SOCIO-ECONOMIC ANALYSIS

Legal name of applicant(s):	Vetter Pharma-Fertigung GmbH & Co. KG
Submitted by:	Vetter Pharma-Fertigung GmbH & Co. KG
Substance:	4-(1,1,3,3-Tetramethylbutyl)phenol, ethoxylated (covering well-defined substances and UVCB substances, polymers and homologues); (Octylphenolethoxylates, OPnEO).
Use title:	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.
Use number:	1

CONTENTS

TABLES

FIGURES

GLOSSARY

Term	Explanation
AA-EQS	Annual Average Environmental Quality Standard
AfA	Application for Authorisation
AMD	Age-related Macular Degeneration
AoA	Analysis of Alternatives
ASP	'Abfall-Sammler-Pastös', German for a container for collecting hazardous, paste-like material
CEC	Corporate Executive Committee
CER	Coupon Equivalent Rate
CHF	Swiss francs
CMO	Contract Manufacturing Organisation
CRI	Chronic Renal Insufficiency
CSR	Chemical Safety Report
DC 365	DOW CORNING® 365, 35 % DIMETHICONE NF EMULSION
DC 366	DOW CORNING® 366, 35 % DIMETHICONE NF EMULSION
DNA	Deoxyribonucleic acid (contains the genetic code of organisms)
EBITA	Earnings Before Interest, Taxes, Depreciation, and Amortisation It is an accounting measure calculated using a company's net earnings, before interest expenses, taxes, depreciation, and amortisation are subtracted, as a proxy for a company's current operating profitability (i.e., how much profit it makes with its present assets and its operations on the products it produces and sells, as well as providing a proxy for cash flow).
ECHA	European Chemicals Agency
ECS	Environmental Contributing Scenario
EEA	European Economic Area The area in which the Agreement on the EEA provides for the free movement of persons, goods, services and capital within the European Single Market.

Term	Explanation
EHS	Environment Health and Safety
EIONET	European Environment Information and Observation Network
EMA	European Medicines Agency
EQS	Environment Quality Standard from the EU Water Frame Directive 2013/39/EU
ERC	Environmental Release Category
ERC 4	Environment Contributing Scenario - Use of non-reactive processing aid at industrial site (no inclusion into or onto article)
EU	European Union
EUR	Euros
EUSES	European Union System for the Evaluation of Substances, version 2.0. National Institute of Public Health and the Environment (RIVM), the Netherlands
FDA	US Food and Drug Administration
FTE	Full-Time Equivalents It is a unit that indicates the workload of an employed person in a way that makes workloads or class loads comparable across various contexts.
GMP	Good Manufacturing Practice
HEPA	High Efficiency Particulate Air filter
IBC	Intermediate Bulk Container
ICPR	International Commission for the Protection of the Rhine
ISO standards	International Organisation for Standardisation standards
IU	International Units A unit for biological activity used in pharmacology.
IW	Industrial end use at site
LEV	Local Exhaust Ventilation
logKoc	Organic Carbon-Water Partition Coefficient

Term	Explanation
MAC-EQS	Maximum Allowable Concentration Environmental Quality Standard
MSDS	Material Safety Data Sheet
Non-EEA	All countries outside the European Economic Area (EEA)
NP	4-nonylphenol, branched and linear
NP1EC	4-nonylphenoxyacetic acid
NP1EO	nonylphenolmonoethoxylate
NP2EC	4-nonylphenoxyethoxyacetic acid
NP2EO	nonylphenoldiethoxylate
NPnEO	4-nonylphenol, branched and linear, ethoxylated (substances with a linear and/or branched alkyl chain with a carbon number of 9 covalently bound in position 4 to phenol, ethoxylated covering UVCB- and well-defined substances, polymers and homologues, which include any of the individual isomers and/or combinations thereof), 4-NPnEO [Corresponding to entry 43 of Annex XIV of the REACH regulation as defined in regulation 2017/999/EU]
NPV	Net Present Value It is a measurement of profit calculated by subtracting the present values (PV) of cash outflows (including initial cost) from the present values of cash inflows over a period of time. Incoming and outgoing cash flows can also be described as benefit and cost cash flows, respectively.
OECD	Organisation for Economic Co-operation and Development
OP	4-(1,1,3,3-tetramethylbutyl)phenol (4-tert-OP, 4-t-OP)
$OP_{equiv.}$	4-(1,1,3,3-tetramethylbutyl)phenol Equivalent

Term	Explanation
OPnEO	4-(1,1,3,3-tetramethylbutyl) phenol, ethoxylated (covering well-defined substances and UVCB substances, polymers and homologues), 4-tert OPnEO [Corresponding to entry 42 of Annex XIV of the REACH regulation as defined in regulation 2017/999/EU]
OSH	Occupational Safety and Health
PBT	Persistent, Bioaccumulative and Toxic
PC29	Article category - Pharmaceuticals
PEC	Predicted Environmental Concentration
PFS	Pre-Filled Syringes
PNEC	Predicted No Effect Concentration
PPE	Personal Protective Equipment
PROC	Process Category
PROC5	Worker / Consumer contributing scenario: Mixing or blending in batch processes for formulation of preparations (multistage and/or significant contact)
PROC7	Worker / Consumer contributing scenario: Industrial spraying
PROC8a	Worker / Consumer contributing scenario: Transfer of substance or preparation (charging / discharging) from / to vessels / large containers at non-dedicated facilities
PROC9	Worker / Consumer contributing scenario: Transfer of substance or preparation into small containers (dedicated filling line, including weighing)
PW	Professional end use
R&D	Research and Development
RAC	Committee for Risk Assessment
RDG	Roche Diagnostics GmbH Part of the diagnostic division of F. Hoffmann-La Roche Ltd. It is located in Germany (Mannheim and Penzberg). On a RDG site (Mannheim) the manufacturing of medicinal products takes place

Term	Explanation
REACH	Regulation on Registration Evaluation, Authorisation and Restriction of Chemicals European Regulation (EC) No 1907/2006
RMM	Risks Management Measure
Roche	F. Hoffmann-La Roche Ltd. and its affiliates are collectively referred to as 'Roche'
RVS	Ravensburg Vetter Süd; Vetter production facility
SD	Supporting document
SEA	Socio-Economic Analysis
SEAC	Socio-Economic Analysis Committee
SIN list	'Substitute it Now!' list
SOP	Standard Operating Procedure
spERC	specific Environmental Release Category
STP	Sewage Treatment Plant
SU20	Sector of Use - Health services
(s)WfI	(sterile) Water for Injection
SVHC	Substances of Very High Concern A SVHC is a chemical substance (or part of a group of chemical substances) which meets the criteria of art.57 REACH In fact, listing of a substance as an SVHC by the European Chemicals Agency (ECHA) is the first step in the procedure for limiting the use of a chemical (either with an authorisation or a restriction).
U.S. (A)	United States of America
UVCB	Substance of Unknown or Variable composition, Complex reaction products or Biological materials
VEGF-A	Vascular Endothelial Growth Factor A
Vetter	Vetter Pharma-Fertigung GmbH & Co. KG in Ravensburg, Germany

Term	Explanation
Vetter Group	Vetter Pharma-Fertigung GmbH & Co. KG and its affiliates
VLA	Vetter Langenargen; Vetter production facility
vPvB	Very Persistent very Bioaccumulative
WCS	Worker Contributing Scenario
WHO	World Health Organisation

DECLARATION

We, Vetter Pharma-Fertigung GmbH, request that the information blanked out in the 'public version' of the Socio-Economic Analysis is not disclosed. We hereby declare that, to the best of our knowledge as of today (16th of May 2019) the information is not publicly available, and in accordance with the due measures of protection that we have implemented, a member of the public should not be able to obtain access to this information without our consent or that of the third party whose commercial interests are at stake.

Signature:

Date, Place:
16.05.2019, RAVENSBURG

Jörg Zimmermann, Vice President Development Service at Vetter

1. SUMMARY

Headquartered in Ravensburg, Germany, the Vetter Group (Vetter Pharma-Fertigung GmbH & Co. KG, hereinafter referred to as 'Vetter', and its affiliates) is a global leading contract development and manufacturing organisation with production facilities in Germany and the United States (U.S.(A)).

Vetter is applying for an authorisation to continue the use of Octylphenolethoxylates (OPnEO) after the sunset date until complete substitution. This socio-economic analysis (SEA) evaluates the following use:

Use 1: Use of Octylphenolethoxylates as emulsifier in the siliconisation of glass containers used as primary packaging for two specific medicinal products of one pharmaceutical company.

Vetter currently engages the silicone emulsion DC 365 which contains the substance OPnEO as emulsifier for the siliconisation of glass containers of two medicinal products, which are commercialised by F. Hoffmann-La Roche Ltd. F. Hoffmann-La Roche Ltd. and its affiliates are collectively hereinafter referred to as 'Roche', where the term 'Roche', as context requires, may refer to all or some of such affiliates. Roche is a Swiss multinational healthcare company that, together with its affiliates, works worldwide under two different main divisions: Pharmaceuticals and Diagnostics.

This dossier covers the two medicinal products NutropinAq® and Lucentis®. NutropinAq® is available on the market in cartridges for injection pens. Lucentis® is commercialised in pre-filled syringes (PFS). As mentioned before, Vetter acts a CMO of Roche for these medicinal products. This means that Vetter receives the active ingredient from Roche and then according to the order agreement and agreed specifications, Vetter produces the agreed quantity of final medicinal product. The production of the medicinal products includes the preparation of the glass container (including the siliconisation), its filling, and the packaging for shipment of the bulk ware. Roche is the holder of the marketing authorisation of the final medicinal products covered in this dossier.

PFS and cartridges for injection pens have emerged as one of the fastest-growing choices for parenteral dosage forms for a defined unit dose medication in the pharmaceutical market, because for the end user the injection becomes more user-friendly, making injections easier and safer allowing even self-administration. Also, with this type of dosage form, pharmaceutical companies are able to minimise drug waste and increase product life span.

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. It is commercialised by Roche in the U.S. and Canada. Roche licensed its marketing rights to Ipsen Pharma for other markets.

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. The macula provides the vision needed to see detail for everyday tasks such as driving, reading and recognizing faces. Lucentis® is commercialised by Roche only in the U.S.

In the 'non-use' scenario, Vetter will stop siliconising the glass containers of the affected medicinal products using OPnEO until the necessary steps to switch to an alternative emulsifier (DOW CORNING® 366, 35 % DIMETHICONE NF EMULSION (DC 366)) are completed. This includes

- where required - adapted or new marketing authorisations for different markets. Therefore, an interruption of the supply of the medicinal products is expected until substitution will be completed.

In principle, biosimilars could be used instead of NutropinAq® and Lucentis®. Therefore, patients are expected to be switched to these competitor products or to Lucentis® vials. Pre-requisite is the availability of these medicinal products on the market (e.g. resource availability in competing companies). The competitor products for NutropinAq® may also be affected by the usage of OPnEO for the glass container siliconisation and authorisation limiting their availability in case an authorisation is not granted. In addition, there are, unique characteristics of Lucentis®: competitors do not have approval for prescription in case of Myopic Choroidal Neovascularisation (U.S. Market). Moreover Lucentis® is the only product available as PFS in the U.S. Social impacts will therefore include the unavailability of the convenient and safe dosage form of PFS for Lucentis® in the U.S.. Furthermore, patients will be confronted with uncertainties regarding the interchangeability of a reference drug like NutropinAq® and Lucentis® and a biosimilar and with the unpredictable reactions triggered by the disposition of the individual patient.

In case of the non-use scenario, Vetter would face economic impacts with an estimated loss of EBITA per kg OP_{equiv}. emitted of [redacted] mio EUR/kg $OP_{equiv.}$ (10'000-100'000 mio EUR/kg $OP_{equiv.}$). If Vetter is not able to comply with the contractual supply obligations in place with Roche, Roche might ask for a compensation. Roche would also face economic impacts and a loss in reputation as well as potentially business-critical customer claims for breach of contracts. Additionally, due to the common usage of DC 365 in the pharmaceutical industry, it is expected that overall more pharmaceutical companies with manufacturing facilities outside the EEA will gain leading to a shift of pharmaceutical production and economic benefits outside the EEA.

Due to the uncertainties associated with the endocrine disrupting properties of the degradation products of OPnEO, the applicant decided to assume no threshold for the endpoint 'endocrine disrupting properties for the environment, as the safest option. The CSR demonstrates that the used amounts of OPnEO at the current stage are already very low. The current environmental exposure levels through release to wastewater are already reduced as far as technically and practically feasible by risk management measures, i.e. collection and incineration of surplus silicone oil emulsion. Remaining emissions to the environment with regard to the use of OPnEO will be completely eliminated by substitutions over the course of the review period. Therefore, risks related to the continued use of OPnEO can be considered as minimised.

This AfA is a bridging application with an already identified alternative and has demonstrated that a 5-year authorisation is needed to enable the completion of the replacement of OPnEO in the siliconisation process for the two affected medicinal products covered in this AfA. This period is requested due to the complexity of the substitution projects as an extensive feasibility and stability testing phase is required as well as marketing authorisation changes in multiple countries. It has been demonstrated that the socio-economic benefits of continued used outweigh the potential costs of the risk of a continued use of OPnEO.

2. GENERAL INTRODUCTION

The present dossier describes the use of DC 365 for the production of empty siliconised glass containers by Vetter for the medicinal products NutropinAq® and Lucentis®, which are commercialised by Roche.

Vetter is a CMO of Roche, and Roche is the holder of the marketing authorisation of Lucentis®. In the case of NutropinAq®, Roche is the holder of the marketing authorisation for USA and Canada and licensed its marketing rights to Ipsen Pharma for other markets. In this SEA further information on this license holder is not provided as the focus is on Roche as owner of the medicinal products and client of Vetter. Vetter receives the active ingredient from Roche and then produces the agreed quantity of final medicinal product according to the order agreement in place with Roche (see Figure 1).

