Analysis of Alternatives and Socio-Economic Analysis

Public Version

Legal name of applicant: MeiraGTX UK II Limited

Submitted by: MeiraGTX UK II Limited

Substance: 4-(1,1,3,3-tetramethylbutyl)phenol, ethoxylated [covering well-defined substances and UVCB substances, polymers and homologues]

Use title: Use of 4-tert-OPnEO as a manufacturing aid in the production of gene therapies

Use number: 1

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Declaration

The Applicant is aware of the fact that evidence might be requested by the Health and Safety Executive to support information provided in this document.

Also, we request that the information blanked out in the "public version" of the Analysis of Alternatives and Socio-Economic Analysis is not disclosed. We hereby declare that, to the best of our knowledge as of today (15th January 2021) 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: 18TH JAN 2021
LONDON
UK

1. Summary

1.1. Background

This report consists of the Analysis of Alternatives (AoA) and Socio-Economic Analysis (SEA) (AOA-SEA) in support of the Application for Authorisation of MeiraGTx UK II Limited ('the applicant') for the substance 4-(1,1,3,3-tetramethylbutyl)phenol, ethoxylated, covering well-defined substances and UVCB substances, polymers and homologues (i.e. 4-tert-OPnEO or 'the substance').

The applicant intends to use the substance (< 1 tonne per year) in its manufacturing facility in London, Great Britain (GB) following the sunset date written into the 'UK REACH' Regulation, for use in the manufacture of novel genetic treatments for a number of diseases.

Information on the substance, the applicant, their products and the diseases targeted for treatment, potential environmental impact of the substance's use, use and non-use scenarios and the socioeconomic impacts thereof, are detailed throughout the report.

1.1.1. Status of alternatives and length of the review period

Four potential alternatives to the substance were identified by the applicant and evaluated for their suitability as a replacement in the applicant's manufacturing process. These are considered in detail in Section 5 and summarised in Table 1-1.

Table 1-1: Summary of potential alternatives and their suitability

Potential alternative	**Suitability**
1 – not using a detergent	Unsuitable – fails essential criterion (efficiency of cell lysing)
2 – sorbitan monolaurate, ethoxylated	Unsuitable – fails essential criterion (efficiency of cell lysing) To note: no environmental hazards
3 – sorbitan monooleate, ethoxylated	Unsuitable – fails essential criterion (efficiency of cell lysing) To note: no environmental hazards
4 – N,N-dimethyltetradecylamine N-oxide	Unsuitable – fails essential criterion (GMP grade not available) To note: shows potential as an efficient cell lysing agent, but has known intrinsic hazards

A 'long review period' of 12 years (1) is requested for this application due to – for example – the long investment cycle, the novel nature of the treatment provided for by the applicant's products, and the low likelihood of a suitable alternative being implemented within a 7-year period. This is discussed in detail in Section 5, however the justification for a 12-year review period can be summarised here:

- The applicant's investment cycle is very long and a large amount of capital has been invested prior to manufacturing being initiated. No profits are expected to be generated until a[redacted], a[redacted] years after the initial investment.
- One potential future alternative has been identified, but this is unlikely to be available within the normal review period of 7 years; also, this has similar hazards to the substance.
- The costs of using an alternative, if theoretically available, are potentially very high if new studies / trials are required to ensure stability of process and continuity of supply.
- Delays to the manufacturing process and eventual release to market will dramatically reduce the investment return, resulting in a significantly higher product cost. This would impact both the investment strategies and the availability to patients of treatments using the applicant's products.
- The risk resulting from the use of the substance is low, and the net socio-economic benefits are high.

Comparison of benefits and costs

The benefits and costs associated with the applicant's use of the substance have been quantified and detailed throughout this report. These data are summarised in Table 1-2 and used to provide an ultimate net benefit figure in support of an authorisation to be granted.

Table 1-2: Benefits, costs and final net benefit arising from a successful application for authorisation

Benefits [annualised to £ million per year]		**Monetary costs [annualised to £ million per year]**	
Avoided investment / production costs related to the adoption of an alternative	>7.5 (d[redacted])	Environmental (estimated)	5.04
Estimated profits	>1,000 (c[redacted])		
Avoided cost of decommissioning and moving production (one-off cost within first 12 months following authorisation refusal, spread over 12-year review period)	>0.1 (d[redacted])		
Avoided cost of lost investment of London facility (one-off cost of site purchase, spread over 12-year review period)	>0.25 (d[redacted])		
Avoided additional cost for transportation, quality testing, etc.	>0.75 (d[redacted])		
Health burden remaining, as treatment not available	410		
Costs of unemployment	>0.25 (e[redacted])		
Lost income for suppliers	>5 (f[redacted])		
Total[1]	>1,500 (c,d,e,f[redacted])	**Total**[2]	5.04

Net benefit [annualised to £ million per year] (1 – 2)	>1,500 (c,d,e,f)

The net benefit of the applicant's use of the substance following the granting of an authorisation is therefore >£1,500 million (c,d,e,f) per year.

