The Agency for UK REACH

The Agency for UK REACH Opinion

on an Application for Authorisation for

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

used as a manufacturing aid in the production of gene therapies.

Submitting Applicant: MeiraGTx UK II Limited

UK REACH Reference: AFA002-01 Opinion

Date: 15/03/2022

Opinion of the Agency for UK REACH (Henceforth the Agency)

on an Application for Authorisation

Having regard to Regulation EUR 2006/1907[1] of the European Parliament and of the Council 18 December 2006 concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals (the REACH Regulation), and in particular Chapter 2 of Title VII thereof, the Agency has adopted its opinion in accordance with Article 64(4)(a) and (b) respectively of the REACH Regulation with regard to an application for authorisation for:

Applicant	**MeiraGTx UK II Limited**
Role of the applicant in the supply chain	Upstream ☐manufacturer ☐importer ☐only representative ☐formulator Downstream ☒downstream user
Use performed by	☒Applicant ☐Downstream user(s) of the applicant
Substance ID EC No CAS No	**4-(1,1,3,3-tetramethylbutyl)phenol, ethoxylated (4-tert-OPnEO) (OPEO)** - 9036-19-5

[1] References to "EUR 2006/1907" are to the retained version of Regulation (EC) No 1907/2006, as amended. The retained version of that Regulation is available online at https://www.legislation.gov.uk/eur/2006/1907/contents

Intrinsic properties referred to in Annex 14	☐Carcinogenic (Article 57(a)) ☐Mutagenic (Article 57(b)) ☐Toxic to reproduction (Article 57(c)) ☐Persistent, bioaccumulative and toxic (Article 57(d)) ☐Very persistent and very bioaccumulative (Article 57(e)) ☒ Other properties in accordance with Article 57(f) – endocrine disrupting properties for the environment
Use title	**Use of 4-tert-OPnEO as a manufacturing aid in the production of gene therapies**
	Other connected uses: None
	Similar uses applied for: None
Indicative number and location of sites covered	This process takes place at a single site in London, England.
Annual tonnage of Annex 14 substance used per site (or total for all sites)	< 1 tonne per year. Future use.
Function(s) of the Annex 14 substance.	4-tert-OPnEO is used as a cell lysing agent during a manufacturing step in the production of gene therapies.
Type of products (e.g., articles or mixtures) made with Annex 14 substance and their market sectors	Gene therapy products to be used in the treatment of diseases (ocular, neurodegenerative, salivary gland) using the adeno-associated virus (AAV).
Annex 14 substance present in the concentrations above 0.1% in the products (e.g., articles) made	No
Review period requested by the applicant (length)	12 years
AfA Reference number	AFA002-01

This document provides the opinions of the Agency based on their scientific assessment of the application for authorisation. It provides scientific input to the Secretary of State's decision to grant or refuse an authorisation in accordance with Title VII, Chapter 2.

Process information for this opinion can be found in Annex 1 and a list of acronyms/abbreviations in Annex 2. Where values are redacted or shown as ranges with an *, the exact figure has been claimed confidential.

THE OPINION OF THE AGENCY

Summary: The Agency has assessed the application and has concluded that the OCs and RMMs have not been shown to be appropriate and effective at limiting the risks, because minimisation of environmental exposure has not been demonstrated. There are currently no technically or economically feasible alternatives and the socioeconomic benefits from the use of the substance are significant and positive. If authorisation is granted, the Agency recommends a review period of 12 years.

The Agency has formulated its opinion on:

- the risks arising from the use applied for,
- the appropriateness and effectiveness of the operational conditions and risk management measures described,
- the assessment of the hazards related to the alternatives as documented in the application,
- the socioeconomic factors and
- the suitability and availability of alternatives associated with the use of the substance taking into account the information in the application as well as
- other available information.

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

The Agency concluded that the operational conditions and risk management measures described in the application **are** potentially appropriate and effective in limiting the risk, but this cannot be confirmed. This is because the applicant has **not** demonstrated that environmental exposure will be reduced to as low as technically and practically possible. The Agency proposes that the authorisation should include a condition requiring the applicant to identify and implement any measures needed to resolve this deficiency, or to expedite such investigations that may be necessary to demonstrate that no further reduction in emissions is technically or practically possible.

The use applied for may result in <100g* per year releases of the substance to the environment.

The Agency concluded on the analysis of alternatives and the substitution plan that:

- The applicant has demonstrated that there are currently no technically and/or economically feasible alternatives available for the applicant with the same function and similar level of performance. The Agency also therefore did not evaluate the potential risk of alternatives.
- There is no information available in the application for authorisation indicating that there are alternatives available that are technically and economically feasible in the UK.
- The applicant did not submit a substitution plan.

The Agency concluded that the applicant has demonstrated that the socioeconomic benefits of granting an authorisation are >£100,000,000/kg/year* of emissions of 4-tert-OPnEO as a result of continuing the use applied for.

The expected socioeconomic benefits of granting an authorisation are estimated to be >£10 million* per year consisting of avoided producer surplus losses, avoided relocation costs and avoided cost of unemployment to society.

The Agency has estimated that the use applied for may result in <100g* of emissions of 4-tert-OPnEO per year to the environment. Given that the impact of these emissions cannot be quantified using the threshold approach for the SVHC, the Agency assessed environmental risk by reference to a well-characterised endocrine disruptor with the same mode of action; ethinylestradiol. Taking into account differences in potency, the Agency concluded that the use applied for will have no adverse environmental impacts in relation to endocrine disruption.

The Agency has not identified any remaining uncertainties of such magnitude that they may affect its conclusions.

PROPOSED CONDITIONS, MONITORING ARRANGEMENTS AND RECOMMENDATIONS

The Agency proposes to include one condition within the authorisation:

The applicant shall identify and implement any risk management measures needed to ensure that environmental exposure is reduced to as low a level as is technically or practically possible or shall expedite and report such investigations as may be necessary to demonstrate that no further reduction in emissions is technically or practically possible.

No monitoring arrangements for the authorisation are proposed.

No recommendations for the review report are made.

REVIEW PERIOD

Taking into account the information provided in the application for authorisation submitted by the applicant, a **12-year** review period is recommended for this use.

JUSTIFICATIONS:

1. Short description of use

The applicant, MeiraGTx UK II Limited, applies for the future use[2] of 4-tert-OPnEO in the manufacture of gene therapies on one site located in London, England.

The purpose of the use is to produce gene therapies using 4-tert-OPnEO as a manufacturing aid. The use takes place in an underground facility and 4-tert-OPnEO is used in an isolated environment, with the exception of one sink connected to the public sewerage system.

For this use, <0.1 tonnes of 4-tert-OPnEO will be used per year.

1.1. Description of the process in which Annex 14 substance is used

The use of 4-tert-OPnEO during manufacturing has the following steps:

- Receipt (WCS 1.1 – PROC 0) – the bottles are received at the manufacturing facility and cleaned. There is no release of 4-tert-OPnEO to the environment from this process.
- Transfer of excess 4-tert-OPnEO (WCS 1.2 – PROC 8b, WCS 1.3 – PROC 3) – excess 4-tert-OPnEO not required in the manufacturing process is transferred to the waste room. It is disposed of off-site by a contractor for hazardous waste incineration. Apparatus is double-bagged and transferred to the waste room to be sent to hazardous waste incineration. There is no release of 4-tert-OPnEO to the environment from this process.
- Cell feeder room (WCS 1.4-1.9 – PROC 3, 8b, 9) – rejected 4-tert-OPnEO is disposed of off-site by a contractor for hazardous waste incineration. Apparatus is double-bagged and transferred to the waste room to be sent to hazardous waste incineration. There is no release of 4-tert-OPnEO to the environment from this process.
- Quality Control samples (WCS 1.7, 1.9, 1.11 – PROC 9, 15) – samples are disposed of off-site by a contractor for hazardous waste incineration. Samples shipped to external contractors for testing are disposed of as clinical waste via incineration
- Filter permeate (WCS 1.10 – PROC 3, 8b) – lost to wastewater, contains 4-tert-OPnEO. The applicant has claimed the quantity of 4-tert-OPnEO lost to wastewater to be confidential. The loss is via a single sink at the facility connected to the municipal sewerage system.