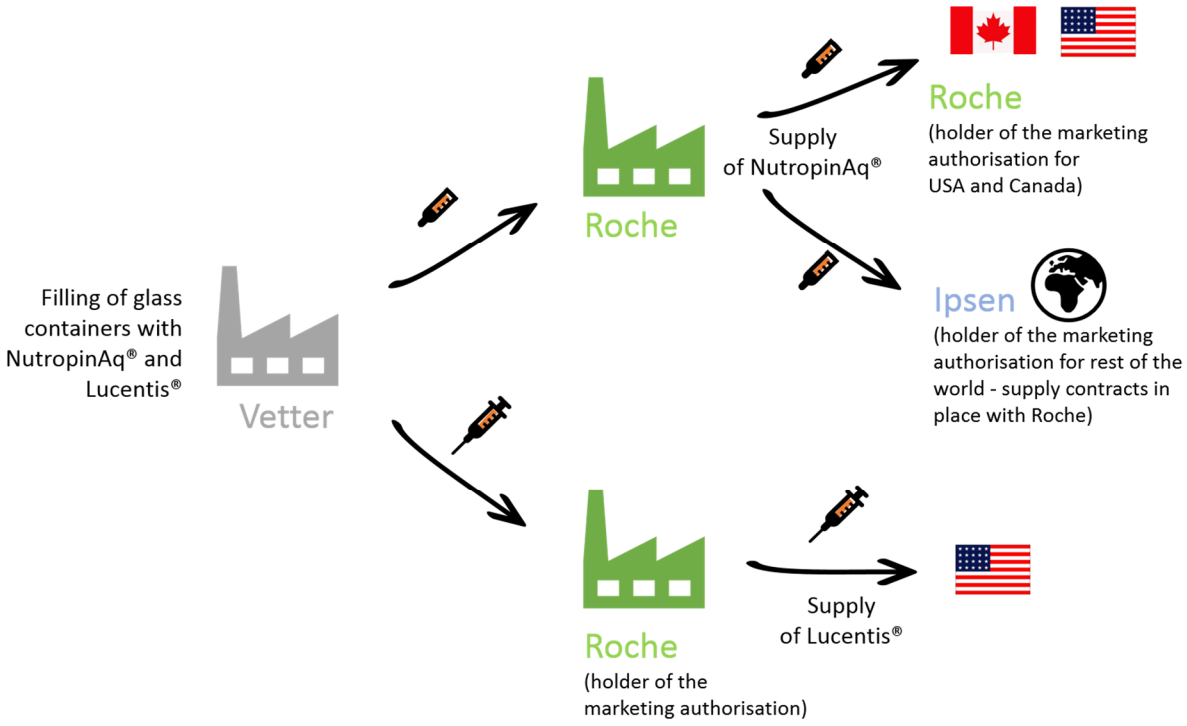

Figure 1. Overview of the relationship between Vetter - Roche.

2.1 Presentation of Roche - as Holder of the Marketing Authorisations for NutropinAq® and Lucentis®

- ⇨ **F. Hoffmann-La Roche Ltd**. (Roche) is a Swiss multinational healthcare company and the owner of the two medicinal products NutropinAq® and Lucentis®.
- ⇨ It is subdivided in two main divisions: **Pharmaceuticals** and **Diagnostics**.
- ⇨ 40 % of the 93'734 employees are based in Europe.
- ⇨ Roche is one of the world's leading providers of **clinically differentiated medicines** and **personalised healthcare**.
- ⇨ **137 million patients** were **treated** with Roche's medicine in 2017.

Since Roche is the holder of the marketing authorisation of the final medicinal product covered in this dossier, a brief description of this pharmaceutical company is given below.

Founded in 1896**, F. Hoffmann-La Roche Ltd.** is a Swiss multinational healthcare company that, together with its affiliates, works worldwide under two main different divisions: Pharmaceuticals and Diagnostics. The Roche group headquarter is in Basel, Switzerland. In 2017, the company **employed 93'734 people** worldwide (i.e. number of employees expressed in full-time equivalents (FTEs)); invested 8.7 billion EUR in research and development and posted sales of 44.4 billion EUR[1]. Most of the sites and more than 40 % of the worldwide FTEs are in Europe.

Roche is one of the **world's leading providers of clinically differentiated medicines and personalised healthcare**[2]. Personalised healthcare is based on the separation of patients into different sub-groups according to biological differences such as genetic make-up or disease subtype. Using this information, physicians can treat patients more precisely.

In 2017, **137 million patients were treated with Roche's medicine**. In total 30 medicines developed by Roche are included in the World Health Organisation (WHO) Model List of Essential Medicines.

[1] Roche in Brief, 2017: https://www.roche.com/dam/jcr:5e7bf87e-616f-448f-be00-a3144b62fedf/en/rib17e.pdf
[2] Roche website, Personalised Healthcare: https://www.roche.com/about/priorities/personalised_healthcare.htm

2.2 Presentation of Vetter - as Manufacturer of the Medicinal Products

- ⇨ **The Vetter Group:** Global leading contract development and manufacturing organisation.
- ⇨ **Services** range from early stage development support to clinical manufacturing and numerous packaging solutions for vials, syringes and cartridges.
- ⇨ 4’500 employees.
- ⇨ Sales (2017): **562 Mio EUR.**
- ⇨ For Vetter, meeting the highest quality and safety standards is essential.
- ⇨ Environmental protection and sustainability is an important goal for the company.

Headquartered in Ravensburg, Germany, the Vetter Group is a global leading contract development and manufacturing organisation with production facilities in Germany and the United States (Figure 2).

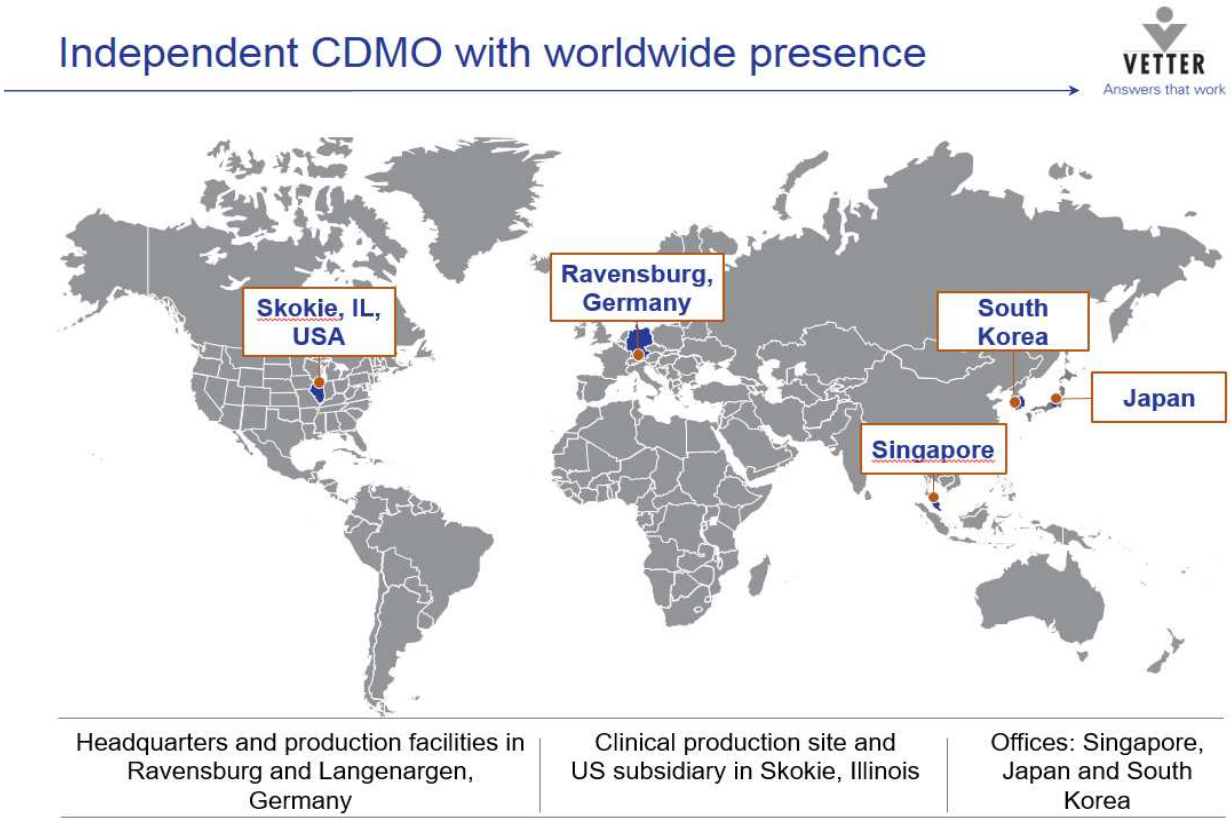

Figure 2. Vetter Group's global presence (data from 2017).

Currently, the Vetter Group is **employing 4'500 individuals** worldwide (Figure 3) 4375 of which are employed in Germany. the company has long-term experience in supporting biotechnology and pharmaceutical customers both large and small. In **2017**, the Vetter Group posted **sales of 562 mio EUR** with an **investment of 140 mio EUR**. The Vetter Group services range from early stage development support including clinical manufacturing, to commercial supply and numerous packaging solutions for vials, syringes and cartridges. As a leading solution provider, the Vetter Group appreciates its responsibility to support the needs of its customers by developing devices that contribute to increased patient safety, convenience, and enhanced compliance. Great importance is also given to social responsibility including environmental protection and sustainability.

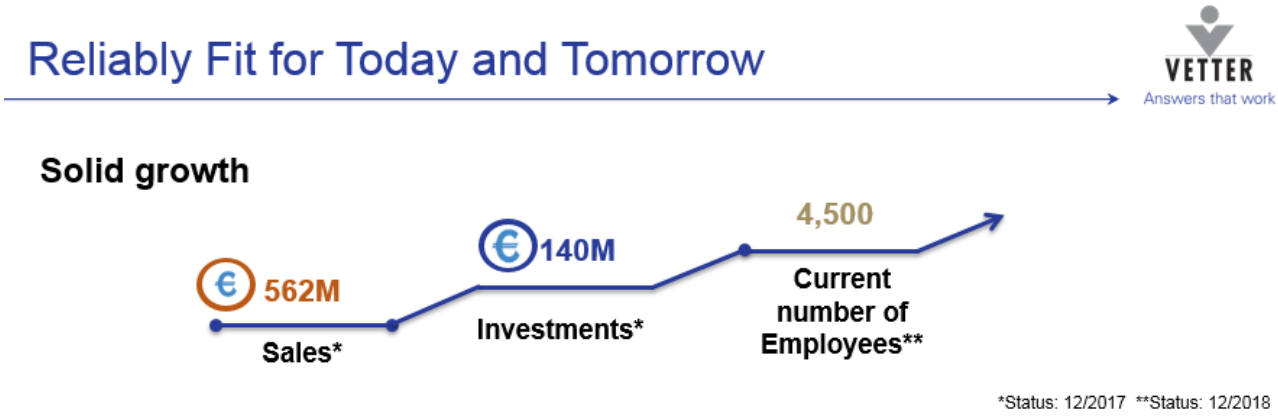

Figure 3. Overview of Vetter Group's sales, investments and employees.

The Vetter Group has a global Environment Health and Safety (EHS) policy. The global EHS-policy and program contains the following aspects:

- Resource Conservation: Limit the impact of emissions, noise, waste or wastewater on the environment to an economically justifiable minimum.
- Energy Efficiency: Using state-of-the-art technology and target specifications not only for its energy-consuming processes but also for its procurement, product, process and site development activities.
- Environmental Aspects: Concrete objectives and actions of environmental and resource protection are implemented in all divisions of the company focusing on avoiding and reducing environmental damage:
    - Reduction of paper consumption by 1 % relative to gross value added.
    - Protection of ground, water and air.
    - Decrease of the total energy consumption with regard to the gross value added by 1 % / year.
    - Making the energy consumption more transparent.

Vetter is successfully certified according to the following ISO standards:

- 14001 (environmental safety).
- 18001 (industrial safety).

- 50001 (energy management).

Currently 48 % of the required energy for the production is obtained by alternative energy sources (photovoltaics, geothermal energy, and biogas).

If a hazardous substance might be required for a new production process, a meticulous evaluation is conducted in order to assess if that specific hazardous substance can be replaced by a less hazardous substance.

3. AIMS AND SCOPE OF SEA

3.1 Aims and Scope of SEA

- ⇨ **OPnEO** was included in **Annex XIV**, because of its endocrine disrupting properties for the environment.
- ⇨ Sunset date: **4th of January 2021**.
- ⇨ This SEA concerns the use of OPnEO as emulsifier in the siliconisation of glass containers used as primary packaging for medicinal products of F. Hoffmann-La Roche Ltd.
- ⇨ Affected medicinal products: **NutropinAq® and Lucentis®**.

OPnEO was included in Annex XIV (entry 42) of the REACH Regulation by the European Chemicals Agency (ECHA) because of its endocrine disrupting properties for the environment of the degradation products with a sunset date on the 4th of January 2021.

The current SEA was developed to support Vetter's AfA to continue the use of Octylphenolethoxylates (OPnEO) as emulsifier in the siliconisation of glass containers used as primary packaging material for medicinal products, particularly in the production of NutropinAq® cartridges for injection pens and pre-filled syringes (PFS) of Lucentis®.

In its note from December 2017[3], the Committee for Risk Assessment (RAC) leaves the decision to the industry to define if a threshold can be derived for the endpoint 'endocrine disrupting properties for the environment' for OPnEO. This was also confirmed by the Socio-economic analysis committee (SEAC) note on 'SEA-related considerations in AfAs for endocrine disrupting substances for the environment, specifically OPnEO and NPnEO'[4]. Because of the uncertainties associated with these specific properties, the applicant decided to assume that no threshold applies for this endpoint as the safest option. Therefore, the applicant will demonstrate that the benefits of continued use outweigh the risks in this SEA.