2. Aims and scope of the analysis

2.1. Aim of the combined AoA and SEA

2.1.1. Regulatory background for 4-tert-OPnEO

4-(1,1,3,3-tetramethylbutyl)phenol, ethoxylated, covering well-defined substances and UVCB substances, polymers and homologues (i.e. 4-tert-OPnEO or 'the substance') was added to Annex XIV of Regulation (EU) 1907/2006 (EU REACH Regulation) on 4th July 2017. It was appointed a latest application date of 4th July 2019 and a sunset date of 4th January 2021.

When used within the market, 4-tert-OPnEO may be released into the environment and, once present, can be chemically degraded into 4-(1,1,3,3-Tetramethylbutyl)phenol. This degradation product is a known endocrine disruptor for the environment and, therefore, 4-tert-OPnEO was confirmed to meet the criteria set out in REACH Article 57(f).

The United Kingdom (UK) left the European Union on 31st January 2020 and created its own version of REACH regulation (i.e. so-called 'UK REACH Regulation'). The UK REACH Regulation is applicable to Great Britain (England, Scotland, Wales and associated islands) and predominantly a copy of the EU REACH regulation with some minor modifications to make it appliable to the UK's circumstances. Latest application dates and sunset dates for the 4-tert-OPnEO were written into the UK law and this means that the substance cannot be placed on the market or used in the UK unless an authorisation is granted, an exemption applies or transitional arrangements are in place.

2.1.2. SEA requirements and aims

The applicant is a downstream user of 4-tert-OPnEO, where the substance is used as cell lysing agent during a manufacturing step in the production of gene therapies (i.e. the applicant's 'products').

The applicant's products are intended to be used in the treatment of diseases. The products are at various stages of development, and it is estimated that they will begin to be commercially produced from a .

Table 2-1: Summary of the applicant's products that are currently in development (2)

Applicant's Product	Targeted Disease	Stage of development	Programme
AAV-RPGR	X-Linked Retinitis Pigmentosa	Phase I or II	Ocular
AAV-RPE65	Leber's Congenital Amaurosis / Early-Onset Severe Retinal Dystrophy	Phase I or II	Ocular
AAV-CNGA3	Achromatopsia	Phase I or II	Ocular
AAV-CNGB3	Achromatopsia	Phase I or II	Ocular

AAV-GAD[1]	Parkinson's	Phase I or II	Neurodegenerative
AAV-AQP1	Xerostomia	Phase I or II	Salivary Gland
AAV-AQP1	Sjögren's syndrome	Preclinical	Salivary Gland

[1] Please note that AAV-GAD is used throughout to refer to both AAV-GAD65 and AAV-GAD67.

The purpose of this AOA-SEA is to show that there are currently no technical or commercially feasible alternatives to 4-tert-OPnEO. In addition, the benefits of continued use of the substance outweighs the risks to the environment, according to REACH Articles 60(3) and 60(4), during the requested review period of 12 years.

An exposure-response relationship cannot be derived for 4-tert-OPnEO so the applicant will pursue the so-called 'socioeconomic route' in their application. Under this approach, the applicant will explore a qualitative assessment on the impact to the environment for continued use. In addition, because the application products are still in development and the applicant cannot report any profits, the application will lean on the negative impacts to society and the economy in a 'Non-Use' Scenario (NUS).

2.2. Temporal and geographical boundaries of the SEA

2.2.1. Temporal boundaries

This SEA calculations were based on an anticipated review period of 12 years. The applicant expects full commercial production of the products to commence in a [redacted] and the period considered was a [redacted].

This 12-year review period is requested primarily due to the lack of available alternatives. If a suitable alternative is identified in the future, then the timescales for testing and implementing that alternative also take a significant amount of time. This is because of the nature of the applicant's products and that they are subject to other regulatory requirements.

2.2.2. Geographical boundaries

The applicant's use of 4-tert-OPnEO will only take place in one production location in London, UK. Additionally, the applicant's products will be used within Great Britain and in other regions around the world. Unless otherwise stated, any statistics, references and calculations used within the SEA are based on the primary market, i.e. Great Britain.