The manufacturing steps show that during purification of the product, the majority of the 4-tert-OPnEO used in the process is collected for off-site incineration as hazardous waste. A small proportion is discharged to sewer and could enter the aquatic environment.

[2] The applicant is applying for the future use of the substance and their current use is exempt from authorisation under Article 56(3).

Table 1: Contributing Scenarios presented in the Use

Contributing scenario	ERC / PROC	Name of the contributing scenario	Size of the exposed population
ECS1	ERC 4	Use of non-reactive processing aid at industrial site (no inclusion into or onto article)	Not applicable to the environmental concern
WCS 1.1	PROC 0	Receipt and storage of 4-tert-OPnEO	Not applicable to the environmental concern
WCS 1.2	PROC 8b	Transfer of 4-tert-OPnEO	Not applicable to the environmental concern
WCS 1.3	PROC 3	Excess 4-tert-OPnEO sent for disposal	Not applicable to the environmental concern
WCS 1.4	PROC 8b	Transfer from bioprocessing bag	Not applicable to the environmental concern
WCS 1.5	PROC 3	Storage of bioprocessing bag	Not applicable to the environmental concern
WCS 1.6	PROC 8b	Contents of bioprocessing bag transferred to bioreactor	Not applicable to the environmental concern
WCS 1.7	PROC 9	Sampling of bioreactor	Not applicable to the environmental concern
WCS 1.8	PROC 8b	Transfer of contents from the bioreactor to the bioprocessing bag	Not applicable to the environmental concern
WCS 1.9	PROC 9	Sampling of lysate	Not applicable to the environmental concern
WCS 1.10	PROC 3 PROC 8b	Purification of lysate	Not applicable to the environmental concern
WCS 1.11	PROC 15	Laboratory analysis of final product	Not applicable to the environmental concern

1.2. Key functions provided by the Annex 14 substance and technical properties/requirements that must be achieved by the products made with the Annex 14 substance.

The technical function of 4-tert-OPnEO in this use is as a cell lysis agent for the extraction of proteins and organelles during the manufacture of gene therapy products. The substance is formulated into a buffer solution which is subsequently introduced to cells in culture which have been engineered to produce the gene therapy vector; when the cells are lysed the vector is released into the lysate. The lysate is then filtered and purified via successive downstream processes in order to yield the applicant's product.

1.3. Type(s) of product(s) made with Annex 14 substance and market sector(s) likely to be affected by the authorisation

The products are various gene therapy vectors intended to be used in the treatment of targeted diseases. The products use the adeno-associated virus (AAV) as the vector for delivering genes. The diseases targeted for such treatment can be grouped into 3 development programmes – ocular, neurodegenerative and salivary gland.

1.4. For application: Downstream User survey

Not relevant.

2. Operational Conditions and Risk Management Measures

2.1. Workers

Not relevant.

2.2. Consumers

Not relevant.

2.3. Environment/Humans via Environment

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

Air:

The applicant stated that there are no releases to air during the batch preparation process as the substance is non-volatile and the process takes place indoors in controlled areas.

Water:

The applicant stated that there will be a release of up to [redacted] 4-tert-OPnEO to wastewater per batch, with a maximum of [redacted] batches per day. This corresponds to [redacted] of octylphenol released per day, which is the Substance of Very High Concern that gives rise to the endocrine disruption concerns.

During each production batch the unused 4-tert-OPnEO, filtration losses, affinity chromatography AAVX flow through, AAVX capture column washes, Anion Exchange AEX1 flow through, discarded samples and used single use apparatus are collected and taken off-site by an external contractor for hazardous waste incineration. The applicant has indicated that this wastewater collected for incineration totals approximately [redacted]. The AEX1 column strip and column wash are collected and then drained to sewer. The second stage anion exchange AEX2 flow through, column strip, and column wash are also collected and drained to sewer. The eluate from AEX2 is subject to tangential flow filtration, during which [redacted] of column permeate is released to sewer. The applicant provided additional information on the volumes of all the flows to sewer, and these sum to approximately [redacted] per production batch.

The applicant has considered that emissions of 4-tert-OPnEO to water will be minimised by the collection and incineration of >99.9% of 4-tert-OPnEO used on the site. Only minimally contaminated aqueous waste streams will be released to sewer. The applicant has stated that they are investigating further measures to divert this release from the municipal sewerage system to ensure that emissions of 4-tert-OPnEO to the environment are as low as is technically and practically possible.

Uncertainty around the release factor appears to be primarily related to the analytical Level of Detection for 4-tert-OPnEO, stated to be [redacted]

There is no wastewater treatment onsite. The applicant has assumed 100% conversion of 4-tert-OPnEO to octylphenol at the point of entry to the receiving municipal STP, with zero degradation during sewage treatment.

Soil:

The applicant stated that there is no direct release to soil during the batch preparation process as it takes place indoors in controlled areas. The release factor for non-agricultural soil is, therefore, specified to be 0%.

Indirect release to soil by using STP sludge for agricultural purposes cannot be excluded. The applicant has provided a local Predicted Environmental Concentration (PEC_{local}) for agricultural soil.

Waste:

All solid waste is collected for off-site incineration. The effectiveness in limiting emissions to the

environment from solid waste is assumed to be 100%.

Table 2: Environmental RMMs

Compartment	RMM	Stated Effectiveness
Air	Low vapour pressure and indoor use in controlled areas will prevent atmospheric emissions.	100%, no atmospheric emissions
Water	Some contaminated wastewater is released to sewer for treatment at the local STP and discharge to surface water (Thames Estuary)	For incineration of aqueous wastes a 100% effectiveness is assumed. For releases to sewer, the applicant has assumed 28.49% effectiveness for removal from wastewater, and an overall RMM effectiveness of 99.9%.
Soil	Indoor use in controlled areas.	100% for direct emissions to soil. Potential for indirect release to agricultural soils unless sewage sludge is incinerated.

2.4. The Agency's evaluation on the OCs and RMMs

Since all single-use apparatus that has been in contact with 4-tert-OPnEO is collected and disposed of as waste for incineration and all significantly contaminated wastewater is collected for incineration, no significant shortcomings to the OCs and RMMs have been identified.

From mass balance considerations it is clear that the effectiveness of RMMs and OCs in avoiding releases exceeds 99% and may exceed 99.9%. Nevertheless, the applicant has not explained why all aqueous wastes cannot be incinerated, and so has failed to demonstrate that emissions have been minimised as far as technically and practically possible.

2.5. The Agency's conclusions on the OCs and RMMs

The applicant has demonstrated that the RMMs and OCs are at least 99% effective in avoiding releases of 4-tert-OPnEO to the environment. The release of some potentially contaminated wastewater to sewer represents a minor shortcoming because the applicant has failed to show that this release cannot be further minimised.

Overall conclusion

Are the operational conditions and risk management measures appropriate[3] and effective[4] in limiting the risks?

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

Concern that the RMMs may not reduce exposure to as low as technically and practically possible leads to a proposed condition in the authorisation.

3. Exposure assessment

3.1. Inhalation exposure

Not relevant.

3.2. Dermal exposure

Not relevant.

3.3. Biomonitoring

Not relevant.

3.4. Environmental exposure

Air:

The applicant considered that releases of 4-tert-OPnEO to air are negligible, given the low vapour

[3] 'Appropriateness' – relates to the following of the principles of the hierarchy of controls as well as prevention or minimisation of releases in application of OCs and RMMs and compliance with the relevant legislation.

[4] 'Effectiveness' – evaluation of the degree to which the OCs and RMM are successful in producing the desired effect – exposure / emissions reduction, taking into account for example proper installation, maintenance, procedures and relevant training provided.

pressure of the substance and the operational conditions of use. The applicant modelled a Predicted Environmental Concentration in air. This has not been evaluated, given the non-threshold approach taken by the applicant.