The present SEA concerns the following use:

Use 1: Use of Octylphenolethoxylates as emulsifier in the siliconisation of glass containers used as primary packaging for two specific medicinal products of one pharmaceutical company.

[3] RAC, Risk-related considerations in applications for authorisation for endocrine disrupting substances for the environment, specifically OPnEO and NPnEO: https://echa.europa.eu/documents/10162/13637/npneo_and_opneo_for_agreement_final_en.pdf/026cbafc-6580-1726-27f3-476d05fbeef0

[4] SEAC note (SEAC/37/2017/03): https://echa.europa.eu/documents/10162/13637/seac_ed_approach_opneo_npneo_en.pdf/26c7779a-7228-2670-ad41-085d10ca056b

The geographical focus of this SEA is Germany as the preparation of siliconised glass containers as packaging material takes place in this country[5] (Figure 4). However, the **affected medicinal product NutropinAq®** is sold in Europe as well as worldwide. Lucentis® is only sold in the U.S. Consequently, the impacts concern the worldwide market and patients. Therefore, despite the **geographical focus on Germany**, the geographical scope of this SEA is the entire European Economic Area (EEA). In addition, worldwide impacts are also considered as NutropinAq® and Lucentis® are available on the **global market and in the U.S.,** respectively.

As outlined in the analysis of alternatives (AoA), Vetter is applying for an **authorisation for a review period of 5 years** to complete the replacement of OPnEO in the siliconisation process for the two affected medicinal products. This period is requested due to the complexity of the substitution projects as an extensive feasibility and stability testing phase is required as well as marketing authorisation changes in multiple countries. Therefore, this SEA examines impacts of the non-use scenario starting from the sunset date on 4th of January 2021 until the end of the applied for review period, i.e. 4th of January 2026.

Figure 4. The Vetter Group has several locations in Germany (here, two of them are shown as illustrative examples)[5].

[5] Vetter Website: https://www.vetter-pharma.com/de

3.2 Overview of Affected Medicinal Products and Siliconisation Process

3.2.1 Siliconisation Process

- ⇨ NutropinAq® and Lucentis® are available in siliconised glass PFS / cartridges for injection pen commercialised by Roche but manufactured and filled at Vetter.
- ⇨ A **silicone oil emulsion containing OPnEO** is used to siliconise the **inner surface of the glass containers**.
- ⇨ The glass containers of the PFS / cartridges are siliconised to:
  - Prevent the sticking of plunger stoppers.
  - Reduce the forces required to initiate and perform injections (break loose and gliding forces).
  - Allow a tight connection between the glass container and the plunger stopper.

This dossier covers the siliconisation process for **NutropinAq® cartridges for injection pens** (Figure 5 and Figure 6) and **Lucentis® PFS** (Figure 7). The medicinal products are commercialised by Roche but manufactured and aseptically filled at Vetter Ravensburg and Vetter Langenargen, respectively. At Vetter sites, a silicone oil emulsion, which contains OPnEO, is used to siliconise the inner surface of glass containers to allow for a tight connection between the glass container and the rubber plunger stopper while at the same time allowing an optimal movement of the plunger stopper along the inner surface of the primary container during the administration of the parenteral medicinal product. After siliconisation and sterilisation, the glass containers are aseptically filled with the drug product solution.

Figure 5. NutropinAq® Pen. Injection pen and cartridge.

Figure 6. NutropinAq®NuSpin®.

Injection pens with cartridges (see Figure 5 and Figure 6 for NutropinAq®) and PFSs (see Figure 7 for Lucentis®) have emerged as one of the fastest-growing parenteral dosage forms for a defined unit dose medication in the pharmaceutical market. This is because the application is user-friendly, making injections easier and safer allowing even self-administration. Also, with this type of dosage forms, pharmaceutical companies are able to minimise drug waste and increase product life span. The delivery system of a cartridge with an associated device (such as the pen of NutropinAq®) may offer some advantages compared to a PFS delivery system. In this context, patients can benefit from the safe and accurate dosing, as well as an advantage in the flexibility of dosing and the ability to administer multiple doses with one container. For example, NutropinAq® is intended for use only with the NutropinAq® Pen and allows for administration of a specific minimum dose to a specific maximum dose. Integrating a device and cartridge system can help the pharmaceutical manufacturer to differentiate its products on the market.

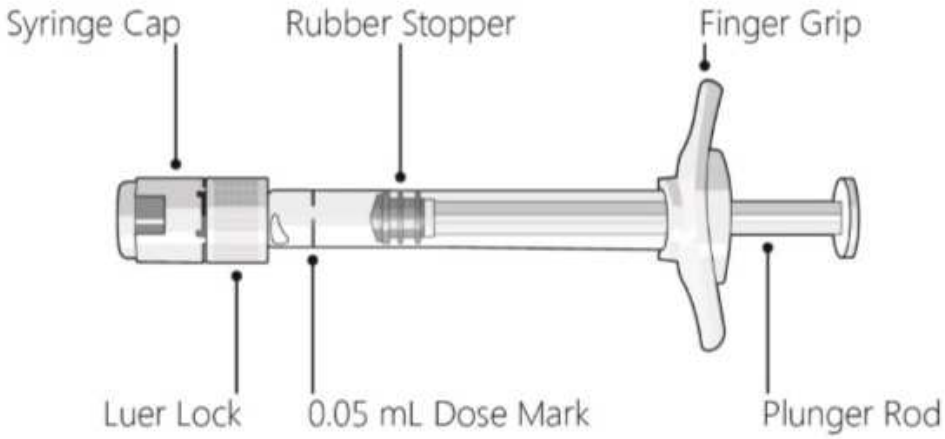

Figure 7. Lucentis® in PFS. V-OVS® System 10.6 consisting of tamper evident seal, Luer lock and tip cap.

DC 365 is a **standard silicone oil emulsion** available on the market that fulfils the stringent compendial requirements of the pharmaceutical industry. OPnEO has historically been used as an emulsifier in this emulsion before endocrine disrupting properties of the main degradation product (OP) of this substance had been identified.

Siliconisation of glass containers for both medicinal products in scope of this AfA is achieved by a **dry-heat siliconisation**. Here, the silicone oil emulsion is sprayed onto the inner surface of the glass

container. Following the siliconisation, the glass container is depyrogenated at ≥300 °C in a dry-heat tunnel, where water and other components of the emulsion evaporate or degrade and a thin silicone oil layer spreads over the inner glass surface. Following the heat treatment under aseptic conditions, sterile closure parts or stopper are placed automatically into the glass containers. Then each glass container is ascetically filled from the other side with the medicinal product and closed on this side with sterilised crimp caps or plugged with sterilised stoppers. The careful optimisation of siliconisation process parameters can help to achieve a uniform coating while minimising free silicone oil [1].

For more details regarding the siliconisation process please refer to Section 3.2 of the AoA. Additionally, for more details on the siliconisation, the production facilities and implemented risk reduction measures to minimise emissions please refer to the CSR.

3.2.2 Affected Medicinal Products

- ⇨ This dossier covers two medicinal products, NutropinAq® and Lucentis®.
- ⇨ The active substance in NutropinAq®, **somatropin**, is identical to the **human growth hormone**.
- ⇨ The active substance of Lucentis®, **ranibizumab**, is used to **treat adults with certain conditions that impair their sight** by damaging the retina.

In this section, a description of the two medicinal products is given.

NutropinAq® is a solution for injection in a cartridge. Each cartridge contains 5 to 20 mg of the active substance somatropin. Somatropin is **identical to human growth hormone** and is produced by recombinant DNA technology. The human growth hormone is a substance secreted by a gland located at the base of the brain, the pituitary gland. It promotes growth during childhood and adolescence, and also affects the way the body handles proteins, fat and carbohydrates. Somatropin stimulates growth rate and increases adult height, thus, it is used to treat children who lack endogenous growth hormone and children who have growth failure due to Turner Syndrome or chronic renal insufficiency (CRI). It is also used to treat adults that have metabolic alterations due to growth hormone production deficiency. The medicinal product is given once a day by injection under the skin, using injection pens specially designed for the NutropinAq® cartridge. The patient or their carer can inject NutropinAq® after training by a physician or a nurse. NutropinAq® cartridges are produced by Vetter in Ravensburg (Germany) and the medicinal product is then distributed in the United States and Canada by Roche and in other parts of the world by Ipsen Pharma (supply contracts in place with Roche).

Lucentis® is a clear, colourless to pale yellow aqueous solution for intravitreal injection (i.e. injection into the vitreous humour). **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). The wet form of AMD is caused by choroidal neovascularisation (i.e. abnormal growth of blood vessels beneath the retina, which may leak fluid and blood and cause swelling). Ranibizumab, the active substance of Lucentis®, is a humanised monoclonal antibody fragment produced in Escherichia coli cells by recombinant DNA technology that has been designed to attach to and block the vascular endothelial growth factor A (VEGF-A). By blocking this factor, Ranibizumab reduces the growth of the blood vessels and controls excessive leakage and swelling. Lucentis® is also used to treat other sight problems associated with choroidal neovascularisation, macular oedema (swelling of the macula) caused by diabetes, or macular oedema caused by occlusion (blockage) of the veins behind the retina. Lucentis® must be administered by a qualified and

experienced ophthalmologist[6]. Lucentis® is available in PFS containing a sterile solution with the additional excipients. Lucentis® PFS are produced by Vetter in Langenargen (Germany) and are then distributed in the **United States by Genentech** (Genentech is a leading biotechnology company, which is a recent member of the Roche Group[7]), and **outside the United States by Novartis**. The medicinal product commercialised by Novartis is not included in the AfA.

[6]European Medical Agency document on Lucentis®:
http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Summary_for_the_public/human/000715/WC500043548.pdf
[7] Genentech website: https://www.gene.com/about-us

Table 1. Description of the medicinal products produced by Vetter for Roche that are covered by this AfA.

Product Name **(active ingredient)**	**Marketed Dosage Form and Strength**	**Alternative Dosage Form**	**Therapeutic Indication Area**	**Possible Therapeutic Alternative**
NutropinAq® (Somatropin)	Cartridge for multidose injection pens in the following strengths: 5 mg/ 2 mL 10 mg/ 2 mL 20 mg/2 mL Additionally, placebo cartridges are produced for clinical studies.	No	Treatment of: - Children who fail to grow because of a lack of growth hormone - Girls from 2 years old who are short because of turner syndrome - Children (before puberty) who fail to grow because of long-lasting kidney disease, up to the time when they receive a kidney transplant - Adults with a deficiency (low levels) of growth hormone	Other recombinant growth hormones
Lucentis® (Ranibizumab)	PFS (monodose) in the following strengths: 6 mg/mL 10 mg/mL Additionally, placebo PFS are produced for clinical studies.	Monodose vials designed to provide 0.05 mL: 6 mg/mL 10 mg/mL	- Treatment of neovascular (wet) age-related macular degeneration -Treatment of visual impairment due to choroidal neovascularisation - Treatment of visual impairment due to diabetic macular oedema - Treatment of diabetic retinopathy -The treatment of visual impairment due to macular oedema secondary to retinal vein occlusion	Competing products are Eylea from Regeneron. Competitors do not have approval for Myopic Choroidal Neovascularisation (U.S.). Lucentis® is unique in the U.S. for its convenient application (i.e. PFS).

3.3 Definition of 'Applied for Use' Scenario

- ⇨ In the **'applied for use'** scenario, Vetter will **continue using OPnEO** as emulsifier in the siliconisation of glass containers used as primary packaging material for both medicinal products until substitution is completed.
- ⇨ Vetter will **able to continue supplying** the medicinal products to Roche complying with contracts.
- ⇨ Roche will be **able to continue supplying** NutropinAq® and Lucentis® to customers.
- ⇨ **Customers** (hospitals / physicians / pharmacies / patients) will be able to continue using both medicinal products for continued therapeutic benefit.

In the 'applied for use' scenario, Vetter will continue to use OPnEO as emulsifier in the siliconisation of glass containers used as primary packaging for the two medicinal products sold by Roche. This description is a projection also called 'business as usual', and it assumes a continued use OPnEO for the use applied for under the conditions described in the chemical safety report (CSR) until substitution is completed.

This scenario is used as baseline to evaluate the impacts under the 'non-use scenario' which is described in Section 3.4. In this scenario, Vetter will use up to **0.281 kg/a in Ravensburg** and up to **0.0254 kg/a of OPnEO in Langenargen to continue the production of glass containers**. Vetter will be able to continue the production of the glass containers in order to produce NutropinAq® and Lucentis®, which are commercialised by Roche. In the applied for use scenario, Vetter will be able to comply with the supply contract with Roche. Therefore, Roche's customers (hospitals / physicians / pharmacies / patients) will be able to continue using both medicinal products to provide therapeutic services to patients. From an economic point of view, Vetter expects to be able to **continue the current business** with the respective siliconised glass containers and to continue to **supply them** to Roche. Roche foresees to continue to be able to sell its medicinal products to its customers.

3.3.1 Economic Figures: Market Share, Net Revenue and EBITA

The aim of this section is to illustrate the economic figures for Vetter and specifically for the glass container production depending on the siliconisation using OPnEO.

Vetter defines its market as the market for fill-finish services for high value pharmaceuticals and biopharmaceuticals. Within this market segment, Vetter is a market leader with approx. [redacted] % share (data: 2017). This represents [redacted] mio filled units per year.

Vetter is a family-owned business which excels in the expertise to develop sophisticated manufacturing processes for its customers. Main competitors are other CMO companies like [redacted] or [redacted], which have grown by acquiring sites that the big pharma companies no longer wanted to operate themselves. These companies are therefore less focused, but rather offer all kinds of dosage forms, from solid oral dosage, semi-solids to oral liquids and injectables. Vetter has a unique position in the market because of its focus on sterile dosage forms. Other competing capacities are the fill-finish operations at the pharma-companies themselves (who in addition to their own production sometimes offer limited contract manufacturing services).