Secondary markets were considered in terms of disease burden and these data are intended to provide an illustrative global view of the long-term potential for treatment with the applicant's products; these markets were the United States of America (USA), the European Union (EU) and Japan.

2.3. Relevant supply chains

2.3.1. Information on the Applicant's operations and products

The Applicant's group

MeiraGTx Holdings plc is a gene therapy company with headquarters in New York, NY, USA and London, Great Britain (GB). (3) The group was founded March 2015 (3) and has been listed on the NASDAQ USA stock exchange as of June 2018. (4)

MeiraGTx work at the clinical stage of gene therapy and are currently undertaking an ambitious work programme developing therapies which, if successful, would provide potentially curative options for patients living with various serious diseases.

Gene therapy can be used to address diseases resulting from mutations in a single gene in a patient's genome. Gene therapy uses a delivery vehicle, referred to as a vector, to insert a gene encoding a therapeutic protein into cells in the body. In such cases, the vector is used to deliver a normal copy of the gene to the cells that are defective due to the lack of the gene function. The normal gene then drives production of the missing protein and potentially offers a therapeutic benefit in patients with the disease.

Gene therapy can also function by adding a new gene function to cells and thereby change cell behaviour and function. Additionally, gene therapy may be used to deliver a therapeutic protein that may block a disease pathway or enhance a deficient cellular pathway in complex diseases caused by more than a single mutation, such as Alzheimer's disease.

Gene therapy has a long history, having been studied for over 50 years with a variety of different vectors used to deliver different therapeutic genes. Since the first gene therapy clinical study in humans in 1990, more than 2,300 gene therapy studies covering a broad range of disease targets have been initiated.

The applicant's products use the adeno-associated virus (AAV) as the vector for delivering genes. AAV is less likely to cause an immune reaction compared to older vectors and it does not readily integrate into the genome of the target cell, reducing the potential for the induction of unwanted treatment effects. Customization of the vector allows for gene therapy to be optimized for different diseases and can have a significant impact on the effectiveness of the treatment. Slight differences in capsid proteins can modulate the efficiency with which the vectors deliver genes to different cells, thus allowing different AAV capsids to be selected to most effectively target specific cell types.

Additionally, promoters may be designed to drive different levels of gene expression or to limit gene expression to specific cell types. Other aspects of the gene sequence may be engineered for optimal gene expression, such as codon usage and synthetic introns, which may enhance levels of therapeutic protein expression. (5)

The diseases targeted for such treatment can be grouped into 3 development programmes (Table 2-2), and will be considered in these groupings when assessing costs of current treatment options and burden of disease (see 4.4.3 Health impacts).

Table 2-2: The applicant's targeted diseases and development programme (2)

Targeted Disease	**Development programme**
X-Linked Retinitis Pigmentosa	Ocular
Leber's Congenital Amaurosis / Early-Onset Severe Retinal Dystrophy	Ocular
Achromatopsia	Ocular
Parkinson's	Neurodegenerative
Xerostomia	Salivary Gland
Sjögren's syndrome	Salivary Gland

MeiraGTx was formed by the merger of Athenavision Ltd (a spin out company from UCL) and a spin out company from Kadmon Corporation. (6) MeiraGTx has invested in a state of the art gene therapy manufacturing facility after purchasing the site from Moorfields Eye Hospital NHS Foundation Trust. Located in London, this facility is compliant with current Good Manufacturing Practice (cGMP) and holds a manufacturing licence for investigational gene therapies from the UK Medicines and Healthcare products Regulatory Agency (MHRA). The facility is designed to accommodate manufacturing to support both clinical development and commercial sales. (4) (3)

The GB business operation is a wholly owned subsidiary of MeiraGTx Holdings plc, titled MeiraGTx UK II Limited, and referred to in this document as "the applicant". (4) The subsidiary companies of MeiraGTx Holdings plc are listed in Table 2-3.

The Applicant's manufacturing and ancillary facilities

The applicant's 29,000 square foot facility was designed to meet multiple regulatory standards, including MHRA, European Medicines Agency (EMA) and FDA standards. This has the required production capacity for all the current activity around the applicant's clinical trial programmes and thereafter is fully capable of scaling up to commercial production capacity for key programmes. The purchase of the site and subsequent installation of this facility was a strategic decision to reduce dependency on third-party contract manufacturing organisations (CMOs) and thereby increase the commercial viability of the business.