Water:

Discarded single use apparatus, discarded samples, and significantly contaminated aqueous waste streams are collected for incineration. Therefore, the environmental release assessment presented by the applicant is based on aqueous releases to sewer containing residual and often undetected concentrations of 4-tert-OPnEO, from a typical batch operation.

Quantities of up to [redacted] of 4-tert-OPnEO released to sewer per batch were estimated from measurement of volumes produced during the process, concentrations measured in samples taken during different stages of the process, by subtraction, and by assuming worst case concentrations for measurements below the analytical level of detection ([redacted]).

The applicant has provided local Predicted Environmental Concentrations (PEC_{local}) for the transformation product octylphenol in surface freshwater (3.89×10^{-8} mg/L) and marine water (5.43×10^{-9} mg/L). These were generated by modelling in EUSES. The Agency notes that the EUSES modelling appears to have been conducted using the physicochemical information for octylphenol. This corresponds to an assumption that all 4-tert-OPnEO released to wastewater is rapidly transformed to octylphenol at the point of entry to the receiving sewage treatment plant. In reality only a small proportion of 4-tert-OPnEO is likely to be transformed to octylphenol during wastewater treatment; the ECHA SVHC support document[5] suggests a value of 21.5% would be a reasonable worst-case assumption. It would have been more appropriate to model 4-tert-OPnEO itself, in which case the proportion of substance retained in treated wastewater (as opposed to sludge) would be higher (the ethoxylate has a lower octanol/water partition coefficient (K_{ow}). Overall, however, the assumption that all 4-tert-OPnEO released to sewer is rapidly transformed to octylphenol is likely to predict conservative (pessimistic) surface water concentrations.

The applicant identified that release to the aquatic environment would be through Beckton wastewater treatment plant, which discharges to the tidal River Thames.

Soil:

The applicant considered that direct releases of 4-tert-OPnEO to soil are negligible. Modelling conducted by the applicant indicated that approximately 26% of the total emission would be via sewage sludge. As explained in the water section above, this may be an overestimate. Nevertheless, there is potential for indirect environmental exposure in agricultural soils. The applicant modelled a Predicted Environmental Concentration in agricultural soils (PEC_{local}) of 4.53×10^{-6} mg/kg ww.

[5] https://echa.europa.eu/documents/10162/17230/suppdoc_4_tert_octylphenol_20111211_en.pdf

This has not been evaluated, given the non-threshold approach taken by the applicant and the absence of sufficient evidence for endocrine disruption in terrestrial species.

Table 3: Summary of releases to the environment

Release route	Release factor	Release per year	Release estimation method and details
Air	0	0	Given the physicochemical properties of the substance, no release is expected.
Water	0.066%	<0.1kg*	Release factor based on a typical batch operation, results from samples, and mass balance. Release to wastewater is estimated at [redacted] per day of operation, approximately <100g* per year. This would correspond to [redacted] octylphenol per year.
Soil	0	0	Direct release to soil is expected to be negligible. Indirect release via sewage sludge is possible, depending on whether the sludge is incinerated or recycled to agriculture.
Waste	0	0	Incineration is assumed to avoid any environmental releases from disposal of single-use apparatus, discarded samples, and highly contaminated aqueous waste streams.

Table 4: Summary of exposure to the environment and humans via the environment

Parameter	Local	Regional
PEC in air (mg/m^3)	0	Not assessed
PEC in fresh water (mg/L)	3.89×10^{-8}	Not assessed
PEC in marine water (mg/L)	5.43×10^{-9}	Not assessed
Daily dose via oral route (mg/kg bw/d)	Not relevant	Not relevant

3.5. The Agency's evaluation of the exposure assessment

Environment and Humans via the environment

As a result of the relatively low vapour pressure of 4-tert-OPnEO (1 Pa at 20 ºC), the type of use (controlled laboratory conditions) and the RMMs and OCs in place, the Agency concludes that releases to air are expected to be negligible. Similarly, the Agency concludes that direct releases to soil are not likely. Indirect releases to soil by use of STP sludge for agricultural purposes cannot be excluded, and according to the information provided by the applicant could account for approximately 26% of the release to wastewater. However, this assumes complete transformation of 4-tert-OPnEO to octylphenol at the point of entry to the STP. Given incomplete transformation, and the lower K_{ow} of 4-tert-OPnEO, a lower partitioning to sludge and release to soil would be expected but the Agency has not assessed what this fraction would be.

The Agency considers that the methodology for assessing the release to water by means of monitoring data, mass balance, estimation and modelling is appropriate. All parameters are transparently reported and adequately justified. The estimates can be considered to be representative and, overall, are not likely to underestimate the release of octylphenol to the environment.

The applicant acknowledged that the actual monitoring method may lead to uncertainties about the real quantities of 4-tert-OPnEO released from the site in wastewater, because some sample results were below the specified limit of detection ([redacted]).

3.6. The Agency's conclusions on the exposure assessment

The Agency considers that the release estimates provided by the applicant are appropriate. The Agency did not identify shortcomings in the methodology used that would invalidate this conclusion.

The Agency notes that some uncertainties remain related to the limit of detection of the analytical

method used, and the approach to modelling the fate of the substance during sewage treatment. The Agency concludes that these uncertainties are unlikely to alter the conclusion that the environmental exposure scenario presented by the applicant represents a reasonable worst case.

4. Risk characterisation

4.1. Workers

Not relevant.

4.2. Humans via Environment

Not relevant.

4.3. Environment

The applicant has treated 4-tert-OPnEO as a non-threshold substance and did not attempt to derive PNECs or RCRs. This approach is in line with the EU REACH guidance paper "Risk-related considerations in applications for authorisation for endocrine disrupting substances for the environment, specifically OPnEO and NPnEO" and RAC's conclusion at its 50th meeting (November 2019) that a reliable threshold for endocrine disrupting effects could not be determined based on currently available data. The Agency has not independently assessed whether a threshold would be appropriate.

The use applied for may result in emissions of 4-tert-OPnEO to the environment of <100g* per year, which could potentially be transformed to [redacted] octylphenol. As this is based on an extreme worst-case assumption of 100% conversion from the ethoxylate, which is not realistic, the actual release of octylphenol to surface waters is likely to be a lot less. Nevertheless, the Agency has evaluated risk to surface waters on this basis.

4.4. The Agency's evaluation of the risk characterisation

The Agency did not directly evaluate the predicted environmental concentrations (PECs) provided by the applicant since they treat 4-tert-OPnEO as a non-threshold substance for its endocrine disrupting properties for the environment and therefore no appropriate PNECs or other benchmark values such as EQSs are available for comparison. However, the Agency has compared the surface water PECs with Environmental Quality Standards proposed for ethinylestradiol (EE2), an endocrine disruptor with the same estrogenic mode of action[6]. Given the much greater potency of

[6] https://ec.europa.eu/health/sites/default/files/scientific_committees/scheer/docs/scheer_o_023.pdf

EE2 (100 -1000 times more potent), the Agency has been able to conclude with high certainty that the environmental exposure would not cause adverse impacts on aquatic species through endocrine disruption. It has not been possible to assess risks to terrestrial ecology due to insufficient evidence for endocrine disruption in terrestrial species.

The modelling assumption of complete transformation of 4-tert-OPnEO to octylphenol at the point of entry to the STP represents a minor shortcoming, because this would direct a greater proportion of the substance to sludge rather than to water. Overall, though, risks to surface waters are likely to have been overestimated, as transformation of 4-tert-OPnEO to octylphenol during or immediately after wastewater treatment is likely to be very limited.

4.5. The Agency's conclusions on risk characterisation

The Agency is of the view that the applicant has demonstrated that releases to environmental compartments have been effectively limited but not necessarily minimised (with a view to minimising the likelihood of adverse effects) considering the OCs and RMMs in the exposure scenario, notably the type of production process (laboratory conditions, the use of 4-tert-OPnEO in mainly closed systems) and incineration of solid and liquid wastes.

The use applied for may result in emissions of 4-tert-OPnEO to the environment of <100g* per year, which could potentially be transformed to up to [redacted] of octylphenol. Based on comparisons with the endocrine disruptor ethinylestradiol, which has the same mode of action, the Agency considers that these residual emissions would not result in discernible adverse environmental impacts at species population levels in the receiving surface waters.