Table 2. Vetter: Historical and current net revenue and EBITA development for the affected product portfolios.

EUR	**2008**	**2012**	**2017**
Net Revenue NutropinAq®	[redacted]	[redacted]	[redacted]
EBITA NutropinAq®	[redacted]	[redacted]	[redacted]
Net Revenue Lucentis®	[redacted]	[redacted]	[redacted]
EBITA Lucentis®	[redacted]	[redacted]	[redacted]

In 2017, the Vetter **net revenue** and **EBITA** for the two products were [redacted] **mio EUR** and [redacted] **mio EUR,** respectively. Table 2 shows the **historical** and the **current net revenue and EBITA for Vetter's production of the final medicinal products**. The commercial production of Lucentis® started directly in 2017. The EBITA trend decreases between 2008 and 2012 because the filling process for NutropinAq® was in development (Process Qualification) in 2008. Then NutropinAq® was approved and commercial production started in 2011.

Vetter future trend should be based on predictions of orders by Roche. However, the order from Roche to Vetter are not yet confirmed for future years. In Table 3, it is possible to see the estimated Roche sales development for both medicinal products. The future trend is estimated to be [redacted]. As Vetter is the only manufacturer of these medicinal products, for the calculation of the Vetter impacts [redacted] orders were assumed.

Table 3. Roche: Historical, current and predicted sale development for the affected products[8].

mio EUR	2007	2012	2017	2018	2019	2020	2021*	2022*	2023*	2024*	2025*
Sales Lucentis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Sales NutropinAq®	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

*The order from Roche is not yet confirmed for those years.

In the 'business as usual' scenario, Vetter expects to be able to **continue the current business** with the respective glass containers.

In the 'business as usual' scenario, Roche expects to continue the **supply of their medicinal products** to their patients.

[8] The given financial data are taken from the source in $ and calculated in EUR with the exchange rate of 1.00$=0.89 EUR.

3.3.2 Supply Contract

- ⇨ Vetter has contractual obligations towards Roche.
- ⇨ Roche has contractual obligations towards their customers.
- ⇨ Vetter and Roche will be able to comply with the supply agreements in place.

Vetter has specific **contractual obligations** towards Roche. In fact, Vetter and Roche are parties to supply **agreements** regarding the **manufacture and supply** of the medicinal products covered in this dossier.

Depending on the stage of forecast and / or purchase orders of Roche, Vetter is obliged to deliver the products. In case of a failure of Vetter to make any timely delivery, Roche might be able to claim for compensation.

Roche has also contractual obligations towards their customers, e.g. license holders.

Under the applied for use scenario, Vetter will therefore be **able to continue supplying the medicinal products** to Roche complying with the supply contracts in place. Consequently, Roche will be able to supply their customers complying also with their supply contracts. Most importantly, Roche will be able to deliver the medicinal products to the patients.

3.3.3 Employment

- ⇨ Vetter has estimated that [redacted] **(20-50) employees** are dedicated to the pharmaceutical business affected by this authorisation in Ravensburg and Langenargen (Germany) (data: 2017).
- ⇨ Vetter and Roche will **continue to employ the staff responsible** for the activities associated with NutropinAq® and Lucentis®.

It is not possible to accurately determine the exact number of employees dedicated to the production and business of both medicinal products. However, **Vetter has estimated that [redacted] (20-50) employees** were dedicated to this business in 2017 ([redacted] and [redacted] employees for NutropinAq® and Lucentis®, respectively).

Under the applied for use scenario, Vetter will therefore **continue to employ** and allocate these FTE units for the production of both medicinal products. Similarly, FTEs at Roche are dedicated to these products e.g. for sales, supply chain management etc. Figures cannot be given here due to confidentiality reasons.

Under the applied for use scenario, **Vetter and Roche will continue to employ the staff responsible for the activities associated with NutropinAq® and Lucentis®**.

3.3.4 Patients

- ⇨ Patients benefit from the **therapeutic health** services of both medicinal products.
- ⇨ Estimated number of **patients** who benefit from **NutropinAq®** worldwide: [redacted].
- ⇨ Estimated number of **patients** who benefit from Lucentis® in the U.S.: [redacted]

Under the applied for use scenario, patients will be able to be treated 'as usual' and **benefit from the therapeutic health services** offered by NutropinAq® and Lucentis® (see benefit and treatment description in Section 3.2). Both **medicinal products will be available to patients reliably** (i.e. without any interruption).

The number of patients who annually benefit from NutropinAq® (data from 2017) and from Lucentis® (data from 2018) is estimated in Table 4.

Table 4. Number of patients who benefit from the NutropinAq® (data from 2017) and Lucentis® (data from 2018).

Medicinal Products	**Estimated number of patients who benefit from the medicine annually***		**Total**
	EEA	**Non-EEA**	
NutropinAq®	[redacted]	[redacted]	[redacted]
Lucentis®	[redacted]	[redacted]	[redacted]
TOTAL	[redacted]	[redacted]	[redacted]

* If the number of patients who benefit from the medicine annually is not available, then it was estimated. In fact, estimated number of patients who benefit from the medicine annually reflects the amount of the product consumed by an average patient each year. For example, if an average patient is treated with the 10mg configuration and he/she consumes one 10mg cartridge every month, then a patient / year ratio would be twelve cartridges. If 120 cartridges would be sold, then the estimate would be ten patients who benefit from the medicine annually.

In 2018, around [redacted] patients in the U.S. were treated with Lucentis®. Among these, approx. [redacted] patients are treated for the Myopic Choroidal Neovascularisation.

3.3.5 Investment into R&D and Planned Substitution

- ⇨ OPnEO **substitution is ongoing** with a promising alternative emulsifier.
- ⇨ Evaluation and implementation tests have been conducted and finalised by Vetter. However, an orientation stability study using sterile Water For Injection (sWfI) filled syringes is still ongoing.
- ⇨ Product-specific stability studies are still ongoing.
- ⇨ OPnEO use is part of the **strict marketing approval** of the medicinal products → Any change is subjected to changes in marketing authorisations by Roche.
- ⇨ Vetter investment: [redacted] **EUR.**
- ⇨ Vetter applies for an authorisation to **gain additional time** for the necessary evaluations and regulatory approvals by Roche needed for the substitution project including associated risks.
- ⇨ Review period: **5 years**.

Vetter is currently working on the **substitution of OPnEO in the applied for use**. As described in the AoA, substitution projects, especially the stability studies, are **ongoing**. An **alternative has been proposed** for the silicone oil emulsion containing OPnEO used in the production of glass containers.

It is expected that the feasibility and stability studies will identify it as a technically suitable alternative for replacement of the aforementioned silicone oil emulsion. Data demonstrating that the resulting medicinal product complies with the specification at the end of the shelf life and the replacement has no adverse impact on the quality of the medicinal product will need to be reported by Roche to the corresponding health authorities.

Even though under very favourable conditions it may be possible to complete the change before the sunset date, there is a **high risk** that this will not be possible. This is due to the strict requirements that medicinal products must fulfil, the considerable effort that is needed for testing their quality, e.g. performance and stability over long periods of time, and the time needed to obtain marketing authorisations in the countries where these products are commercialised.

In case any of the steps of the replacement process have to be repeated for any of the products, finalisation of the replacement process will be delayed.

It is also possible that the **regulatory approval** takes more than a year in some countries, that is why even if no technical difficulties arise, a REACH authorisation is needed until the necessary approvals on the updated marketing authorisations from all countries are received and the production process of that product can be started with the alternative silicone oil emulsion. The planned substitution corresponds to an **investment** in the order of [redacted] **EUR** (here, only the costs for the studies conducted by Vetter are taken in account). Since Roche is the marketing authorisation holder for NutropinAq® and Lucentis®, further investment required to complete the substitution of DC 365 (containing OPnEO) in the production of this medicinal product, is made by Roche. Due to confidentiality reasons, the costs cannot be disclosed in this dossier.

This application is a bridging application for an already identified alternative. It is likely that substitution with the alternative could be completed by the end of 2021, i.e. one year after the sunset date. However, the replacement timeline might be delayed due to limited personnel resources and the facilities' capacity to produce the batch / batches needed for the stability testing. Furthermore, in case any of the steps of the replacement process have to be repeated for the product, finalisation of the replacement process will be delayed. It is also possible that the regulatory approval takes more than the currently estimated one year in some countries. That is why even if no technical difficulties arise, a REACH authorisation may be needed until the necessary (changed) marketing authorisations from all countries are received and the production process of that product can be started with the alternative silicone oil emulsion. **Taking into account the described risks, substitution is expected to be completed at the latest by the end of 2025** (see Figure 8).

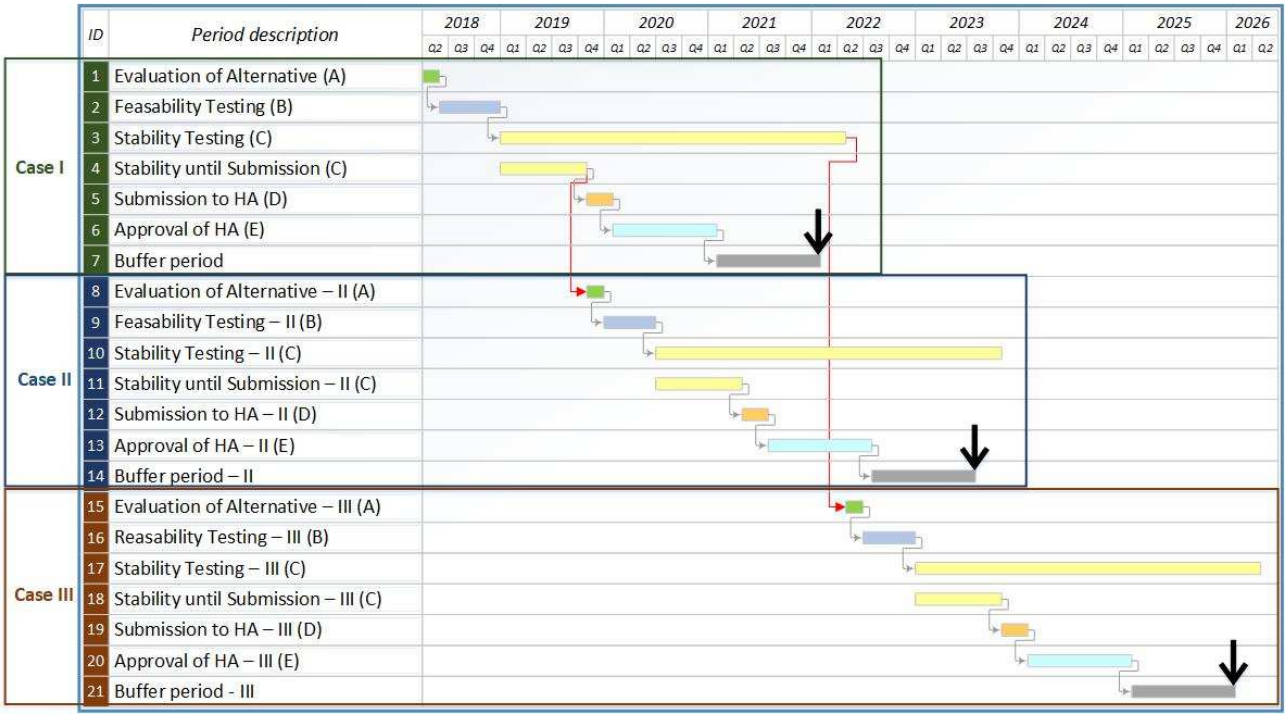

Figure 8. Expected replacement timelines based on different risk scenarios (for more details please refer to the AoA Section 7.1.2). The capital letters in parenthesis refer to the Steps as listed in Table 3 of the AoA. Grey arrows show dependencies of Steps, while red arrows apply in case stability results do not fulfil the acceptance criteria. Black thick arrows show the time when the switch from DC 365 to DC 366 would be implemented.

3.3.6 Emissions and Risk Reduction Measures

- ⇨ Maximum total annual usage of OPnEO in Ravensburg and Langenaragen at the sunset date: **0.306 kg/a** (based on maximum expected orders from Roche).
- ⇨ The usage should diminish to **reach zero by the end of 2021** (likely case) or at the end of the review period (end of 2025, worst-case).
- ⇨ Release to wastewater: maximum 0.00093 kg/a (0.7 % of used amount in Ravensburg and 0.27 % of used amount in Langenargen).

The above described Vetter activities will lead to emissions as described in the CSR (maximum **emissions to wastewater of 0.93 g/a of OPnEO after the sunset date**). The total maximum annual usage of OPnEO in Ravensburg and Langenargen for the use under consideration was assessed based on maximum expected orders by Roche between the sunset date and the end of the review period. As a worst-case, emissions will reach 0 at the end of the review period. This assumption was made in order to ensure that the assessment covers the maximum possible usage of OPnEO. For comparison, Figure 9 also represents the expected scenario in which substitutions would be finalised as scheduled (i.e. finalisation be the end of 2021).

Release to wastewater in 2018 is already reduced to 0.7 % in Ravensburg and 0.27 % in Langenargen of the total annual tonnage of OPnEO due to risk management measures (e.g. collection and incineration of surplus, minimisation of releases to wastewater during cleaning).