The London facility is flexible and scalable, with notable features including:

- eleven independent air handling units to segregate manufacturing operations
- two cell culture suites to facilitate multiple production streams
- three separate viral vector production suites, allowing the production of multiple product candidates in parallel.

This facility can therefore accommodate up to three independent parallel manufacturing streams of viral vector products that are isolated within dedicated production areas. (3) (4)

Other global locations for MeiraGTx subsidiaries (3) (4) (7) are:

- The principal offices in New York City, NY, USA;
- Offices and research and development facility, London, GB;
- Offices in Amsterdam, Netherlands;
- Offices and manufacturing facility, Co. Clare, Ireland (in development).

The Applicant's products

The applicant's products are intended to be used in the treatment of diseases. The products capitalise on the adeno-associated virus vector (AAV) as a platform for gene therapies. The products are at various stages of development, and it is estimated that they will begin to be commercially produced from a [redacted].

The products are stated alongside the targeted disease and intended programme of treatment in Table 2-1.

Auxiliary operations and contractors

The subsidiary companies of MeiraGTx Holdings plc are listed in Table 2-3.

Table 2-3: Subsidiaries of MeiraGTx Holdings plc (4)

Subsidiary	Trade name	Registered location
MeiraGTx Limited	Meira Limited	Great Britain (limited company under the laws of England and Wales)
MeiraGTx, LLC	Meira LLC	Delaware, USA
BRI-Alzan, Inc.	BRI-Alzan	Delaware, USA
MeiraGTx B.V.	Meira BV	Netherlands
MeiraGTx Neurosciences, Inc.	Meira Neuro	Delaware, USA
MeiraGTx UK II Limited	Meira UK II	GB (limited company under the laws of England and Wales)
MeiraGTx UK Limited	Meira UK	GB (limited company under the laws of England and Wales)
MeiraGTx Ireland	MeiraGTx Ireland	Shannon, Republic of Ireland (note that facility is under construction, operational end 2021) (7) (8)

MeiraGTx also contract with various unnamed suppliers and service providers.

2.3.2. Information on users and recipients of the drugs

The applicant's products are intended to utilise gene therapy as a therapeutic option in the treatment of a range of conditions. These conditions are categorised into three development programmes: ocular, neurodegenerative and salivary gland. Table 2-2 shows an overview of this categorisation, and section 4.4.3 provides detail on the conditions, their symptoms, and the associated socioeconomic burden. In the majority of cases, there are no available therapies that reverse or even halt the progression of the disease, and there is a definite (and sometimes progressive) effect on quality of life for the patient and, in many cases, their family and/or carer(s).

2.3.3. Information on suppliers of raw materials

The raw materials required for each production run are sourced from both within GB and from other markets. The materials costs are estimated to be f [redacted] per batch, with approximately f [redacted] sourced from GB.

At full production, the applicant can manufacture g [redacted] of product per year, which totals f [redacted] for the cost of raw materials. Approximately >£5 million (f [redacted]) is spent on sourcing from GB suppliers.

3. Consultations

The applicant retains much of its technical capability in-house and primarily relied on these experts to identify information on alternatives. The applicant also undertook literature searches and liaised with its suppliers in order to identify potential alternatives.

4. Applied for Use Scenario

4.1. Market and business trends including the use of the substance

4.1.1. Market situation for the drugs

The applicant's products are intended to be used for the treatment of a range of target diseases, including:

- X-Linked Retinitis Pigmentosa
- Leber's Congenital Amaurosis / Early-Onset Severe Retinal Dystrophy
- Achromatopsia due to mutations in either the CNGB3 or CNGA3 genes
- Parkinson's disease
- Xerostomia
- Sjögren's syndrome

The applicant's products are new, one-time gene therapies that are anticipated to provide a meaningful and transformative quality of life improvement to patients that have the target disease. Except where stated in Table 4-1, there is no accepted treatment or cure for the diseases targeted by the applicant's products.

Table 4-1: Alternatives to the applicant's products that are available on the market

Applicant's Product	**Targeted Disease**	**Alternative**
AAV-RPGR	X-Linked Retinitis Pigmentosa	Two potential alternatives in development (9) (10)
AAV-RPE65	Leber's Congenital Amaurosis / Early-Onset Severe Retinal Dystrophy	One approved and in use [LUXTURNA® (Novartis Pharmaceuticals UK)]
AAV-CNGA3	Achromatopsia	None known
AAV-CNGB3	Achromatopsia	None known
AAV-GAD	Parkinson's	None known
AAV-AQP1	Xerostomia	None known
AAV-AQP1	Sjögren's syndrome	None known

There is a global demand for gene therapies that offer significant improvement in the patient's condition and the applicant anticipates that their products will be well received in the markets where they are eventually approved.