5. Analysis of Alternatives and substitution plan

5.1. The Agency's evaluation of the applicant's approach to the analysis of alternatives and the substitution plan

The applicant uses the 4-tert-OPnEO as a cell lysis agent in the production of gene-therapy vectors for therapeutic applications. These gene-therapy vectors are isolated from genetically modified organisms.

The applicant's search for alternatives was somewhat limited and consisted of: internet searches; contacting suppliers of cell lysis detergents; and checking similar applications for authorisation submitted under EU REACH. Through this they selected 4 alternatives. These were:

1. Not using a detergent
2. Sorbitan monolaurate, ethoxylated
3. Sorbitan monooleate, ethoxylated
4. N,N-dimethyltetradecylamine N-oxide

Alternative 1 was identified as a potential alternative, since the applicant had previously observed that some cell lysis occurred in the absence of a detergent.

There was no apparent systematic approach to selection of the alternatives and instead an approach based on in-house expertise and judgement, combined with the easily available information appears to have been used. A wider screening approach could have been used to create a 'long-list' and 'short-list' of potential alternative detergents that considered factors such as:

- the ionic character of the detergents (anionic, cationic and non-ionic detergents are known)
- Hydrophile-Lypophile Balance (HLB) value
- availability at pharmaceutical grade
- critical micelle concentration
- etc.

Although the applicant knew and cited the HLB value for 4-tert-OPnEO it was not used as a parameter to screen for alternative substances. Despite these shortcomings in the search for alternatives, the criteria against which the 4 selected alternatives were judged did include the availability at pharmaceutical grade and any known incompatibility with their production process (which is related to the ionic character of the detergent). In addition, testing of the alternatives was conducted.

The full list of criteria against which the alternatives were judged is:

- Cell lysing efficiency - >90% compared to 4-tert-OPnEO
- Availability at pharmaceutically approved Good Manufacturing Practice (GMP) grade
- Incompatibility with cell materials
- Impact on quality
- Intrinsic hazards

The applicant was challenged on their use of a high cell lysis efficiency criterion. This was on the basis that a lower efficiency could be balanced by using larger batch sizes and/or an increased number of batches to yield the same quantity of product. In response the applicant clarified that the lysis efficiency needed to be high as the subsequent purification stages led to large losses of material and the overall yield was relatively low. They claimed that a lower lysis efficiency would lead to significantly reduced yields. In addition, they clarified that they were already operating the maximum number of batches and batch sizes. The agency considered this to be a plausible explanation.

5.2. Availability and technical and economic feasibility of alternatives for the applicant and in the UK in general

Has the applicant demonstrated that there are currently no alternatives with the same function and similar level of performance that are technically and/or economically feasible for the applicant?

☒Yes ☐No

Is there information available in the application for authorisation or the comments submitted by interested third parties in the consultation indicating that there are alternatives available that are technically and economically feasible in the UK?

☐Yes ☒No

No comments were received during the public consultation and the applicant has concluded that there are currently no technically feasible alternatives.

The Agency's evaluation of the availability and technical and economic feasibility of alternatives for the applicant and in the UK in general

The applicant identified 4 alternatives for their use of 4-tert-OPnEO as a cell lysis agent in the production of gene-therapy vectors for therapeutic applications. These are:

1. Not using a detergent
2. Sorbitan monolaurate, ethoxylated
3. Sorbitan monooleate, ethoxylated
4. N,N-dimethyltetradecylamine N-oxide

Alternative 1 was identified as a potential alternative, since the viral gene-therapy vectors had been detected in supernatant solutions in the absence of any lysis. Upon investigation this was determined to be vector specific and some of the treatment vectors were apparently leaking from the cells, but others were not. Cell lysis efficiency was determined to be [redacted]. This is far below the threshold of 90% and would lead to significant production losses. No further investigation of this option was carried out and it was dismissed.

Alternative 2 was tested at 3 different concentrations from [redacted]. These achieved lysis efficiencies of [redacted]. This would be sufficient to exclude the substance from further consideration as an alternative. However, the increasing lysis efficiency at higher concentration suggests that further concentration increases could yield higher lysis efficiency. Coupling this with the favourable hazard profile and availability of GMP grade materials suggests that further

concentration increases could lead to the 90% lysis efficiency criterion being met. The applicant considered this but dismissed further testing as they claimed that increasing the detergent concentration further would lead to other complications in the recovery processes. These claims seem plausible. On this basis alternative 2 was dismissed, by the applicant. The Agency found information freely available on the internet indicating that at a concentration of 1% the sorbitan monolaurate, ethoxylated is already above the critical micelle concentration. On this basis we agreed that further increases would be unlikely to significantly increase lysis rates and decided not to challenge the applicant's dismissal.

Alternative 3 was also tested at 3 different concentrations from [redacted]. These achieved lysis efficiencies of [redacted]. This is sufficient to exclude the substance from further consideration as an alternative. On this basis alternative 3 was dismissed by the applicant. The Agency also determined that at the highest concentration used the substance was above the critical micelle concentration meaning that further concentration increases are unlikely to yield higher lysis efficiency and decided not to challenge the applicant's dismissal.

Alternative 4 was proposed by the current supplier of the 4-tert-OPnEO. Initial trials showed that it achieved the required level of cell lysis. However, to date a suitable supply of pharmaceutical grade (GMP) material has yet to be found. This means that currently the material is not sufficiently available. This alternative has some hazardous properties; this should exclude it on the basis of the applicant's selection criteria. However, the high lysis efficiency makes it an attractive possibility. Should such a source be found then further development work would be needed to look at the effects on product recovery and residues. Residues could affect the use of the final pharmaceutical product but may not exclude it. Upon challenge, the applicant clarified that, given the biological origin of the gene-therapy vector, a change to an alternative lysis agent is likely to be viewed as a major change in the drug production process. This would lead to additional requirements for regulatory approval under medicines legislation. An outline of likely requirement was provided together with cost estimates. Of note would be the difficulty in performing additional clinical trials given the low prevalence of the ocular diseases and difficulty in identifying suitable patients. On this basis, alternative 4 is currently not a feasible alternative.

5.3. Risk reduction capacity of the alternatives

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

☐Yes ☐No ☒Not applicable

Based on the following classification of N,N-dimethyltetradecylamine N-oxide:

H410 (Aquatic chronic)

The applicant claims that the identified alternative presents a similar toxicity for the environment to 4-tert-OPnEO but does not expect the identified alternative to have any endocrine disruptive properties. The alternative is not currently available at the grade required for this use.

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

5.4. Substitution activities/plan

Did the applicant submit a substitution plan?

☐Yes ☒No

5.5 The Agency's conclusions on the analysis of alternatives and the substitution plan

The Agency concluded on the analysis of alternatives that:

- The applicant has demonstrated that there are currently no alternatives available with the same function and similar level of performance that are technically and/or economically feasible for the applicant.
- There is no information available in the application for authorisation or in the comments submitted by interested third parties in the consultation indicating that there are alternatives available that are technically and economically feasible in the UK. The applicant did not submit a substitution plan. However, no substitutes are currently available. The applicant has indicated that more research will be conducted for Alternative 4 should a suitable source become available.

The Agency has not identified any remaining uncertainties of such magnitude that they may affect its conclusions.

6. Socioeconomic Analysis

Did the applicant demonstrate that the socioeconomic benefits of continued use[7] exceed the risks of continued use?

☐Yes ☐No ☒Not relevant (the risk cannot be compared with the costs of non-use)

6.1. Socioeconomic Analysis: General Methodological Considerations

This authorisation application takes the socioeconomic route to Authorisation. Therefore, a complete socioeconomic analysis has been conducted by the applicant, MeiraGTx UK II Limited. The socioeconomic analysis monetises most of the major impacts associated with the continued use of 4-tert-OPnEO ("applied-for-use scenario") versus not being able to use 4-tert-OPnEO, i.e., assuming authorisation is not granted ("non-use scenario"). In this application, 4-tert-OPnEO is used as a manufacturing aid in the production of gene therapies. The analysis aims to show that the societal benefits outweigh the risks of applied for use within the analytical timeframe considered by the applicant.