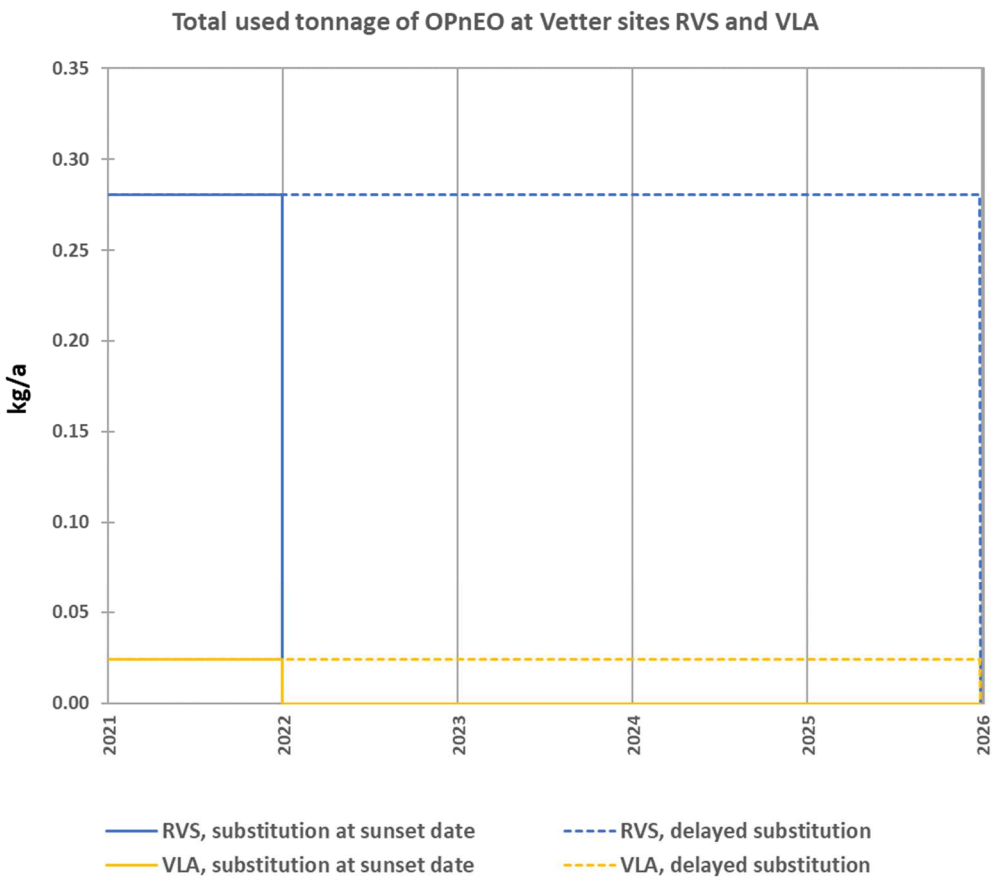

Figure 9 Evolution of the total annual use of OPnEO between 2021 and end of 2025 for Use 1 of this application at Vetter manufacturing sites Ravensburg (RVS) and Langenargen (VLA) considering the planned substitution and maximum expected orders placed by Roche.

3.4 Definition of 'Non-Use' Scenario

- ⇨ **OPnEO replacement** has been initiated but will most likely **not be completed at the sunset date**.
- ⇨ Production changes might need an **update of the marketing authorisations** for both medicinal products requested by Roche according to the requirements of the health authorities of each country.
- ⇨ Non-use scenario: **Vetter production process with OPnEO will need to be interrupted** and **Roche will not be supplied.**
- ⇨ Any other option from Vetter and Roche's perspective would either a) take longer than the exchange of the silicone oil emulsion, such as relocation to a facility in a non-EEA country, or b) is not feasible, such as stock building of unfilled containers.

The purpose of this section is to describe the reaction of Vetter and Roche in case of authorisation refusal to continue use of OPnEO after the sunset date on the 4th of January 2021.

In the **'non-use' scenario**, the dosage forms of medicinal products produced in a primary glass container siliconised with OPnEO will be not produced by Vetter**.** The **Vetter production process will need to be interrupted starting from the 4th of January 2021 until** the necessary steps to **switch to a silicone oil emulsion containing an alternative emulsifier** (i.e. DC 366) are completed. This will include - where required - the need for Roche to request an **update for the marketing authorisations** for both medicinal products on the affected markets. Therefore, an **interruption of the supply** of NutropinAq® and Lucentis® to Roche is expected until substitution is completed. Consequently, **Roche will not be able to supply both medicinal products to their customers**.

The **commercialisation of a medicinal product is highly regulated**, and the medicinal products must meet pre-determined specifications that are an integral part of the marketing authorisation. Marketing authorisations are applied for per dosage of the medicinal product and per manufacturing location. Changes in the marketing authorisation of medicinal products require the approval from regulatory bodies (i.e. health authorities) in each country where the product is placed on the market. Each change will require extensive testing and generation of stability data demonstrating that the resulting medicinal product complies with the specification at the end of the shelf life and the change has no adverse impact on the quality of the medicinal product. Depending on the level of the change, the reporting category could range from a minor 'notification' to a major 'prior approval variation'.

Consequently, even if an alternative silicone oil emulsion has been identified to be technically feasible, the substitution can likely only be implemented after the sunset date due to the **time needed to obtain all marketing authorisations**. Note that modifications of the production process can be implemented only after the marketing authorisations for all countries have been obtained (for more details see AoA Section 5). Also, the company that commercialises the medicinal product (in this case Roche) is the holder of the medicinal product marketing authorisation. This means that even though the primary packaging of the medicinal products is done by Vetter, the changes to the manufacturing process will be reported to the competent health authorities by Roche.

In order to overcome the interruption of the supply, the following options **from the perspective of Vetter** were analysed:

1) **Moving the production of PFS and cartridges or including the siliconisation of the glass containers to a non-EEA site**: This is not possible for the following reasons: Firstly, even if Vetter has some production facilities in the United States (U.S.), this facility is only a development side where no production activities for commercial market supply is conducted. Therefore, no alternative siliconisation sites outside the EU are available. The filling of the active substance in pre-siliconised glass container produced outside the EEA is also not possible. It is expected, that switching to ready-to-use components, which have been siliconised by a supplier outside the EU would be time consuming and would increase costs that need to be invested in the project. Reason for this is that pre-siliconised glass containers cannot be processed in clean rooms using a coherent process as for the processes for NutropinAq® and Lucentis® in place at the moment at Vetter sites. Thus, the usage of pre-siliconised glass containers would result in internal transfer of clean room, which requires a transfer of the process including performance qualification, stability testing, and approval by the respective health authorities (e.g. FDA, EMA). Estimated time frame for such change is estimated to be 4 to 6 years, out of which 2 to 3 years are needed for process transfer (performance qualification and stability testing). Further 2 to 3 years would be required for assessment procedures and approval of the transferred process by the competent authorities. According to the given timeline, a relocation would take at least as long as the substitution of the silicone oil emulsion and as discussed previously, Roche would need still need approval form the health authorities for such a change.
2) **Use of pre-siliconised glass containers obtained from external sources**: This is not considered a suitable alternative for NutropinAq® and Lucentis®. This is due to the fact that the washing / siliconising and filling is a coherent process which is related to a specific clean room and both is part of the marketing authorisation as explained before.
3) **Stock building of unfilled pre-siliconised glass containers** is not an option because the siliconisation of both medicinal products are part of the production process as discussed before.

From the **perspective of Roche** as the holder of the marketing authorisations of the medicinal products there are the following options to overcome the stock out of both medicinal products:

1) **Moving the production of the affected products to its non-EEA facilities or other CMO outside the EEA**: Transfer of the production processes to another facility involve extensive testing, performance qualification and approval by the competent health authorities. This process takes several years. Therefore, this alternative is not considered viable.
2) **Stock of the final product**: NutropinAq® has a shelf life of 2 years, whereas Lucentis® has 3 years. Both medicinal products are kept with a safety margin at stock. Considering the non-use scenario, after about 6 months for NutropinAq® and after eleven months for Lucentis®, these products will not be available on the market anymore. The exact time will depend on the country. The reason for such short times in comparison to the product shelf life is due to the complexity of the global supply chain. In fact, several tender businesses and / or some local affiliates need to be supplied with products which have a remaining shelf life of at least 80 %. Furthermore, due to limited available production capacity of the manufacturing sites (based on the current shift models) an increase of the production within a short timeframe is limited.
3) **Alternative dosage forms**: Another alternative would be the commercialisation of the medicinal products in alternative containers. This alternative is not possible since Roche does not have marketing authorisation from the health authorities to distribute the affected medicinal products in any other dosage form (including for example multidose vials, non-siliconised glass syringes and plastic syringes). Therefore, even if Vetter could produce this dosage alternatives for Roche, an update of marketing authorisations would need to be applied for by Roche at the competent

health authorities. This process takes several years. In addition to PFS, Lucentis® is also commercialised in a monodose vial. However, PFS is the preferred dosage form because it makes the injection process easier, increasing safety. This is supported by the fact that once Lucentis® became available as the first PFS for its indication areas, physicians almost completely switched from vials to PFS within a short time.

In summary, for NutropinAq® and Lucentis® the **replacement of OPnEO in the manufacturing process has been initiated** but will most likely **not be completed at the sunset date** (4th of January 2021) for the reasons outlined in the AoA. Therefore, if authorisation to continue the use of the silicone oil emulsion containing OPnEO is not obtained, NutropinAq® and Lucentis® PFS will have to be taken off the market.

3.5 Information for the Length of the Review Period

- ⇨ An alternative has been identified but the substitution projects is complex.
- ⇨ The **rigorous requirements** for **marketing authorisations** of medicinal product lead to an extended feasibility and stability testing phase.
- ⇨ Vetter is applying for an authorisation to use OPnEO for a period of **5 years.**

Vetter is applying for an authorisation to use OPnEO for a period of 5 years starting from the sunset date on the 4th of January 2021.

An **alternative**, non OPnEO-containing silicone oil emulsion, i.e. DOW CORNING® 366, 35 % DIMETHICONE NF EMULSION (**DC 366**), has been proposed by the manufacturer. The composition of the proposed emulsion was evaluated and experiments to test this emulsion as alternative were defined. First results obtained regarding physicochemical properties as well as machinability behaviour were promising. However, the process required for the substitution of the OPnEO containing silicone oil emulsion requires extensive testing and generation of stability data of 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.

This period of time is justified in detail in the AoA (see the AoA document and Section 3.3.5). **Five years** after the sunset date is requested to complete the replacement of this substance in the siliconisation of the glass containers for the two affected medicinal products covered in this AfA. This period is requested due to the **complexity of the substitution projects** as an extensive feasibility and stability testing phase is required as well **as marketing authorisation changes** in multiple countries.

4. ANALYSIS OF IMPACTS

4.1 Environmental Impacts

- ⇨ **Exposure to the environment** with regard to the use of OPnEO **is reduced** as much as technically and practically feasible by collection and incineration of surplus silicone oil emulsion. OPnEO emissions will be completely eliminated by substitutions over the course of the review period.
- ⇨ The amount of the total annual OPnEO release to wastewater is 0.932 g/a.
- ⇨ Risks related to the continued use of OPnEO can thus be considered as minimised.

4.1.1 General Introduction

In its note on 'risk-related considerations in AfAs for **endocrine disrupting substances for the environment**, specifically OPnEO' [2] the RAC indicates that in case the applicant does not propose a dose-response relationship under the socio-economic route for applying for authorisation, the AfA will be evaluated on the same basis as an application for a Persistent, Bioaccumulative and Toxic (PBT) / very Persistent very Bioaccumulative (vPvB) substance. As for the latter type of substances, the releases to the environment can be considered as a proxy for the environmental impacts, the applicant should minimise releases to the environment as far as technically and practically possible, to guarantee minimisation of the likelihood of adverse effects.

Risks to human health do not need to be assessed in this assessment as OPnEO was listed on Annex XIV only on the basis of their endocrine disrupting properties for the environment (Article 62(4)).

For the applicant to conclude that the benefits of continued use outweigh the risk, the note published by the SEAC [3] recommends to further provide the following parts of the assessment:

- A monetised estimate of the benefits of continued use,
- A quantified release estimate accompanied with a qualitative description of where the releases occur (e.g. dilution capacity of a river and number of release sources and their temporal and geographical distribution),
- A qualitative description of the potential impacts (e.g. on fish populations).

Sometimes, abovementioned information is not sufficient to conclude that the benefits of the use under consideration outweigh the risk when based on qualitative comparison. In these cases, the applicant may provide the following supporting information:

- Further contextual information on the likelihood and significance of potential impacts (e.g. the margin of safety between predicted or measured environmental concentrations and relevant thresholds of exposure / adverse effect in biota or quality standards from other legislation) or
- Illustrative quantitative assessments (e.g. based on worst-case scenarios or break-even analysis).

Considering the abovementioned **guidance of the RAC and the SEAC, the following information will be summarised / discussed** in the following subsections:

- Total annual use of OPnEO at the production site over time, taking into account maximum orders by Roche as well as planned substitutions,
- Releases of OPnEO / OP (4-(1,1,3,3-tetramethylbutyl)phenol) equivalents over time, taking into account maximum orders by Roche, planned substitutions, and risk management measures,
- Comparison of predicted environmental concentrations with concentrations of monitoring campaigns,
- Geographical and temporal distribution,
- Qualitative description of impacts,
- Margin of safety when comparing predicted environmental concentrations with existing environmental quality criteria.

Part of the information discussed below is taken from the CSR submitted in view of this AfA. Where this is the case, reference to the respective parts in the CSRs is made for more detailed discussion.

4.1.2 Use of OPnEO at the Vetter Production Sites

For the purpose of the CSR, the total annual usage at the sunset date serves as a basis for the exposure assessment. As a worst-case, **maximum expected orders by Roche at the sunset date were used**. These maximum expected orders remain constant over the years from 2021 until the end of the review period (4th of January 2026) (see Figure 12). This assumption was made in order to ensure that the assessment covers the maximum possible usage of OPnEO.

Also, the total annual usage of OPnEO is expected to cease at the end of 2021 (likely scenario) or to cease at the latest at the end of 2025 (worst-case) due to completed substitutions of OPnEO in the siliconisation process covered in the present dossier.

Figure 12 provides an overview of the total used amount of OPnEO over time for the activities covered in the use considering maximum orders by Roche for two cases:

- 'Substitutions completed as planned': Expected decrease in the total amount of OPnEO used over time considering the planned substitution based on the most likely timeline (see AoA for details).
- 'Substitutions delayed': Expected development of total used amount of OPnEO over time considering that the planned substitutions are delayed to the end of the review period as a worst-case.