The applicant's products are intended to be sold in the UK, US, EU and Japanese markets and other global markets over time. The primary market for the purpose of this assessment is Great Britain (England, Scotland, Wales and associated islands). Where possible, figures such as population data, prevalence and calculated financial costs (e.g. burden of disease) relate to Great Britain and do not include figures for Northern Ireland. Where this is not possible, and only the UK data is available, a calculation factor of 0.97 has been used to account for this. This factor was determined as follows:

Great Britain (GB) population (64,903,140) / UK population (66,796,8907) (11) *= 0.97.*

4.1.2. Manufacturing operations

Produced quantities and sales value

The applicant's London facility currently has capacity to manufacture g batches per year with up to g vials, or doses of treatment, per batch. Up to g vials per batch are removed for the purposes of sampling, process checks and audit procedures; an assumption of g doses per batch is therefore used.

The unadjusted sales values could be in the hundreds of millions of pounds if all products are successfully brought to market. Most individual indications are quite rare, however, and the lower end of sales value expectations would be in the tens of millions if only certain products were approved.

As these are novel therapies, predicting potential sales values is not straightforward. However, an equivalent treatment could be used as an illustrative example. Voretigene neparvovec (also known by its registered name, LUXTURNA®) is a gene therapy for vision loss caused by RPE65-mutation mediated inherited retinal dystrophy (IRD). The treatment is initially planned for patients with Leber's congenital amaurosis (LCA). (12) (13) LCA is a condition resulting from RPE65 gene mutations, as are the conditions in the applicant's Ocular Programme. The list price for voretigene neparvovec of £613,410 per patient is therefore considered to be relevant in providing illustrative figures for the applicant's products' sales values within the Ocular Program. For the product within the Neurodegenerative program, the total procedure cost for deep brain stimulation (£73,077) (14) was used as an equivalent cost value. For products within the Salivary gland program, pricing will be based on clinical efficacy which, whilst showing promise with 2 out of 3 patients treated having complete resolution of xerostomia symptoms, (15) will be determined during Health Technology Assessment with the National Institute for Health and Care Excellence (NICE) later in development. For the modelling of potential values for this program, a value of >£75,000 (c) has been used as the assumed list price (a mid-range point of the estimated c range). (15)

It must be noted that due to the conditions of the 'Budget Impact Test' imposed by the National Health Service (NHS), the sales figures must be capped at £20 million per year (16) for years 1-3 of the 12-year review period, with the list price, production capacity and dosage information used for estimates relating to years 4-12.

This approach does include a number of uncertainty factors which, while unavoidable, must briefly be acknowledged. These factors are:

- Date of commercialisation – it is assumed that all products will be commercially available from a for the length of the review period;
- Price of products – it is assumed that prices have been accurately estimated as part of the applicant's overall investment strategy and will be suitable and competitive for the market;
- Cost of production – it is assumed that production costs have been accurately estimated by the applicant and will remain within an acceptable range;
- Demand for products – it is assumed that demand will be sufficient to match full production capacity;
- Competitor reaction – it is assumed that the applicant will not face significant threats to market share from competitors' products.

The sales values estimated using the data and assumptions as described are shown in Tables 4-2 to 4-5.

Table 4-2: Estimated sales value of the applicant's products (Ocular program)

	Ocular program			
Product	AAV-RPGR	AAV-RPE65	AAV-CNGA3	AAV-CNGB3
List price of equivalent product (per patient) (£)	613,410	613,410	613,410	613,410
Manufacturing potential of GB site (batches / product / year)[1]	g	g	g	g
Doses per batch	g	g	g	g
Manufacturing potential of GB site (doses / product / year)	g	g	g	g
Number of doses per patient	c	c	c	c
Total number of treatments	g	g	g	g
Total potential sales revenue (per year) (£)	c,j	c,j	c,j	c,j
Total potential sales revenue (years 4-12) (£)	c,j	c,j	c,j	c,j
Capped annual sales (years 1-3) (£)	60,000,000	60,000,000	60,000,000	60,000,000
Total potential sales revenue, per product (12-year review period) (£)	c,j	c,j	c,j	c,j
Total potential sales revenue, Ocular program (12-year review period) (£)				c,j

[1]Total of g batches per year, divided across 7 products in production and rounded down to nearest whole number. The manufacturing has been divided equally across the products to enable the modelling. Whilst this is not anticipated to be the case ultimately, deriving more accurate predictions is not possible until clinical doses and addressable patient populations have been determined during clinical development.