The analytical timeframe (temporal scope) of the SEA is 12 years, the duration of the review period being sought by the applicant. The applicant adopts the "annualised" approach in the analysis, but it is unclear whether the values with different base years are adjusted for comparison, and the projected values have not been discounted. Also, due to the nature of the products, their targeted diseases and the evolution of potential market demand (see the Benefits section), some of the annualised benefits of applied for use may not be fully realised each year within the review period. Despite these inadequacies in handling values over time, this approach provides an acceptable comparison of impacts over the time period selected.

The geographical scope of the analysis is Great Britain, including the impacts occurring within GB caused by the applicant's operation in GB in the applied-for-use scenario, and the impacts occurring within GB caused by the applicant's operation in the EU (or the rest of the world) in the non-use scenario. When presenting the societal benefits of the applied-for-use scenario, the applicant adjusted the relief of health burden of patients from the values of the UK to GB values using the UK/GB population proportion. The benefits presented by the applicant also include the avoided direct and secondary costs of unemployment, and the avoided loss in income for GB raw material suppliers.

The applied-for-use scenario describes the use of 4-tert-OPnEO when authorisation is granted for the applicant to manufacture a series of drugs in three development programmes for gene therapies (ocular, neurodegenerative and salivary gland; to relieve diseases such as X-Linked Retinitis Pigmentosa, Leber's Congenital Amaurosis/Early-Onset Severe Retinal Dystrophy,

[7] Benefits of continued use are the avoided societal costs of not granting an authorisation.

Achromatopsia, Parkinson's, Xerostomia and Sjögren's syndrome) in their London production facility. The non-use scenario defines the consequences of a refused authorisation based on the most likely responses of the applicant. According to the applicant, they would react to a refused authorisation (under UK REACH) by either moving their production to their production facility in Ireland or using a Contract Manufacturing Organization (CMO) located outside the EU and the UK. The applicant adopts the former as the non-use scenario and claims that it is their preferred scenario out of the two, while the Agency considers using the CMO to be the most likely reaction because the applicant's response is obviously conditioned on whether authorisation is granted for the same use in Ireland under (EU) REACH. Given the non-use scenario, the applicant considers the direct financial costs to their operations (in terms of loss of profits, relocation or closure costs, transportation costs) in the event of not being granted an authorisation, as well as impacts related to unemployment, patients' welfare, and lost income for raw material suppliers. The Agency accepts the applicant's chosen non-use scenario because the impacts and consequences in both (their preferred/chosen vs. most likely) scenarios are almost identical.

The assessment of quantitative economic impacts undertaken by the applicant is in general based on a suitable methodological approach to cost assessment using expenditures related to additional resources having to be transferred from other competing uses, as well as the loss of productive values of resources that are rendered unemployed, as a consequence of the non-use scenario. However, the Agency is unable to decompose and verify some of the computations of unemployment cost in the event of a refused authorisation. The Agency also disagrees with how the applicant disregards the value of alternative use of the site investment. More importantly, the major benefits of applied for use, avoided direct financial loss to the applicant (profits) and the additional health burden relieved by the applicant's therapies, are also likely to be overestimated by the applicant. For the monetised risks of applied for use, the applicant estimates the quantity of emissions, qualitatively describes the environmental risks associated with the emissions, and attempts to monetise the environmental risks. The Agency does not agree with the adopted method and hence does not accept the monetisation of risks. However, given the amount of release to wastewater (<100g per year*) and some certain societal benefits of applied for use, the Agency finds that these shortcomings would have no consequences on the conclusions derived from the analysis.

6.2. Human health and environmental risks (monetised impacts) of continued use

The Agency's evaluation of the impacts on human health and the environment

The applicant quantifies the environmental impact of their use of 4-tert-OPnEO in the manufacturing of their products at full production capacity at the London facility. The applicant claims that <100g* of 4-tert-OPnEO will be released to wastewater per year and assumes all will rapidly degrade to 4-tert-OP (endocrine disruptor) at the point of entry to the receiving sewage treatment plant, and this is the worst-case scenario proposed by the applicant. Assuming a lower rate of degradation during sewage treatment would reduce the amount of OP and reduce the proportion in sludge. This is because 4-tert-OPnEO has a lower tendency to bind to sewage sludge.

So, the assumption of complete transformation to 4-tert-OP does not produce a worst-case scenario for surface waters. Nevertheless, the Agency considers the scenario sufficient to give conservative estimates of environmental risks in this application. Then the applicant proceeds to monetise the environmental impacts in three affected sites using generic OECD estimates for the disruption to an ecosystem caused by a reprotoxic chemical and applies a dilution factor of 10. While the Agency doubts whether these estimates are transferrable and appropriate for estimating damage costs of their release and whether applying the dilution factor as such is appropriate, the Agency accepts that there is currently no agreed methodology for monetising the environmental impacts of endocrine disrupting substances. As mentioned in section 4.5, the Agency considers the residual emissions would not result in discernible adverse environmental impacts at population level.

6.3. Socioeconomic benefits of continued use[8]

The Agency's evaluation of the socioeconomic benefits of continued use

Non-use scenario

The applicant's analysis of the benefits of continued use is based on the non-use scenario in which they transfer the production to their production facility in Ireland and shut down the corresponding facility in London. When the Agency questioned the credibility and plausibility of this non-use scenario, the applicant acknowledged two shortcomings in their reply: first, the credibility of this scenario depends on the whether the applicant would be granted authorisation for the use in the Irish facility under (EU) REACH (given the non-use scenario means that the UK REACH authorisation is refused); second, the applicant explained that whereas moving production to Ireland is their preferred scenario, the most likely response would actually be contracting out the production to a Contract Manufacturing Organization (CMO) outside the EU. While the Agency still finds the CMO option more credible, the chosen non-use scenario preferred by the applicant is acceptable to the Agency due to the similar impacts brought by the two scenarios.

According to the applicant, relocating the production to their facility in Ireland would have two major effects: first, it would delay the products' market entrance for a certain number of years (figures claimed confidential), subsequently leading to the applicant losing market shares to their competitor(s); second, the applicant would shut down the equivalent production facility in London, causing employment associated losses to GB (for details of these effects, see the Benefits section). The applicant also claims that the alternative non-use scenario of using the CMO would delay market entrance for a certain number of months (figures claimed confidential), which is a shorter delay than the relocation. With the other effects of using the CMO being identical to the effects of the relocation, the consequence of the delay in market entrance is the key difference of the two scenarios. The applicant elaborates that because of the nature of the therapies (fast-acting; a few doses) and the low prevalence of some of the targeted genetic conditions (and thus rapidly

[8] Avoided societal costs of not granting an authorisation

decreasing market sizes after the initial market entrance), any delay will lead to the applicant losing the 'first-to-market' advantage and subsequently all their profits in both scenarios. If competitors are ready to enter the markets (at the same time as the applicant's planned market entrance), the Agency agrees with the applicant that the delay would be detrimental to their ability to capture the markets of certain products (in the ocular programme). And this could bring financial losses to the applicant[9], and societal costs to GB such as scarring costs of unemployment and early retirement of capital in both non-use scenarios. Although the applicant could have chosen the most likely scenario in which the drugs would be produced by the CMO outside the EU and GB, the agency finds the impacts of the chosen scenario similar to the most likely scenario in this aspect. The actual length of delay will matter but the loss in producer surplus of the applicant (that is not offset by their competitors) and the social costs of unemployment are certain in either non-use scenario.

Benefits (economic impacts) of continued use

The benefits of continued use are mainly based on the applicant's calculation of the avoided costs of the non-use scenario. These benefits are the applicant's projected avoided financial costs to the applicant and other actors in the supply chain, avoided economic (opportunity) costs of alternative use of resources (capital and labour), and monetised benefits for patients. It is unclear whether the applicant has adjusted price levels to the same base year and has correctly annualised the figures with discounting, although the Agency judges that the effects of these shortcomings would be insignificant to the conclusion. While the Agency considers the applicant's approach to assessing the economic and social impacts to be based on an acceptable general methodological framework, it is unclear to what extent some of these benefits would be realised. The applicant lists the "avoided profit loss due to ceasing the use applied for" and "avoided other societal impacts" as the benefits with the largest magnitude (figures claimed confidential). Following the principle of proportionality, the Agency scrutinises the magnitudes and credibility of these benefits as follows.