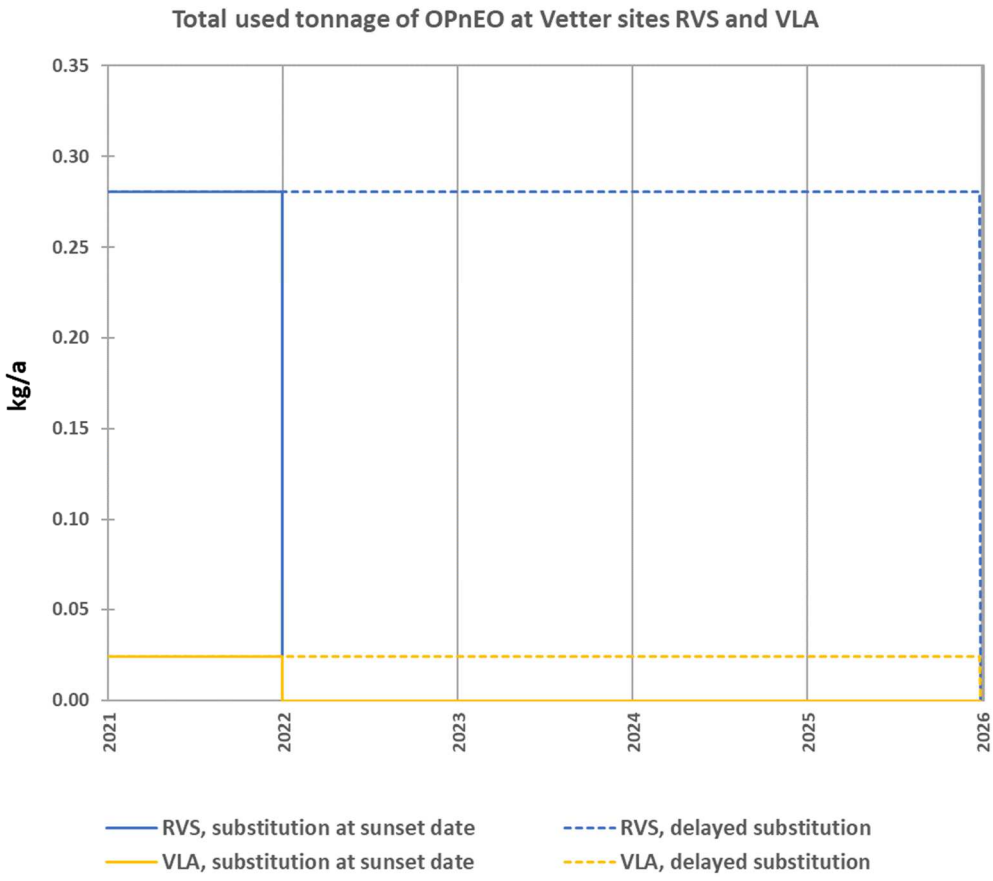

Figure 10. Evolution of the total annual use of OPnEO between 2021 and end of 2025 for Use 1 of this application at Vetter manufacturing sites Ravensburg (RVS) and Langenargen (VLA) considering the planned substitution and maximum expected orders placed by Roche.

In addition, a mass balance for OPnEO based on amounts used and releases to wastewater at both Vetter sites is provided in Table 5. The actual values are provided for 2017 as well as values based on maximum expected orders by Roche as assumed for the sunset date in 2021. Any losses to the environment of the OPnEO used per year are directly linked with the release to surface water from the sewage treatment plant (STP) as there is no direct release of OPnEO to air / soil.

Table 5. Mass balance for OPnEO based on amounts used at Vetter sites RVS and VLA in the siliconisation process and calculated releases to wastewater and waste for 2017 and at the sunset date on the 4th of January 2021 assuming production for maximum expected orders by Roche.

Production site	**RVS**		**VLA**	
	Annual amount based on actual figures in 2017	**Annual amount at the sunset date on the 4th of January 2021**	**Annual amount based on actual figures in 2017**	**Annual amount at sunset date on the 4th of January 2021**
	kg/a	**kg/a**	**kg/a**	**kg/a**
Total annual usage	[redacted]	**0.281 (100%)**	[redacted]	**0.0254 (100 %)**
Total release to wastewater	[redacted]	0.000755 (0.27 %)	[redacted]	0.000177 (0.70 %)
Total amount removed during depyrogenation step	[redacted]	0.0374 (13.33 %)	[redacted]	0.00702 (27.7 %)
Total amount incinerated (via RMM)	[redacted]	0.243 (86.40 %)	[redacted]	0.0182 (71.60 %)

The **main fraction** of the total amount of OPnEO used in the siliconisation (i.e. 86.4 % in RVS and 71.6 % in VLA) **is removed by incineration** of surplus siliconisation solution. During the depyrogenation step 13.3 % (for RVS) and 27.7 % (for VLA) of the total amount of OPnEO are removed. **No OPnEO remains in the final products** (siliconised glass containers) since the processing of the glass containers in the dry-heat tunnel (see process description in Section 9.3.1 of the CSR) leads to complete decomposition of OPnEO. **The release to wastewater is 0.27 % and 0.70 %** at RVS and VLA, respectively. This distribution of OPnEO will remain constant over time independent of actual amounts used.

4.1.3 Releases of OPnEO at the Production Sites and Discussion on Risk Management Measures

Release pathways

- **Wastewater:** The releases of OPnEO occur via the direct emission to wastewater which is released to the municipal STP.
- **Soil:** Due to the fact that no direct emissions to soil arise at the production sites during the siliconisation process and that the sludge generated by the STPs is collected and incinerated,

releases to soil are not expected at either site. However, release to the soil after the STP via the air by way of (wet or dry) deposition can still occur even if the emission to air is expected to be very small.

- **Air:** Direct release is set to zero due to the very low vapour pressure of OPnEO. Releases to air during the removal process taking place in the STP are not set to zero but are minimal.

Overview of releases to surface water in OP equivalents ($OP_{equiv.}$)

As can be seen in Table 5, **based on the implemented risk management measures, the total release of OPnEO to wastewater at RVS will be a maximum of 0.000755 kg/a and at VLA 0.000177 kg/a** at the sunset date and should reach 0 by end of 2021 if the substitutions are completed in time at both sites. However, if the substitutions are delayed to the end of the review period, these maximum total annual releases to wastewater could occur as a worst-case until the end of the review period.

The wastewater is subsequently released to two municipal STPs (STP Langwiese for RVS and STP Kressbronn-Langenargen for VLA), which both are **equipped with an activated carbon filter** as an additional RMM to remove micropollutants. OP precursor substances (OPnEO) are degraded (partly) to OP in the course of the wastewater treatment and are (partly) removed with the sewage sludge (which is incinerated). The activated carbon filter further reduces the amount of OPnEO and its degradation products in the STP effluent. **As a worst-case, it was assumed for the modelling that only OP is additionally removed** by the activated carbon treatment (85 %). Table 6 gives an overview of the modelled total annual release of $OP_{equiv.}$ to surface water at the sunset date and by the end of the review period, for both scenarios (delay of substitution or not), as well as the total (integrated) release of $OP_{equiv.}$ to surface water over the review period (2021 until end of 2025).

Table 6. Expected and worst-case releases to surface water after the STP per year in kg/a OP_{equiv} from 2021 until the end of the review period based on model calculations.

		Unit	RVS	VLA	TOTAL
Release to surface water after the STP at the sunset date (04.01.2021)	Expected release considering substitutions	kg/a OP_{equiv}	**0.0000804**	**0.0000261**	**0.000107**
	Max total releases with delayed substitutions	kg/a OP_{equiv}	**0.0000804**	**0.0000261**	**0.000107**
Release to surface water after the STP 6 months before the end of the review period (04.07.2025)	Expected release considering substitutions	kg/a OP_{equiv}	**0**	**0**	**0**
	Max total releases with delayed substitutions	kg/a OP_{equiv}	**0.0000804**	**0.0000261**	**0.000107**
Total release to surface water after the STP over the review period (2021- end of 2025)	Expected release considering substitutions	kg/5a OP_{equiv}	**0.0000804**	**0.0000261**	**0.000107**
	Max total releases with delayed substitutions	kg/5a OP_{equiv}	**0.000402**	**0.000131**	**0.000533**

Overview of risk management measures and discussion on additional risk management measures

At the production sites RVS and VLA of Vetter the following risk management measures were already in place at the time of preparation of the dossier:

- Collection and incineration of solid waste,
- Collection and incineration of surplus,
- Minimisation of release to wastewater (few equipment parts in wet cleaning).

OPnEO enters the wastewater during the cleaning of the compounding equipment after use and during the sanitising of the siliconisation equipment after each batch processed. Collecting these fractions of wastewater would be a great effort as these steps take place in a Good Manufacturing Practice (GMP) area. Further, the washing area in VLA is also used for other machine equipment from non-OPnEO containing processes. Separate collection would require an evaluation project, a requalification and could not be done during productive runs. The additional shut-down would require all customers (even those not using OPnEO processes) to be involved and production delayed. Therefore, the implementation period of such a reconstruction would be in the same range as the period of this application for authorisation. Consequently, further reduction of emissions is not feasible.

Other risk management measures which are currently already in place at the production sites of RVS and VLA are summarised below:

- Both municipal STPs are equipped with an **activated carbon treatment step** (additional effort to remove micropollutants) before discharge to a sand filter.
- The sludge of both STPs is treated in a digester and dewatered. The **dewatered sludge is used thermally in the cement industry (incineration)**. There is no application of sludge to agricultural soil. OPnEO and degradation products adsorbed to the sludge are thus incinerated.

In conclusion, emissions of OPnEO to wastewater are already minimised as far as technically and practically feasible.

Geographical and temporal considerations

The municipal STP treating wastewater from the production site RVS is discharging into the **River Schussen** that flows into the **Lake Constance** 18 km downstream of the STP. The medium low water discharge of the River Schussen is 3.51 m^3/s. Considering a mean wastewater flow from the STP of 0.4 m^3/s this leads to a dilution factor of 1:9.7. The municipal STP treating the wastewater from the production site VLA directly discharges into the Lake Constance. A dilution factor of 1:10 was assumed for the model calculations.

Some temporal variation could be expected in the release of OPnEO to wastewater of Vetter's production sites, since the production processes take place in batches. **The current number of emission days is varying between** [redacted] The predicted environmental concentrations (PECs) further discussed below are given for the sunset date based on the daily release rates. As shown in Table 6, emissions are expected to decrease with time after the sunset date due to planned substitutions.

Comparison of predicted environmental concentrations with measurements from monitoring campaigns and an existing environmental quality standard (EQS)

Before comparing modelled concentrations with EQS values [4] it should be noted that this comparison is only for illustration. In this application for authorisation it is assumed that currently, **no reliable threshold values for endocrine disrupting effects** in aquatic organisms can be assigned for the substances under consideration. Moreover, the EQS values for OP under the Water Framework Directive [4] is currently under revision and will be prone to change. Also, all modelling results presented in this dossier are given as OP_{equiv}. However, in most cases, only OP concentrations are available in case of measured concentrations reported in databases or the literature. Available measurements therefore do not take into account original OPnEO or intermediate degradation products. This should be kept in mind when drawing conclusions. Altogether, only indicative conclusions can be drawn from the comparisons made below.

A monitoring campaign was not envisaged because both Vetter sites (RVS and VLA) are connected to municipal STPs where not only wastewater from the respective production sites is treated. Hence, measured data of OPnEO and its degradation products at the outlet of the STP would not only reflect emissions from the Vetter sites, but would likely represent a mixture of several sources: from a larger area with several industries and population equivalents of 184’000 (RVS) and 24’000 (VLA).

The local PEC in surface water downstream of STP Langwiese (RVS), was calculated to be **0.00938 ng/L OP_{equiv}** (local concentration due to Use 1 at RVS + regional concentration; Table 7). This concentration is a factor of 10’000 lower than the measured **concentration of OP in the River Schussen of 98 ng/L**. In reality, the relative contribution of Vetter’s emissions to OP concentrations in the River Schussen will be even lower as the modelled PEC values are OP_{equiv}. (i.e. the sum of OP and all of its precursors) and the measured concentrations are OP concentrations only. Despite these conservative assumptions, the comparison of modelled OP_{equiv}. with measured OP concentrations shows that the local PEC is much smaller than the measured values. Hence, the contribution of the Vetter site RVS including regional exposure covered in the CSR is not likely to contribute much OP to surface waters in comparison to the OP that is already present.

An overview of the comparison of modelled freshwater concentrations of OP_{equiv}. with background and EQS values is provided in Table 7. The local PEC in the River Schussen (0.00938 ng/L, see above) is also approx. 10’000 times lower than the Annual Average Environmental Quality Standard (AA-EQS) of 100 ng/L for OP, resulting in a PEC / EQS ratio of $<10^{-4}$. The local PEC in Lake Constance (0.00734 ng/L, calculated from the local concentration due to Use 1 at VLA + regional concentration) is also approx. 10’000 times lower than the AA-EQS, showing a PEC / EQS ratio of $<10^{-4}$ (see Table 7). Since the modelling assumptions were demonstrated to be very conservative (see Section 9.4.3 of the CSR), this ratio is expected to be even lower.

Table 7. Comparison of local PEC (concentration due to release from the production site including regional concentration) and regional PEC with available reference values for fresh waters in OP_{equiv}.

Site / Region	Unit	Freshwater PEC	Background values	EQS	Ratio PEC / EQS
RVS (including regional)	µg / L	**$8.82 \cdot 10^{-6}$**	0.098*	0.1	< 0.0001
VLA (including regional)	µg / L	**$7.25 \cdot 10^{-6}$**	-	0.1	< 0.0001
Regional	µg / L	**$1.93 \cdot 10^{-8}$**	0.02-0.7**	0.1	$< 2 \cdot 10^{-7}$

* Measurement in River Schussen downstream of STP Langwiese [4].
** Range for surface waters, see CSR.