Table 4-3: Estimated sales value of the applicant's products (Neurodegenerative program)

	Neurodegenerative program
Product	AAV-GAD
List price of equivalent product (per patient) (£)	73,077
Manufacturing potential of GB site (batches / product / year) [1]AAV	g
Doses per batch	g
Manufacturing potential of GB site (doses / product / year)	g
Number of doses per patient	c
Total number of treatments	g
Total potential sales revenue (per year) (£)	c,j
Total potential sales revenue (years 4-12) (£)	c,j
Capped annual sales (years 1-3) (£)	60,000,000
Total potential sales revenue, per product (12-year review period) (£)	c,j
Total potential sales revenue, Neurodegenerative program (12-year review period) (£)	c,j

[1]Total of g batches per year, divided across 7 products in production and rounded down to nearest whole number. The manufacturing has been divided equally across the products to enable the modelling. Whilst this is not anticipated to be the case ultimately, deriving more accurate predictions is not possible until clinical doses and addressable patient populations have been determined during clinical development.

Table 4-4: Estimated sales value of the applicant's products (Salivary gland program)

	Salivary gland program	
Product	AAV-AQP1	AAV-AQP1
List price of equivalent product (per patient) (£)	>75,000 ([redacted])	>75,000 ([redacted])
Manufacturing potential of GB site (batches / product / year)[1]	[redacted]	[redacted]
Doses per batch	[redacted]	[redacted]
Number of doses per patient	[redacted]	[redacted]
Total number of treatments	[redacted]	[redacted]
Total potential sales revenue (per year) (£)	[redacted]	[redacted]
Total potential sales revenue (years 4-12) (£)	[redacted]	[redacted]
Capped annual sales (years 1-3) (£)	60,000,000	60,000,000
Total potential sales revenue, per product (12-year review period) (£)	[redacted]	[redacted]
Total potential sales revenue, Salivary gland program (12-year review period) (£)	[redacted]	

[1]Total of [redacted] batches per year, divided across 7 products in production and rounded down to nearest whole number. The manufacturing has been divided equally across the products to enable the modelling. Whilst this is not anticipated to be the case ultimately, deriving more accurate predictions is not possible until clinical doses and addressable patient populations have been determined during clinical development.

Table 4-5: Total estimated sales value of the applicant's products

Total potential sales revenue, Ocular program (12-year review period) (£)	c,j [redacted]
Total potential sales revenue, Neurodegenerative program (12-year review period) (£)	c,j [redacted]
Total potential sales revenue, Salivary gland program (12-year review period) (£)	c,j [redacted]
Total potential sales revenue, all programs (12-year review period) (£)	>15 billion (c,j [redacted])
Total potential sales revenue, all programs (annualised) (£)	>1 billion (c,j [redacted])

In summary, the potential sales value resulting from the applicant's products is therefore >15 billion (c,j [redacted]) over the requested 12-year review period of the substance, or >1 billion (c,j [redacted]) per year.

This estimated sales value represents the potential revenue over the 12-year review period. Profit margins are not available for the applicant's products as they are not yet available on the market. For an assessment of net income, a representative profit margin was calculated from in-market financial data relating to the example presented earlier (Section 4.1.2), Luxturna®. (12) (13) Note that these figures relate to the company as a whole, and not solely the example product, however these figures can be used to calculate a % profit margin for this assessment in the absence of in-market data.

Table 4-6: Calculating net income using an illustrative in-market example

Novartis (17)		**MeiraGTx**	
Revenue – 12-month period ending 30/09/2020 ($ billion)	49.58	**Revenue – estimated over 12-year review period then annualised (£ billion)**	>1 (c,j [redacted])
Net income – 12-month period ending 30/09/2020 ($ billion)	7.10	**Net income (annual, estimated) (£ billion)**	>0.1 (c,j [redacted])
Profit margin (% of revenue)	14.33	**Profit margin (% of revenue)**	14.33

Net profit for the applicant was therefore estimated as >0.1 billion (c,j [redacted]) annually, or >2 billion (c,j [redacted]) over the 12-year requested review period.

Employment information

The applicant currently employs approximately 160 people at its London-based manufacturing facility. This is explored in the context of a Non-Use Scenario in Sections 6.3.2 and 6.3.3 .

4.1.3. Future cost of raw materials

At full production, the applicant can manufacture g batches of product per year, which totals f for the cost of raw materials (see Section 2.3.3). Approximately >£5 million (f) is spent on sourcing from GB suppliers.