Avoided producer surplus loss

The largest benefit of applied for use claimed by the applicant is by far the "avoided profit loss due to ceasing the use applied for". The applicant calculates this number by estimating the number of potential patients receiving the therapies and multiplying it by the prices of comparable therapies in the market. Therefore, this is the avoided revenue loss instead of "avoided profit loss". The Agency agrees with the applicant that with the products still in trials, the production and marketing of these new products have not started so it is difficult to pin down the sales prices and production costs. But in another part of the analysis, the applicant assumes a profit margin and calculates the corresponding profits. The Agency believes it is less misleading to use this profit figure rather than

[9] If competitors are ready to enter the markets, the applicant's producer surplus losses are not costs to society because they are offset by the competitors' gains in producer surplus.

the sales figure when listing the benefits of applied for use.

The Agency is also concerned about the assumptions made by the applicant throughout their computations of avoided producer surplus loss. An assumption made when computing full amount of sales revenue of the applicant during the review period is using the production capacity to estimate the number of potential patients receiving the therapies. The Agency raised doubts about these sales estimates that the targeted conditions in the applicant's ocular programme are rare and suitable existing patients with these conditions would have been treated in the first three years of the review period and the sales revenues would be overestimated. The applicant has revised the numbers in their reply, and to justify the profits in year 4 to 12, the applicant assumes that after exhausting domestic suitable patients, patients from abroad would travel to GB to receive treatment. The Agency is uncertain whether it is feasible for patients from abroad to travel to GB to receive treatment, and whether exporting the products to these markets abroad would be a more likely outcome. But the Agency finds the revised estimates more plausible and accepts that it is feasible at least for some patients to do so and the administration of the therapies is highly specialised and requires expertise in GB.

The Agency also questioned the credibility of the applicant's claim of losing all profit in the event of a refused authorisation. The applicant supported their claim by citing "first-to-market" advantage in their reply. According to the applicant, their competitors will enter and capture the markets if there is any delay of their products' market entrance. The Agency finds this claim plausible in some of the product markets because the products in the ocular programme are fast-acting, only require a few doses and can reverse the course of disease progression. Once the existing patient base is exhausted, the remaining market size is then limited (by birth rates) for subsequent entrants. However, for the products in the neurogenerative and the salivary programmes which target diseases of higher prevalence rates, the Agency believes that the "first-to-market" advantage is less important and thus the applicant will still be able to profit from these markets despite the delay caused by a refused authorisation. While the applicant shows that the prices for these therapies will be much lower than those for the rare diseases in the ocular programme, the Agency is not convinced that the profit loss computed by the applicant will be fully realised in the event of a refused authorisation.

The applicant also remarks (in a footnote) that the producer surplus losses are not to be included for the whole review period to account for producer surplus gains by their competitors (according to the SEAC note on economic surplus changes). However, the applicant did not take this into account in their calculations. The Agency finds the applicant's "conservative estimate" of net profit resulting from a certain length of delay[10] (figures claimed confidential, section 6.2.2) more credible than the "annualised profit loss" (figures claimed confidential) used throughout the SEA. Although this producer surplus loss is overestimated in the SEA, it is certain that this loss will be incurred in

[10] One member on the Challenge Panel pointed out that sales are not lost, only delayed, so this should be computed through discounting instead. But the Agency includes the total loss in profits within the delay, assuming that the delayed profits will not be realised within the review period because the applicant's sales is constrained by their production capacity and capacity to administer the treatment.

the event of authorisation not being granted[11]. The magnitude of the loss will depend on the length of delay to the products' market entrance and the timing of competitors' entrance.

Health benefits of continued use

The second largest benefit of applied for use stated by the applicant is the "avoided other societal impacts", which is the additional health benefits of patients receiving the treatments from the applicant, rather than their competitor(s) (£205 million per year, revised figure[12]). The applicant arrives at this estimate based on two assumptions: first, the full potential for relief of the illnesses can be realised; second, the applicant estimates that 50% of the health benefits would not be realised if their competitor(s) capture the markets first. For the first assumption, the Agency is unable to determine how much of the full potential for relief of all the conditions listed in the application can be realised. Some symptoms are irreversible and once they have started, the therapies could only slow down the deterioration. Even if the pool of patients has been narrowed down using the suitability index, the number provided by the applicant could be overly optimistic in terms of efficacy of the therapies and the coverage and valuation of health burdens with potential for relief. For the second assumption, the Agency is unable to judge whether the applicant's products are able to relieve double the disease burden than the potential competitor's products. Alternatively, this computation of "avoided other societal impacts" as half of full potential for relief can be a result of combined effect of violating these two assumptions but again the Agency is unable to verify this computation. Despite the uncertainty on the magnitude of this monetised health benefits, the Agency is certain that the benefits are positive. Therefore, the Agency disregards the applicant's monetisation and expresses the benefits as the number of treated patients, which is the number of patients who would otherwise be delaying/missing treatments due to the delay of the products' market entrance in the non-use scenario.

Avoided social cost of unemployment

The Agency is unable to reconcile some inconsistent values throughout the cost of unemployment section. And in the calculation of total unemployment costs (Table 6-10), the applicant (in both the SEA and the reply to the Agency's questions) claims that the loss of output includes the loss of revenue, process transfer costs, decommissioning costs and the lost output from salaries. The applicant claims to have followed the methodology in the ECHA guidance document on unemployment, but the Agency finds that some other effects are included. While these figures could

[11] As long as the competitors' market entrance is later than the start of the review period, the applicant's producer surplus loss will not be completely offset by competitors' gain. This producer surplus loss is caused by the delay in sales only and it is present regardless the validity to the first-to-market argument.

[12] In the original SEA, the applicant claimed the health benefits of patients receiving the treatments to be £410 million per year and this whole amount would be lost in the event of a refused authorisation. The Agency challenged this claim because it was inconsistent with the applicant's claim of potential competitors providing similar treatments when arguing for "first-to-market" advantage.

be accounting for some secondary effects of unemployment, including the unemployed workers cutting their spending on leisure activities (restaurant visits, etc.) locally, it is unclear why they are presented as "the total costs for the non-use scenario". It is also unclear why only scarring effects listed here are included in subsequent summary tables (Tables 6-11 and 6-16) as the benefits of applied for use, excluding leisure benefit, job search and recruitment costs. Therefore, the Agency only accepts the sum of scarring cost, job search and recruitment cost as the social cost of unemployment.

Avoided loss of residual value of capital

The Agency finds that the applicant fails to fully consider the alternative uses of the premises in the calculation of the "avoided residual value of capital", thus overestimating the benefit of applied for use. The applicant purchased a long-leasehold interest on the facility in London and claims that the investment would be lost in the event of a refused authorisation, but it is unclear to the Agency why the property cannot be rented out to avoid further losses. The applicant also claims that "it is possible that the facility may be retained for office space, laboratory work and/or research and development, and so the property investment cost would not be recouped". The Agency disregards this one-off cost of site purchase because the applicant could benefit from the alternative uses of this premise.

Avoided producer surplus loss for suppliers

The Agency also finds the "foregone spill-over impact on surplus of alternative producers" (which is in fact the avoided loss in income for GB raw material suppliers) overestimated. The applicant includes their total cost of raw materials purchased from GB suppliers (instead of their profits) and overlooks that this loss can be offset by supplying to the applicant's competitor(s). The Agency accepts the avoided loss in producer surplus for GB raw material suppliers before the production begins (either by the applicant or competitors). Again, the magnitude of the loss will depend on the length of applicant's delay and the timing of competitors' entrance.

Investment and/or additional production costs related to the adoption of an alternative

The Agency finds this to be irrelevant because the applicant's non-use scenario (relocating production) does not involve the use of the alternative.