Wide dispersive uses

Not applicable.

Overall conclusion

Comparison of modelled concentrations with current EQS values for OP demonstrated that the concentrations were **well below the EQS values**. This broad margin of safety can serve as an indication that the overall releases from Vetter's activities to the environment are not expected to cause issues in the receiving surface waters.

Finally, comparison with environmental concentrations from large surface water monitoring campaigns indicated that modelled concentrations are lower than recently observed 'background' concentrations in the receiving surface waters. This demonstrates that the contribution of the releases from Vetter's activities and downstream uses to total current environmental concentrations is small.

By implementation of RMMs (incineration of surplus and rests of the (diluted) silicone oil emulsion) the **release of OPnEO to wastewater is minimised** as far as technically and practically feasible. Remaining emissions to the environment with regard to the use of OPnEO will be completely **eliminated by substitutions** over the course of the review period. Therefore, risks related to the continued use of OPnEO can be considered as minimised. Maximum yearly emissions to surface water after the sunset date will be 0.107 g OP_{equiv}.

Qualitative description of impacts

Taking all abovementioned information into account, the impacts of the releases from Vetter's activities are considered to be very low. Taking into account the timeline of the planned substitutions, the **releases and the associated potential impacts will be further gradually reduced, reaching zero by latest by the end of the review period** (4^{th} of January 2026).

The **predominant receiving compartment is surface water**, and OPnEO is included in the authorisation list because of its degradation to OP, which is considered as potential endocrine disruptor in the environment. The evidence for OP's endocrine disruptive properties mainly stems from studies in fish. Evidence for other types of organisms is more limited, less clear or experimentally still further being explored. Therefore, **fish populations** are currently **the most important endpoint in the assessment of potential risks / impacts to the environment.**

4.2 Social and Economic Impacts

- ⇨ Social and economic impacts: **Possible reactions of physicians and patients** to the expected unavailability of both medicinal products as a basis to assess impacts.
- ⇨ **Alternative medicinal products** could be used instead of NutropinAq® and Lucentis® in most cases → Expected definitive switch to competitor products for NutropinAq® and partially for Lucentis® and therefore loss of the business for Vetter and Roche.
- ⇨ **Unavailability** of medicinal products in the **dosage form of PFS** for patients in the U.S. for all therapeutic indication areas of **Lucentis®.**

The details of the economic impacts for different actors in case of the non-use scenario as well as social and wider economic impacts are described in the following sections.

As described in the **non-use scenario**, Vetter will have to interrupt the siliconisation of the glass containers with OPnEO in case of a non-authorisation decision and thus interrupt the production of the final medicinal products. The **interruption of the production** will last until the necessary steps to switch to an alternative emulsifier are completed including adapted or new Roche marketing authorisations for the different markets. Because Vetter will not be able to supply the finalised medicinal products to Roche, an interruption of the supply of the products is expected until substitution will be completed. Therefore, this implies an unavailability of NutropinAq® and Lucentis® for patients.

Considering the limited possibility of stock building for the medicinal products and their shelf life as outlined in the non-use scenario, NutropinAq® and Lucentis® (in the U.S.) will not be available on the market for treatment of patients after an estimated 6 months and 11 months, respectively.

To assess the **impacts**, possible **reactions of physicians and patients** to the expected unavailability of NutropinAq® and Lucentis® must be considered. Possible alternatives of the two medicinal products are summarised in Table 1and likely reactions are discussed below.

In principle, **biosimilars could be used** instead of NutropinAq®. Therefore, patients are expected to be **switched to these competitor products**. Pre-requisite is the availability of these products on the market (e.g. resource availability in competing companies). In the case of NutropinAq®, the **competitor products may also be affected by the usage of OPnEO** for the glass container siliconisation and authorisation limiting their availability in case an authorisation is not granted. However, although all glass syringes need to be siliconised, not all processes use a silicone oil emulsion and siliconisation may be taking place outside of EEA. As there are several alternative products available on the market, a **severe lack of supply therefore appears unlikely.** Therefore, for the purpose of this impact assessment, it is assumed that competitors will be able to supply alternative medicinal products. As a consequence, competitors are expected to gain from Vetter's and Roche's loss, but this cannot easily be quantified. Due to the common usage of DC 365 in the pharmaceutical industry, it is expected that overall more pharmaceutical companies or contract manufacturers with manufacturing facilities outside the EEA will gain leading to a **shift of pharmaceutical production and economic benefits outside the EEA**.

In the case of Lucentis® PFS, patients could also be switched to biosimilars. As summarised in Table 1 there are, however, unique characteristics of Lucentis® that cannot easily be replaced by competitor medicinal products. Lucentis® is unique in the U.S for its convenient application (i.e. PFS). The other possible therapeutic alternatives on the U.S. market are not administered with PFSs. Moreover, for the U.S. market, **the competitors do not have approval to treat the Myopic Choroidal Neovascularisation**. Therefore, based on an interruption of supply, the only equivalent approved alternative treatment in the U.S. would be Roche's Lucentis® vial. In addition**, no medicinal products in the dosage form of PFS would be available for patients in the U.S.** for all therapeutic indication areas of Lucentis®. Patients are therefore expected to be switched either to Lucentis® vials or to non-PFS biosimilars.

4.2.1 Economic Impacts

⇨ **Vetter economic impacts** (January 2021-December 2025):
- Maximum net revenue foregone [redacted] mio EUR.
- Maximum EBITA foregone: [redacted] mio EUR.
- Loss of reputation towards Roche.

⇨ **Roche economic impacts** (January 2021-December 2025):
- Expected definitive switch to competitor products and therefore expected permanent loss of the NutropinAq® business.
- For Lucentis®: market may be regained after substitution due to uniqueness of the dosage form PFS.
- Loss of customers and reputation.
- Compensation claims due to the breach of delivery contracts → potentially business-critical situation.

This section estimates the **economic impacts over the course of the review period (January 2021-December 2025)** in case the authorisation would not be granted by the sunset date. This analysis is done from Vetter's and Roche's perspective. To assess the impacts in case of the non-use scenario, economic performance and competitiveness are compared with the situation outlined in the applied for use scenario including predicted developments over the course of the review period (Section 3.3). For more details please refer to the Supporting Document 5 'SD3_SEA_Economic_Impacts_Calculations_Ompi_Use 1_CONFIDENTIAL', which displays the calculations performed. The expected reactions of physicians and patients as described above are considered in this assessment.

Considering the expected reactions of physicians and patients discussed above, there will be a **substantial business impact for both Vetter and Roche**.

1) **<u>From Vetter's perspective:</u>** Assuming that substitution will only be completed for the two medicinal products by the end of the review period, the **loss is considered to occur over ca. 5 years as Vetter would not be able to produce and deliver the medicinal products any more from the sunset date**. In the likely scenario, substitution will already be completed after one year. In Figure 9 and Figure 10, the EBITA foregone was estimated for these extreme scenarios and for each year in which the substitution might be achieved. Obviously, the longer the substitution takes, the bigger is the economic impact for Vetter**.** For expected development of sales and EBITA over the course of the review period, please refer to Section 3.3.1. The **EBITA foregone** due to the inability to supply was estimated to be [redacted] **mio EUR and** [redacted] **mio EUR over the 5 years** until the end of the review period (discounted to NPV at 4 %) for Lucentis® and NutropinAq®, respectively. The net **revenue foregone** was estimated to amount to **a maximum of** [redacted] **mio EUR and** [redacted] **mio EUR over the 5 years** (discounted to NPV at 4 %) for Lucentis® and NutropinAq®, respectively. The EBITA and net revenue forgone for the most likely-case scenario (i.e. one year after the sunset date the substitution will be achieved, see the AoA for more details) for both products together were estimated to be [redacted] and [redacted] mio EUR, respectively (discounted to NPV at 4 %).

Figure 11. Overview of the progression of the Vetter's EBITA foregone in mio EUR for each possible year between the sunset date and the end of the review period, in which the substitution might be achieved, for Lucentis®.

Vetter and Roche are parties to supply **agreements** regarding the **manufacture and supply** of the medicinal products covered in this dossier. In case of a failure of Vetter to maintain its business related to the medicinal products, beside the fact that Vetter would lose the revenue created by Roche at Vetter, by losing Roche´s compensation for the manufacturing of the medicinal products, Roche might be able to claim for compensation.

Figure 12. Overview of the progression of the Vetter's EBITA foregone in mio EUR for each possible year between the sunset date and the end of the review period, in which the substitution might be achieved, for NutropinAq®.

Additionally, Roche will also be directly affected in case of the non-use scenario, as Vetter will not be able to supply the manufactured medicinal products.

2) **From Roche's perspective**: After an estimated 6 and 11 months, respectively, NutropinAq® and **Lucentis®** (in the U.S.) stocks at Roche or at customers will be depleted. This will lead to an unavailability of both products and Roche will be unable to provide complete services to patients. Considering there are alternative medicinal products available on the market, and the expected reactions of physicians and patients discussed above, there will be a business impact for Roche and a loss of **customers, market share, EBITA, and reputation**. For **NutropinAq®**, these **losses are expected to be permanent** as it is likely that patients will not switch back after the substitution. In the case of Lucentis®, some patients may switch to Roche's alternative dosage form of vials, especially for the unique indication area. Also, **patients may switch back to Lucentis® after substitution due to uniqueness** of the dosage form PFS. The EBITA foregone for Roche cannot be provided due to confidentiality reasons. Roche would furthermore face a loss in with a **maximum annual sale forgone of approx. [redacted] mio EUR** (for both medicinal products).
   If Vetter cannot supply the products, Roche will not be able anymore to fulfil customer contracts. A license partnership and long-term local tender and supply commitments are in place. Not being

able to provide the affected medicinal products would lead to Roche not being able anymore to fulfil customer contracts. The **breach of contracts** may lead to customer claims (e.g. from license holders). Customer claims may be based on but are not limited to contractually defined penalties. Claims could be made for any incurred damages. As compensation risk is generally unlimited, this would mean a high financial risk for Roche leading to a potentially business-critical situation. Overall, this breach of contracts will also lead to substantial loss of trust in Roche as a reliable business partner.

4.2.2 Social Impacts

- ⇨ **Unquestionable social value**: [redacted] (100'000-1'000'000) patients will not be able to continue to benefit from healthcare services based on medicinal products produced at Vetter.
- ⇨ **Lack of therapeutic services** for up to 4.1-4.5 years, especially interruption of the convenient and safe dosage form of PFS for Lucentis® in the U.S.
- ⇨ **Patients** will be confronted with **uncertainties regarding the interchangeability** of a reference drug like NutropinAq® and Lucentis®.

The following section summarises the estimated social impacts in case of the non-use scenario.

Apart from the economic considerations and more importantly, the affected medicinal products sold by Roche and produced at Vetter have an **unquestionable social value**. Overall the **Estimated Annual Exposure** is approx. [redacted] **and** [redacted] (total: 100'000-1'000'000) patients, for NutropinAq® and Lucentis® (U.S.), respectively. Detailed numbers are given in Table 4.

Under the non-use scenario, Vetter will not be able to produce and supply to Roche NutropinAq® and Lucentis® from the sunset date. The most important social impact is the potential **lack of therapeutic services** based on these two products for up to 4.1-4.5 years (depending on completion of substitution). NutropinAq® PFS will not be available any more for patients after an estimated 6 months and Lucentis® PFS after an estimated 11 months after the sunset date based on estimated stocks.

As outlined above, **patients will probably switch** to **a biosimilar (if available)**. Therefore, hospitals and physicians would need to seek for medicinal alternatives to offer to their patients. While the equivalence of biosimilars for therapy-naive patients (i.e. previously untreated patient) is not under question the switch of patients that are likely under biologic therapy for years may result in uncertainties in the interchangeability of a reference drug like Lucentis® and NutropinAq® and a biosimilar. Patients would therefore be faced with these uncertainties. It should be noted that in general the change of a patient 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. For NutropinAq®, the switch to a biosimilar would be the only option, as no alternative NutropinAq® dosage forms are available.

For Lucentis®, vials are available as an alternative dosage form. At the same time, Lucentis® PFS is unique in the U.S for its convenient application (i.e. PFS). The other possible therapeutic alternatives on the U.S. market are not administered with PFSs. Moreover, for the U.S. market, the competitors do not have approval to treat Myopic Choroidal Neovascularisation. Therefore, based on an interruption of supply, the only equivalent approved alternative treatment would be Roche's Lucentis® vials. No medicinal products in the dosage form of PFS would be available for all therapeutic indication areas of Lucentis®. PFS make the injection process easier and therefore help avoid mistakes and thus ensure safety for the patient. This is supported by the fact that once Lucentis®

PFS became available as the first PFS for its indication areas, physicians almost completely switched from vials to PFS within a short time.

In addition to social impacts based on therapeutic services, jobs are expected to be affected. With the cease of production [redacted] jobs (20-50) are expected to be re-allocated at the Vetter sites in Germany. In a similar way, some jobs are expected to be re-allocated at Roche. The latter cannot be quantified due to confidentiality reasons. As jobs are expected to be re-allocated, impacts are marginal. The biggest risk is an 'accelerated redundancy' (i.e. risk that there are more than the needed number of employees with a specific skill in the same department) rather than unemployment.

5. COMBINED ASSESSMENT OF IMPACTS

5.1 Comparison of Impacts

- ⇨ NutropinAq® and Lucentis® have **high benefits** for healthcare.
- ⇨ Vetter and Roche will face **economic impact** in case of an authorisation refusal.
- ⇨ Likely shift of pharmaceutical production and economic benefits outside the EEA.
- ⇨ **Low Emissions** to the environment due to implemented risk management measures.
- ⇨ **Benefits of continued use outweigh the risks**.

