill-over impact on surplus of alternative producers	No quantified information available from the applicant
2.3 Avoided consumer surplus loss (e.g. because of inferior quality, higher price, reduced quantity, etc.)	Described qualitatively
2.4 Avoided other societal impacts (e.g. avoided CO_2 emissions or securing the production of drugs)	Described qualitatively
Sum of impacts of continuation of the use applied for	Described qualitatively
3. Aggregated socio-economic benefits (1+2)	€1-10 million

5.3. Combined assessment of impacts

The only quantified impact was the economic impact on the applicant due to the EBITA loss. In addition, the applicant emphasised the high benefits of the concerned products, such as the uniqueness of Lucentis® in the United States. According to the applicant, the loss of EBITA would amount to €10 000-100 000 million per kg emitted, based on the releases to surface waters after the municipal STP treatment.

SEAC notes that if the releases before the municipal STP and EBITA losses for only one year were considered (see the discussion in section 5.4), the cost effectiveness would be approximately €215-2 150 million per kg emitted in the worst case scenario and €1 075-10 750 million per kg emitted in the most likely scenario. The estimate for the worst-case scenario is considered the best estimate for the cost-effectiveness over the requested review period, since the most likely scenario has a shorter assessment period than the review period applied for. The estimate for the worst-case scenario is given in Table 7, while the estimate for the other scenario is given in footnote 13.

Table 6: Socio-economic benefits and risks of continued use

Socio-economic benefits of continued use		**Excess risks associated with continued use**	
Benefits	€1-10 million	Monetised excess risks to workers directly exposed in the use applied for	Not applicable
Quantified impacts of the continuation of the SVHC use applied for on other actors	Not available	Monetised excess risks to the general population and indirectly exposed workers	Not applicable
Additional qualitatively assessed	Vetter and Roche would be able to	Additional qualitatively assessed	Releases to waste water of 0.932 grams

[12] 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).

impacts	comply with their contractual supply arrangements. There would be avoided EBITA losses to Roche (unquantified). 100 000-1 000 000 patients would continue to benefit from both medicinal products.	risks	of 4-tert-OPnEO per year
Summary of socio-economic benefits	**€1-10 million** **Other qualitatively assessed impacts**	**Summary of excess risk**	**Releases to wastewater of 0.932 grams of 4-tert-OPnEO per year**

Table 7: Cost of non-use per kg[13]

	Over review period (worst-case scenario -5 years)
Total cost based on EBITA foregone based on maximum expected orders based on one year profit loss (€)[1]	€1-10 million
Total emissions to wastewater (kg)[2]	0.00465 (0.00093 per year multiplied by 5 years)
Ratio* (€/kg)[3]	**€215-2 150 million per kg**

Notes:
*: This ratio needs to be interpreted with care as any release amount significantly smaller than 1 kg conveys the impression that large costs would occur in the non-use scenario. However, this impression is an outcome of reporting the ratio in € per kg

1. "Total cost" (of non-authorisation) = Benefit of authorisation
2. "Total emissions" (if authorisation is granted) = Estimated emissions to the environment, kg over review period, based on Table 4
3. "Ratio" = Total cost/Total emissions

5.4. SEAC's view on Socio-economic analysis

SEAC considers that the applicant's non-use scenario, which foresees to temporarily cease production until substitution to DC 366 is completed, is justified because of the required stability testing and change notifications.

The only quantified element is the loss of EBITA to the applicant. SEAC considers that changes in EBITA are a relevant measure of changes in producer surplus and appropriate to monetising

[13] **Cost of non-use per kg in alternative scenario considered by SEAC**

	Most likely scenario (1 year substitution)
Total cost based on EBITA foregone based on maximum expected orders based on one year profit loss (€)[1]	€1-10 million
Total emissions to wastewater (kg)[2]	0.00093 per year
Ratio* (€/kg)[3]	€1 075-10 750 million per kg

the welfare implications of continued use. Moreover, the applicant's approach of estimating the impacts over different scenarios, depending on how quickly substitution can be completed, is considered transparent and reasonable.