The applicant also lists the benefits of applied for use including "avoided relocation or closure cost" and "avoided additional cost for transportation, quality testing, etc.". Although the Agency is unable to verify these estimates, the Agency finds these numbers plausible, and the presence of these benefits of applied for use is certain.

The benefits of continued use resulting from the Agency's assessment above are summarised in Table 5. The impacts are calculated assuming:

- the relocation of the applicant's production,
- a delay of [redacted] years for the applicant's products to enter the market, and
- the presence of GB competitors and their products entering the market after the same length of delay.

Table 5: Socioeconomic benefits of continued use

Description of major impacts	**Monetised/quantitatively assessed/qualitatively assessed impacts**	**Notes**
1. Monetised impacts	**£ million per year[1] rough approximation of annual cost**	
Avoided Producer surplus loss due to ceasing the use applied for OR Investment and/or additional production costs related to the adoption of an alternative	>10*	A delay of [redacted] years is assumed. The additional production costs related to adoption of alternative ([redacted]) is disregarded because the alternative is not adopted by the applicant.
Avoided Relocation or closure costs	>0.1*	This is accepted as claimed by the applicant.
Avoided Loss of residual value of capital	0	The London facility value claimed by the applicant is disregarded because the facility has alternative uses.
Avoided Social cost of unemployment	>0.25*	This is the sum of scarring cost, job search and recruitment cost.
Avoided Producer surplus loss for suppliers	>0.1*	A delay of [redacted] years is assumed.

	Description of major impacts	Monetised/quantitatively assessed/qualitatively assessed impacts	Notes
	Monetised impacts	**£ million per year[1] rough approximation of annual cost**	
	Avoided additional cost for transportation, quality testing, etc. (one-off cost within the first 12 months following authorisation refusal, spread over 12-year review period)	>0.75*	This is accepted as claimed by the applicant.
	Sum of monetised impacts	>10*	
2.	**Additional quantitatively assessed impacts**	**Per year**	
	The number of treated patients[2]	>500*	This is based on the prevalence of the conditions and the production capacity of the applicant.
3.	**Additional qualitatively assessed impacts**		
	Please specify	N/A	

Notes:

1. Per average year during the time horizon used in the analysis.

2. Some of these patients might still be able to receive treatment but delayed by [redacted] years in the non-use scenario.

6.4. Combined assessment of impacts

The Agency's evaluation of the combined assessment of impacts

As mentioned in section 4.5, the Agency considers the residual emissions would not result in discernible adverse environmental impacts at population level. While the calculation of the ratio of cost of non-use per kg is incorrect[13] in the application (Table 6-15) and the Agency does not have a benchmark to assess whether it is cost effective to reduce the emission of the substance (endocrine

[13] The applicant wrongly divided the "aggregated monetised excess risk of continued use" with "total emissions", while the correct ratio (cost of non-use per kg and year) is dividing "aggregated socioeconomic benefits of continued use" with "total emissions".

disruptor) with a refused authorisation, the Agency considers that the correct ratio is an acceptable measure of cost effectiveness. In addition, the Agency has concluded that although the precise magnitude of benefits of applied for use is uncertain, the application has demonstrated that such benefits would likely be significant and certainly positive over the 12-year review period requested. The Agency thus affirms the applicant's conclusion that a granted authorisation would have positive net benefits to society, due to the avoided loss in patient welfare and avoided expenditures related to additional resources having to be transferred from other competing uses, as well as the avoided loss of productive values of resources that are rendered unemployed if the authorisation was not granted.

Table 6 compares the socioeconomic benefits of continued use and the excess risks associated with continued use. Since environmental risks are not monetised or quantified, the benefit is compared to the amount of residual emissions. Table 7 shows the costs of non-use per kg per year that is more relevant to the substance in this application. But since the release is significantly less than 1 kg (<0.1kg*), the cost per kg appears to be large and this ratio should be interpreted with caution.

Table 6: Comparison of socioeconomic benefits and risks of continued use

Socioeconomic benefits of continued use		**Monetised excess risks associated with continued use**	
Monetised Benefits (£ per year[1])	>10 million*	Monetised excess risks to workers directly exposed, general population and indirectly exposed workers and monetised environmental risks (£ per year[2])	N/A
Additional quantitatively assessed benefits (per year)	Number of treated patients >500*	Additional quantitatively assessed risks to workers directly exposed, worker/general population indirectly exposed, and environmental risks (per year)	N/A

Socioeconomic benefits of continued use		**Monetised excess risks associated with continued use**	
Additional qualitatively assessed benefits (per year)	N/A	Additional qualitatively assessed risks to workers directly exposed, worker/general population indirectly exposed, and environmental risks (per year)	Environmental impacts associated with <100g* of 4-tert-OPnEO released to wastewater
Summary of socioeconomic benefits	monetised benefits of >£10 million* per year >500* treated patients per year	**Summary of excess risk/environmental risks**	Environmental impacts associated with <100g* of 4-tert-OPnEO released to wastewater per year

Notes:

1. Annualised to a typical year based on the time horizon used in the analysis.
2. Per average year during the time horizon used in the analysis.

Table 7: Cost of non-use per kg and year (for PBT/vPvB substances and endocrine disruptors)

	Per year[4]
Total costs[1] (£)	>10 million*
Total releases[2] (kg)	<0.1kg*
Ratio[3] (£/kg)	>100,000,000*

Notes:

1. "Total costs" (in case of non-authorisation) = Socioeconomic benefits of continued use (avoided societal costs of non-use)
2. "Total releases" (in case of continued use) = Estimated releases to the environment.
3. "Ratio" = Total costs/Total releases. This ratio needs to be interpreted with care as any release amount significantly smaller than 1 kg gives the impression that large costs would occur in the non-use scenario. However, this impression is an outcome of reporting the ratio in £ per kg.
4. Annualised to a typical year based on the time horizon used in the analysis.

6.5. The Agency’s conclusion on the socioeconomic analysis

The Agency considers that the applicant’s socioeconomic analysis, whilst presenting some shortcomings as discussed above, is based on a suitable general methodological approach to such analysis. The Agency considers the non-use scenario to be acceptable, such that it establishes the likely general situation for the applicant in the event of not being granted an authorisation. However, it is difficult for the Agency to verify the precise magnitude of changes in socioeconomic welfare resulting from non-use 4-tert-OPnEO in the use applied for. Despite the shortcomings, the analysis is considered proportionate, and the evidence and information included in the application sufficient for the Agency to reach a definitive conclusion, taking into account the uncertainties in the analysis.

The Agency concludes that the applicant has demonstrated that the socioeconomic benefits of granting an authorisation are >£100,000,000/kg* of avoided emissions of 4-tert-OPnEO as a result of ceasing the use applied for.

The Agency has estimated that the use applied for may result in <100g* of emissions of 4-tert-OPnEO per year of the substance to the environment. Given that the impact of these emissions cannot be quantified, the Agency used the emissions of 4-tert-OPnEO as a proxy for the risk associated with the continued use.

This conclusion of the Agency is made on the basis of:

- the application for authorisation,
- The Agency's assessment of the socioeconomic benefits of continued use,
- The Agency’s assessment of the availability, technical and economic feasibility of alternatives,
- any additional information provided by the applicant, and
- The Agency 's assessment of the risks to the environment.

The Agency has not identified any remaining uncertainties of such magnitude that they may affect its conclusions.

7. Proposed review period

☐ Normal (7 years)

☒ Long (12 years)

☐ Short (…. years)

☐ Other:

When recommending the review period, the Agency took note of the following considerations:

Risk Assessment considerations:

No advice on risk assessment considerations was given.

Substitution and socioeconomic considerations:

When recommending the review period, the Agency took note of the following considerations:

The applicant requests a 12-year review period.

There are currently no technically feasible alternatives available. Should the alternative with similar performance become available at a suitable pharmaceutical grade, further research and development would be required to show full technical equivalence. If alternatives become available regulatory approval under medicines legislation would be required for the drugs produced with this alternative. This could potentially include fresh clinical trials for rare diseases with small pools of people eligible/willing to participate.