In case of the non-use scenario, it is not possible to move the production elsewhere because this would require new and time-consuming marketing authorisations. Therefore, in case of the non-use scenario, the medicinal products will need to be removed from the market leading to the above discussed impacts that are summarised in Table 9. Most importantly, the concerned medicinal products have a **high benefit for healthcare** such as the uniqueness of Lucentis® in the U.S. for its convenient application (i.e. PFS) for all therapeutic indication areas which would be lacking in case of non-authorisation. The other possible therapeutic alternatives on the U.S. market are not administered with PFS. From the perspective of the EEA economy, more pharmaceutical companies or contract manufacturers with manufacturing facilities outside the EEA will gain, likely leading to a **shift of pharmaceutical production and economic benefits outside the EEA**.

The only impact that could be quantified was the economic impact to Vetter due to EBITA foregone. This loss of EBITA would amount to [redacted] mio EUR per g $OP_{equiv.}$ emitted or [redacted] mio EUR/kg OP_{equiv} (10'000-100'000 mio EUR/kg $OP_{equiv.}$). The **potential total loss of EBITA** amounts to [redacted] **mio EUR** over the course of the review period. The EBITA forgone for the most likely scenario (i.e. one year after the sunset date the substitution will be achieved, see the AoA for more details) were estimated to be [redacted] and [redacted] mio **EUR**, respectively for NutropinAq® and Lucentis® (discounted to NPV at 4 %).

In addition, Roche would face **high economic impacts** with a loss in reputation

Roche would furthermore face a loss in reputation, potentially business-critical customer claims for breach of contracts and a maximum annual sale forgone of approx. [redacted] mio EUR.

The most important impacts in case of the non-use scenario are thus impacts that cannot be quantified but are considered to be important in comparison to the **low emissions of OP_{equiv}.**

Table 8. Cost of non-use per kg $OP_{equiv.}$ emitted and year based on EBITA foregone* (for PBT / vPvB substances and endocrine disruptors).

	Per year
Total cost based on EBITA foregone based on maximum expected orders (mio EUR/a)	[redacted]
Max. total release to surface water equiv. (kg/a $OP_{equiv.}$)	**0.000107**
Ratio (mio EUR/kg)	[redacted]

* Important impacts could not be quantified and are therefore not included in this ratio.

Emissions are small due to implemented risk management measures with a theoretical maximum yearly release of 0.000107 kg/a $OP_{equiv.}$ at maximum expected orders by Roche. Taking into the account the high benefits of authorisation for society and for Roche and additionally the high monetised economic benefit for Vetter per g $OP_{equiv.}$ emitted, it can be concluded that the benefits of continued use outweigh the risks associated with continued use of the silicone oil emulsion DC 365 until substitution is completed.

Table 9. Overview of the impacts in the non-use scenario in comparison with the applied for use scenario - Use 1.

Type of impact	**Stakeholders impacted**	**Applied for use scenario**	**Non-use scenario**
Environ-ment	Environment / surface water	Over the 5 years of the review period: <u>Likely case with substitutions on time</u>: Max. release of $OP_{equiv.}$: 0.000107 kg/a <u>Worst-case with substitutions delayed</u>: Max. release of $OP_{equiv.}$: 0.00053 kg/5a Combined PEC(local) (surface water): 0.0000163 µg/L << EQS value	No releases of $OP_{equiv.}$ from Vetter's activities

Type of impact	**Stakeholders impacted**	**Applied for use scenario**	**Non-use scenario**
Economic impacts	Vetter	Vetter will be able to continue their current medicinal products business.	The estimated total loss of EBITA due to the interruption of production of the medicinal products was estimated assuming that substitution can be completed after 1 (likely scenario) to 5 (worst-case) years: Likely scenario: [redacted] and [redacted] mio EUR, respectively for NutropinAq® and Lucentis® (discounted to NPV at 4 %) Worst-case scenario (max)*: [redacted] **and** [redacted] mio EUR, respectively for NutropinAq® and Lucentis® (discounted to NPV at 4 %) Max over the 5-year review period for both medicinal products: [redacted] mio EUR (discounted to NPV at 4 %) Per g OP_{equiv} released: [redacted] mio EUR (=[redacted] mio EUR/kg OP_{equiv}) 10’000-100’000 mio EUR/kg $OP_{equiv.}$
	Vetter	Vetter will be able to keep their contractual obligations towards Roche and continue their business.	Vetter will not be able to comply with the contractual supply obligations in place with Roche. Vetter may possibly face compensation claims from Roche (cannot be quantified).
	Roche	Roche will be able to continue their current business with the two medicinal products.	Loss of sales and EBITA (cannot be quantified).
	Roche	Roche will be able to keep their position on the pharmaceutical market and continue their current business.	Loss of trust in Roche as supplier of medicinal products. Roche may face compensation claims from licence holders (cannot be quantified; potentially unlimited and therefore business-critical).

Type of impact	Stakeholders impacted	Applied for use scenario	Non-use scenario
	Roche / customers	Roche will be able to keep their contractual obligations and Roche's customers will be able to continue their business providing health services.	Due to non-supply, Roche's customers may not be able to provide complete services to patients. Patients will be switched as soon as possible to a biosimilar (if available) or in the case of Lucentis® to Lucentis® vials.
Social impacts	Patients	Overall, [redacted] (100'000-1'000'000) patients will continue to benefit from health services offered by both medicinal products.	Patients will face a lack of therapeutic services from the wo medicinal products over a maximum of 4.1 to 4.5 years (from 6–11 months after the sunset date when stocks are depleted). Unavailability of the convenient and safe dosage form of PFS for Lucentis® in the U.S. Patients will be confronted with uncertainties regarding the interchangeability of a reference drug like NutropinAq® and Lucentis® and a biosimilar.
	Workers	Vetter will continue to employ and allocate [redacted] (20-50) FTE units for the production of NutropinAq® and Lucentis®. Roche will continue to employ the staff responsible for the activities associated with NutropinAq® and Lucentis®.	Impact on employment at Vetter sites: [redacted] (20-50) jobs are expected to be re-allocated. Roche: Some FTEs are expected to be re-allocated.

*Max=Worst-case scenario → Max net revenue foregone over the 5 years (January 2021-end of December 2025) review period.

5.2 Uncertainty Analysis

⇨ **Several assumptions** were made in order to assess the impacts:
- Competitors can take over the market from Roche (best-case scenario).
- Calculations of releases and impacts are based on maximum expected orders.

⇨ Additional **impacts that cannot be quantified**: Impacts on healthcare and loss of reputation and possible compensation claims.

⇨ Conservative assumptions are made in the modelling of releases of $OP_{equiv.}$ to surface water.

⇨ Certain: **Benefits outweigh the risks of continued use of OPnEO**.

In this SEA, **several assumptions** were made for the assessment of impacts that shall be discussed below.

For the impact assessment, it is assumed that **competitors can take over the market from Roche** by providing alternative medicinal products for the non-unique products and indication areas. Because **competitors for NutropinAq® may also face authorisation requirements**, the market supply could be impacted if a larger number of manufacturers did not receive an authorisation. However, this would only make the impacts on the healthcare system **more severe** making the currently presented approach conservative.

It should furthermore be noted that Vetter's competitors, i.e. supplier of siliconised glass containers, cannot substitute Vetter's supply of medicinal products to Roche due to marketing authorisation requirements. Therefore, there is a high certainty that Vetter and Roche will face the described economic impacts.

In addition, the non-use scenario is expected to lead to important **impacts that cannot be quantified**. Namely, **impacts on healthcare** are expected by non-availability of medicinal products (i.e. the need to find an alternative with uncertainties in the interchangeability, non-availability of the PFS dosage form of Lucentis®). Furthermore, there is the possibility of **loss of reputation** of Vetter (towards Roche) Roche (towards customers) as well as the possibility of **compensation claims** towards all two actors in the supply chain.

Absolute figures of EBITA lost based on production at Vetter are also associated with some uncertainty. However, increase or decrease of production will also be associated with a respective increase or decrease of amounts of OPnEO used and associated emissions to surface water. The **ratio of EBITA foregone per g $OP_{equiv.}$ emitted** therefore represents a **more reliable** estimate. Similarly, the estimates of releases to wastewater can be considered as reliable as usage and mass flow within production was directly evaluated. Possible variations in production volumes are accounted for by assuming maximum expected orders from Roche. The used 'Multifate' model uses conservative assumptions, e.g. no mineralisation of OPnEO. Therefore, the presented **releases of $OP_{equiv.}$ to surface** water can be considered as **reliable**. This release is the only release to the environment.

Taking all the above into account, the conclusion that **benefits outweigh the risks of continued use of OPnEO** is associated with a high certainty.

6. CONCLUSIONS

- ⇨ **5-year authorisation** is needed to enable the implementation of the alternative silicone oil emulsion taking into account technical and regulatory risks.
- ⇨ **Socio-economic benefits** of continued used **outweigh** the potential **costs of the risk** of a continued use of OPnEO.

This SEA aims to quantify the relevant environmental, economic and social impacts of the continued use of OPnEO as emulsifier in the siliconisation of glass containers used as primary packaging for the medicinal products Lucentis® and NutropinAq® after the sunset date on the 4th of January 2021.

The use of OPnEO is part of the marketing authorisation of the medicinal products in countries worldwide. Any change related to the change of the silicone oil emulsion will be subject to changes in marketing authorisation in at least some of the countries where NutropinAq® and Lucentis® are sold (submitted to the health authorities by the medicinal product owner). The requested review period is calculated in function of required changes in marketing authorisations and associated stability testing, with uncertainty included for testing issues and marketing authorisation delays. The aim is to not interrupt provision of important medicinal products, especially with a unique feature (i.e. Lucentis® PFS is the only PFS on the U.S. market for its indication areas). If substitution could happen in time, it would be complete for both medicinal products by the end of 2021. However, due to the uncertainties and the need to be prepared for delays some of which are beyond the applicant's control (i.e. administrative delays in countries where marketing authorisations have been applied for, associated risks in the substitution timeline, etc.), a review period of 5 years is requested.

In case of the non-use scenario, Vetter would face economic impacts with an estimated maximum EBITA foregone (discounted to NPV at 4 %) of [redacted] mio EUR over the course of the revue period. The loss of EBITA per kg OP_{equiv}. emitted is calculated as [redacted] mio EUR/kg OP_{equiv} (10'000-100'000 mio EUR/kg OP_{equiv}). If Vetter is not able to comply with the contractual supply obligations in place with Roche, Roche might ask for a compensation. Considering alternative medicinal products available on the market, for the non-unique products / indication areas, Roche will face a loss of customers associated with a loss in market share and profit, as it is likely that patients will not switch back after the substitution. Roche would furthermore face a loss in reputation, potentially business-critical customer claims for breach of contracts and a maximum annual sale forgone of approx. [redacted] mio EUR. Additionally, due to the common usage of DC 365 in the pharmaceutical industry, it is expected that overall more pharmaceutical companies with manufacturing facilities outside the EEA will gain leading to a shift of pharmaceutical production and economic benefits outside the EEA.

In addition, the non-use scenario would have a significant social impact, given the unique features of Lucentis® PFS. Lucentis® is unique in the U.S for its convenient application (i.e. PFS). Moreover, for the U.S. market, the competitors do not have approval to treat Myopic Choroidal Neovascularisation. Therefore, based on an interruption of supply, the only equivalent approved alternative treatment would be Roche's Lucentis® vials. No medicinal products in the dosage form of PFS would be available for all therapeutic indication areas of Lucentis®. In addition, if patients are switched to biosimilars, as expected for NutropinAq® and possibly for Lucentis®, patients will be faced with the uncertainties in the interchangeability of a reference drug like Lucentis® and

NutropinAq® and a biosimilar and the unpredictable reactions triggered by the disposition of the individual patient.

Due to the uncertainties associated with the endocrine disrupting properties of the degradation products of OPnEO, the applicant decided to assume no threshold for the endpoint ‘endocrine disrupting properties for the environment, as the safest option. The CSR demonstrates that the used amounts of OPnEO associated with maximum expected orders from Roche are already very low. The current environmental exposure levels through release to wastewater are already reduced as far as technically and practically feasible by risk management measures, i.e. collection and incineration of surplus silicone oil emulsion.

Remaining emissions to the environment with regard to the use of OPnEO will be completely eliminated by substitutions over the course of the review period. Therefore, risks related to the continued use of OPnEO can be considered as minimised.

In conclusion, this AfA is a bridging application with an already identified alternative and has demonstrated that a 5-year authorisation is needed to enable the completion of the replacement of OPnEO in the siliconisation process for the two affected medicinal products covered in this AfA. This period is requested due to the complexity of the substitution projects as an extensive feasibility and stability testing phase is required as well as marketing authorisation changes in multiple countries. It has been demonstrated that the socio-economic benefits of continued used outweigh the potential costs of the risk of a continued use of OPnEO.

7. REFERENCES

[1] S. Funke, J. Matilainen, H. Nalenz, K. Bechtold-Peters, H-C. Mahler, and W. Friess. Optimization of the bake-on siliconization of cartridges Part I: Optimization of the spray-on parameters. 2016 European Journal of Pharmaceutics and Biopharmaceutics 104: 200-215

[2] ECHA (2018) Committee for Risk Assessment, Risk-related considerations in applications for authorisation for endocrine disrupting substances for the environment, specifically OPnEO and NPnEO (Agreed at RAC-43)

[3] ECHA (2017) SEA-related considerations in applications for authorisation for endocrine disrupting substances for the environment, specifically OPnEO and NPnEO, (Agreed at SEAC 37)

[4] DIRECTIVE 2013/39/EU OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 12 August 2013 amending Directives 2000/60/EC and 2008/105/EC as regards priority substances in the field of water policy (EU Water Framework Directive)

[5] R. Triebskorn (2012) Modellstudie zur Effizienz der Reduktion der Gehalte an anthropogenen Spurenstoffen durch Aktivkohle in Kläranlagen: Monitoring vor Inbetriebnahme der Adsorptionsstufe auf der Kläranlage Langwiese «SchussenAktiv», Final report for project 206/2010 for the Ministry of the Environment, Climate Protection and the Energy Sector Baden-Württemberg