SEAC notes that changes in the applicant's EBITA do not necessarily reflect net changes in economic surplus across the EU economy. In particular, the applicant argues that its direct competitors may take over its market shares in the non-use scenario, since alternative medicinal products are available for its customers. As this would imply producer surplus gains from the production of competitors, these gains would likely compensate in the long run for the surplus losses related to the applicant's production. SEAC asked the applicant whether it could provide an estimate of the possible market share and benefit to its competitors outside of the EEA but the applicant responded that it does not have the information to do so. Nevertheless, SEAC accepts that competitors from the EEA are unlikely to take over the applicant's market share immediately after the sunset date. SEAC uses the EBITA losses to the applicant from substitution one year after the sunset date (€1-10 million) to account for the net changes in producer surplus. SEAC has used this value for the cost-effectiveness calculation outlined in Table 7.

SEAC also notes that the alternative medicinal products for Lucentis® do not offer application through pre-filled syringes. SEAC finds the applicant's argument that pre-filled syringes make the injection process easier and therefore help to avoid mistakes credible.

5.5. Conclusion on the socio-economic analysis

SEAC has no substantial reservations on the quantitative and qualitative elements of the applicant's 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,
- SEAC's assessment of the availability, technical feasibility and economic viability of alternatives,
- any additional information provided by the applicant or its downstream users,
- RAC's assessment of the risks to the environment.

6. Proposed review period

☐ Normal (7 years)

☐ Long (12 years)

☐ Short (…. years)

☒ Other: 5 years

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

6.1 RAC's advice

RAC gives no advice on the length of the review period.

6.2. Substitution and socio-economic considerations

- SEAC considers that the applicant has been proactive in undertaking R&D efforts to implement the 4-tert-OPnEO substitution.
- The applicant has started the process to substitute to the alternative silicone oil emulsion DC 366.
- The applicant expects the substitution to be completed for both medicinal products by the end of 2021. However, to be prepared for possible delays which may be beyond the applicant's control (e.g. administrative delays in countries where marketing authorisations have been applied for), the applicant requests a review period of 5 years.
- SEAC has no substantial reservations on the quantitative and qualitative elements of the applicant's assessment of the benefits and the risks to the environment associated with the continued use of the substance.

Taking into account these points, SEAC recommends a **5**-year review period.

7. Proposed additional conditions for the authorisation

Were additional conditions[14] proposed for the authorisation?

☐ Yes

☒ No

7.1 Description

RAC

Proposed additional conditions

No conditions in addition to those described in the application are proposed.

SEAC

Proposed additional conditions

No conditions.

7.2. Justification

RAC is of view that:

[14] 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.

- the applicant has demonstrated that releases to environmental compartments have been minimised as far as technically and practically possible based on the OCs and RMMs in the ES;
- the exposure estimates provided by the applicant are appropriate.

8. Proposed monitoring arrangements for the authorisation

Were monitoring arrangements[15] proposed for the authorisation?

☐ Yes

☒ No

8.1 Description

No monitoring arrangements are proposed.

8.2 Justification

RAC is of view that:

- the applicant has demonstrated that releases to environmental compartments have been minimised as far as technically and practically possible based on the OCs and RMMs in the ES;
- the exposure estimates provided by the applicant are appropriate.

9. Recommendations for the review report

Were recommendations for the review report made?

☐ Yes

☒ No

9.1 Description

No recommendations are proposed.

9.2 Justifications

RAC is of view that:

- the applicant has demonstrated that releases to environmental compartments have been minimised as far as technically and practically possible based on the OCs and RMMs in the ES;
- the exposure estimates provided by the applicant are appropriate.

[15] 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.

10. Comments on the draft final opinion

Did the applicant provide comments on the draft final opinion?

☐ Yes

☒ No

Comments of the applicant

Was action taken resulting from the analysis of the comments of the applicant?

☐ Yes

☐ No

☒ Not applicable – the applicant did not comment

Reasons for introducing the changes and changes made to the opinion

Not applicable

Reasons for not amending the opinion

Not applicable