Table 4-7: Annual cost of raw materials (GB)

Raw material cost (per batch) (£)	f
Raw material cost, GB suppliers (per batch) (£)	f
Batches produced (per year)	g
Annual cost, GB suppliers (£)	>5 million (f)

4.2. Analysis of the substance function(s) and technical requirement(s) for the product(s)

4.2.1. Description of the technical function provided by the Annex XIV substance

4-tert-OPnEO [Chemical name: 4-(1,1,3,3-tetramethylbutyl)phenol, ethoxylated; CAS number 9036-19-5] is part of an identified Substance of Very High Concern (SVHC) group entry: 4-(1,1,3,3-tetramethylbutyl)phenol, ethoxylated [covering well-defined substances and UVCB substances, polymers and homologues].

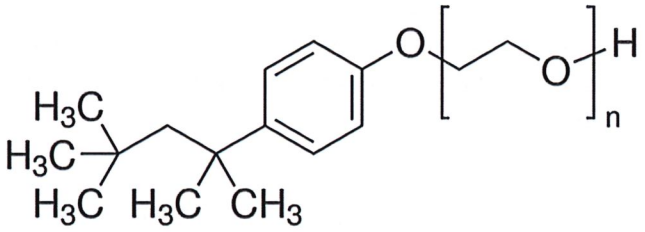


Figure 4-1: Chemical Structure of 4-tert-OPnEO (18)

The average number of oxyethylene moieties (denoted as n in Figure 41) is 9 to 10 for CAS 9036-19-5.

4-tert-OPnEO has molecular weight of 625, average aggregation number of 140, critical micelle concentration of 0.24 mM, cloud point of 64 °C and a Hydrophile-Lipophile Balance (HLB) of 13.4. (18)

As can be seen from its chemical structure, the substance has a hydrophilic polyethylene oxide chain (on average it has 9.5 ethylene oxide units) and an aromatic hydrocarbon hydrophobic group fitting to a group of chemicals known as non-ionic surfactants.

The surfactant properties of the substance allow it to lower the interfacial tension between two liquids. It is this property that helps solubilize a variety of chemical species by dissociating aggregates and unfolding proteins which is the technical function that the applicant wants to make use of to allow for lysing cells in order to extract protein and other cellular organelles.

4.2.2. Description of the product(s) resulting from the use of the Annex XIV substance

The applicant uses 4-tert-OPnEO as a manufacturing aid in the production of seven gene therapies:

- AAV-RPGR
- AAV-RPE65
- AAV-CNGA3
- AAV-CNGB3
- AAV-GAD65
- AAV-GAD67
- AAV-AQP1

AAV-RPGR (2) (19)

AAV-RPGR is designed to treat the most common form of X-linked retinitis pigmentosa (XLRP) caused by mutations in the eye-specific form of the RPGR gene called RPGR open reading frame 15 (RPGR-ORF 15). Both rod and cone photoreceptors require RPGR-ORF 15 to function. AAV-RPGR has received Fast Track and Orphan Drug designations from the FDA and PRIME, ATMP and Orphan Medicinal Product designations from the EMA. The applicant is currently conducting an ongoing Phase I/II clinical trial of AAV-RPGR in adult and paediatric patients and expects to progress AAV-RPGR into the Phase III Lumeos clinical trial.

Retinitis pigmentosa (RP) is a group of inherited retinal disorders (IRDs) which represent the most common genetic cause of blindness. The condition is characterized by progressive retinal degeneration and vision loss that ends in complete blindness. RP initially presents as night-time blindness during childhood or early adulthood, progressing to peripheral visual field loss and "tunnel vision," central visual impairment, reduced visual acuity and, ultimately, complete blindness.

XLRP represent some of the most severe forms of RP, with an early onset in childhood and rapid progression to blindness by the time patients reach 20 to 30 years old. In XLRP, both rods and cones function poorly, leading to degeneration of the retina and total blindness. There are currently no approved treatments for XLRP.

AAV-RPE65 (2) (19)

AAV-RPE65 is a gene therapy product candidate in which expression of a codon-optimized RPE65 gene is driven by a novel synthetic retinal pigment epithelium (a thin layer of cells at the back of the eye) cell-specific promoter. The RPE65 protein is essential for rod function as it recycles the light sensing machinery in rod photoreceptors. The codon and vector optimization resulted in a gene therapy that is 100 to 1,000 times more potent than the first-generation therapy. The FDA and EMA each granted orphan status to AAV-RPE65 for the treatment of Leber's Congenital Amaurosis (LCA). The FDA also granted AAV-RPE65 rare paediatric disease designation for the treatment of inherited retinal dystrophy due to biallelic RPE65 mutations. The applicant is currently conducting a Phase I/II clinical trial of AAV-RPE65 in both adult and paediatric patients.