While a potential alternative (alternative 4) has been identified by the applicant, the applicant will need to conduct bridging studies which include repeating the steps detailed in section 5.3.4 to be able to use patient response data from the preceding clinical studies. Under medicines legislation, additional requirements for regulatory approval would be required. Also, the Agency acknowledges the difficulty in identifying suitable patients and performing additional clinical trials given the low prevalence of the ocular diseases. These factors suggest that a 7-year review period is insufficient for the substitution to take place. In addition, no information on alternatives was received from the public consultation.

The Agency acknowledges that it is not economically meaningful to substitute for the use of 4-tert-OPnEO because the investment cycle is demonstrably very long and profits can only be generated a number of years (figure claimed confidential) after the initial investment. A 7-year review period will not give the applicant sufficient time to recoup their investment.

The socioeconomic impacts have been identified and mostly quantified by the applicant. There is clearly a positive and substantial socioeconomic benefit (such as avoided producer surplus loss, patient welfare, avoided unemployment impacts) despite the Agency's doubts on the validity of some of the applicant's claims. Uncertainties are unlikely to change the situation in the next decade.

The environmental risks are shown to be limited and the applicant does not expect an increase in future emissions. Although the Agency does not accept the monetised risks proposed by the applicant, estimates on emissions are provided and the effects are described qualitatively, and the Agency finds the estimates to be credible. As mentioned in section 4.5, the Agency considers the residual emissions would not result in discernible adverse environmental impacts at population level.

Taking into account all of the above points, a 12-year review period is recommended for this use.

8. Proposed additional conditions for the authorisation proposed

Were additional conditions proposed for the authorisation?

☒Yes ☐No

8.1. Description:

The Agency proposes that the authorisation should include a condition requiring the applicant to:

identify and implement any measures needed to ensure that environmental exposure will be reduced to as low as technically and practically possible or carry out such investigations as may be necessary to demonstrate that no further reduction in emissions is technically or practically possible.

8.2. Justification:

The applicant has not explained why it is not technically or practically possible to collect all wastewater flows containing 4-tert-OPnEO for incineration.

9. Proposed monitoring arrangements for the authorisation

Were monitoring arrangements proposed for the authorisation?

☐Yes ☒No

10. Recommendations for the review report

Were recommendations for the review report made?

☐Yes ☒No

11. Challenge Panel's Recommendation on the Draft Opinion

At the Challenge Panel meeting held on 25 January 2022, the Panel agreed with the Agency's recommendation that an authorisation should be granted and made the following consensus recommendations to the Agency:

Table 8: Challenge Panel Recommendations

	Recommendation	Response to Recommendation
1	The draft opinion should be reviewed and revised to: • Ensure key words to convey the intended meaning are not inadvertently omitted • Explain as necessary the content of tables • Avoid unnecessary repetition • Avoid subjective non-scientific terminology • Improve clarity and transparency	We have amended the draft Opinion to positively address all these recommendations.
2	Clarify that the applicant has not demonstrated that emissions have been minimised as far as technically and practically possible	We have amended the draft Opinion to make this clear.
3	The applicant should assess the feasibility and practicality of further minimisation of emissions. Article 60(10) of REACH already requires that the authorisation holder shall ensure that the exposure is reduced to as low a level as is technically and practically possible. The Agency should consider whether to make this a condition of authorisation	We have amended the draft Opinion to add a condition in line with the recommendation.
4	Clarify that the application is for authorisation of a future use in manufacturing and not for R&D (R&D use does not require authorisation)	Text amended and footnote included.
5	Look at the recent European Court case on lead chromate and consider whether there are issues that affect the draft Opinion	This was reviewed and considered not to be relevant.
6	Clarify the source of information about critical micelle concentration	Text revised to account for the comment
7	Although a review period of 12 years is generally supported, clarify that the main justification for 12 years is proportionality	We agree that proportionality is a consideration and have added text to reflect this. However, we are also of the opinion that a longer review is justified to

		allow the company to transition to an alternative lysis agent (should one be found). In particular, the paucity of suitable patients for clinical trials would add significant delay.
8	Clarify relative toxicity of alternative 4 compared to the substance in question, and challenge the applicant's assertion that alternative should be non-hazardous	Text added
9	Clarify what was tested for alternative 4 for technical feasibility and why it is not also available for use at the relevant grade	Text added to clarify that the issue is principally one of availability.

12. Applicant's comments on the draft final opinion?

Did the applicant provide comments on the draft opinion?

☐Yes ☒No

12.1. Comments of the applicant

Was the opinion or the justifications to the opinion amended as a result of the analysis of the applicant's comments?

☐Yes ☐No ☒Not applicable – the applicant did not comment

ANNEX 1: PROCESS INFORMATION FOR ADOPTION OF THE OPINION

Date of submission of the application	19 January 2021
Date of payment	19 April 2021
Was the Application submitted by the Latest Application Date for the substance and can the applicant consequently benefit from the transitional arrangements described in Article 58(1)(c)(ii)?	☐Yes ☒No
Date of Public Consultation on use, in accordance with Article 64(2)	Start date: 14 July 2021 End Date: 8 September 2021 REACH – Applications for authorisation AFA002-01 – OPEO - Health and Safety Executive - Citizen Space (hse.gov.uk)
Were comments received in the public consultation	☐Yes ☒No
Request for additional information in accordance with Article 64(3)	☐Yes ☒No
Stakeholder Consultation meeting	11 November 2021
Was the time limit set in Article 64(1) for the sending of the draft opinions to the applicant extended?	☐Yes ☒No
Did the application include all the necessary information specified in Article 62 that is relevant to the Agency's remit?	☒Yes ☐No Comment:

Relevant scientific advice sought in accordance with Article 77	☒Yes ☐No Justification if not sought:
Challenge Panel Endorsement of Draft Opinion	☒Yes ☐No by Challenge Panel meeting on 25 January 2022: ☒ Consensus Recommendations given ☐ No Consensus Recommendations ☐ Minority recommendations
Date of agreement of the draft opinion in accordance with Article 64(4)(a) and (b)	10/02/2022, agreed by Agency.
Date of sending of the draft opinion to the applicant	17/02/2022
Date of decision of the applicant not to comment on the draft opinion, in accordance with Article 64(5)	04/03/2022
Date of receipt of comments in accordance with Article 64(5)	Not relevant
Action(s) taken resulting from the analysis of the comments?	Not relevant
Challenge Panel advice sought on Final Opinion?	☐Yes Action taken: ☒No Reason: No further changes were made to the opinion following consideration of the Challenge Panel recommendations on the Draft Opinion

Date of adoption of the opinion in accordance with Article 64(5)	15/03/2022, adopted by Agency.
Agency AFA Secretariat	Michelle Wilson Amanda Cockshott Ross Orrett Joshua Walmsley Stavros Georgiou
Case Team Members	Gary Dougherty: Analysis of Alternatives Chau-Man Fung: Socioeconomic Analysis Richard Dean: Environmental Risk Assessment
Challenge Panel Members	Robin Foster (Chair) Derrick Jones Paul Ylioja Richard Dubourg Michael Holland Thea Sletten Chris Hughes Edwin Routledge Richard Murray-Smith

ANNEX 2: LIST OF ACRONYMS

AfA	Application for authorisation
AoA	Analysis of alternatives
bw	Body weight
CBA	Cost-benefit analysis
C-E	Cost-effectiveness
CSR	Chemical safety report
DNEL	Derived no-effect level
ES	Exposure scenario
ECS	Environmental contributing scenario
LAD	Latest application date
LEV	Local exhaust ventilation
OC	Operational condition
PBT	Persistent, bioaccumulative and toxic
PNEC	Predicted no-effect concentration
PPE	Personal protective equipment
REACH	Regulation on registration, evaluation, authorisation and restriction of chemicals
RMM	Risk management measure
RP	Review period
RR	Review report
SDS	Safety data sheet
SEA	Socioeconomic analysis
SP	Substitution plan
SSD	Sunset date
vPvB	Very persistent and very bioaccumulative
WCS	Worker contributing scenario