Achromatopsia gene therapy vectors AAV-CNGB3 and AAV-CNGA3 (2) (19)

ACHM is an inherited retinal disease that specifically prevents cone photoreceptors from functioning. ACHM patients are legally blind from birth and usually suffer from severely reduced visual acuity of 20/200 or worse, photophobia (a disabling sensitivity to light), total colour blindness and nystagmus (involuntary eye movements). ACHM occurs in approximately one in 30,000 people in the UK (20), which equates to 2,163 people in Great Britain.

CNGA3 and CNGB3 are two parts of the same cell membrane channel where mutation in either gene results in achromatopsia. Mutations in three other genes are also known to lead to achromatopsia; however, mutations in CNGA3 and CNGB3 are more commonly identified with prevalence of 25% (CNGA3) and 50% (CNGB3).

Both are gene therapy treatments designed to restore cone function and are delivered via subretinal injection to the area of the eye where most of the cones in the retina are located. The AAV-CNGB3 gene therapy product candidate was granted orphan drug, rare paediatric disease designation and Fast Track designations by the FDA, and orphan drug and PRIME designations by the EMA. AAV-CNGA3 has the same designations with the exception of the EU PRIME designation.

Both gene therapy vectors are in Phase I/II clinical trials.

AAV-GAD65 and AAV-GAD67 (2) (19)

AAV-GAD is an investigational gene therapy designed to deliver the glutamic acid decarboxylase (GAD) gene to the subthalamic nucleus in order to increase production of GABA, the primary inhibitory neurotransmitter in the human brain. GAD is the rate-limiting enzyme in the synthesis of GABA. The therapeutic principle is that increasing subthalamic nucleus GAD expression through gene therapy will result in normalization of motor circuits and improve symptoms in Parkinson's disease patients, without affecting other brain regions that can be responsible for complications of existing therapies.

Parkinson's disease affects nearly 10 million worldwide and around 145,000 in the UK (21); this equates to 140,650 in GB. It is the second-most common neurodegenerative disease after Alzheimer's disease. It is associated with a progressive loss of motor control (e.g. shaking or tremor at rest and lack of facial expression), as well as non-motor symptoms (e.g. depression and anxiety). There is no cure for Parkinson's disease, and the incidence rates are 60,000 and 18,000 new diagnoses annually in the United States and United Kingdom, respectively (22), which equates to 17,460 new diagnoses annually in Great Britain.

AAV-AQP1 (2) (19)

The applicant is developing AAV-AQP1 to treat radiation-induced xerostomia (RIX) by increasing water conduction in the salivary glands damaged by radiation therapy. As saliva plays such a critical role in the physiology and protection of upper gastrointestinal tract issues, patients with chronic RIX suffer ling-term complications that have a significant impact on the patient's daily living, including difficulty swallowing (dysphagia), oral discomfort, malnutrition, oral mucositis, changes in taste, increased oral infections and dental cavities.

The gene therapy works by introducing a water conducting channel into the remaining epithelial cells of these damaged glands. The applicant is currently conducting a Phase I clinical trial in patients who have remained cancer-free for five or more years following treatment for head and neck cancer and are suffering from grade 2 or 3 radiation-induced late xerostomia. The applicant has also initiated the AQUAx trial, which is a multi-site Phase I/II clinical trial enrolling participants who have been diagnosed with grade 2 or 3 radiation-induced xerostomia RIX and who have remained cancer-free for at least five years (or two years if HPV+) after receiving radiation treatment for head and neck cancer.

Additionally, the vector can be used to treat xerostomia caused by Sjögren's syndrome, a disease affecting more than two million people in the United States and 324,581 people in the United Kingdom (23) (11), which equates to 314,844 people in Great Britain. Sjögren's syndrome is an autoimmune disease in which a patient's immune system may target the salivary glands. Chronic

inflammation of the salivary glands results in long term damage and chronic xerostomia in many Sjögren's patients.

4.2.3. Description of the technical requirements that must be achieved by the products(s) made with the substance

The applicant uses 4-tert-OPnEO as a cell lysing agent during the manufacture of their gene therapies. 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 AAV vector is released into the lysate. The lysate is then filtered and purified via successive downstream processes in order to yield the applicants product. h

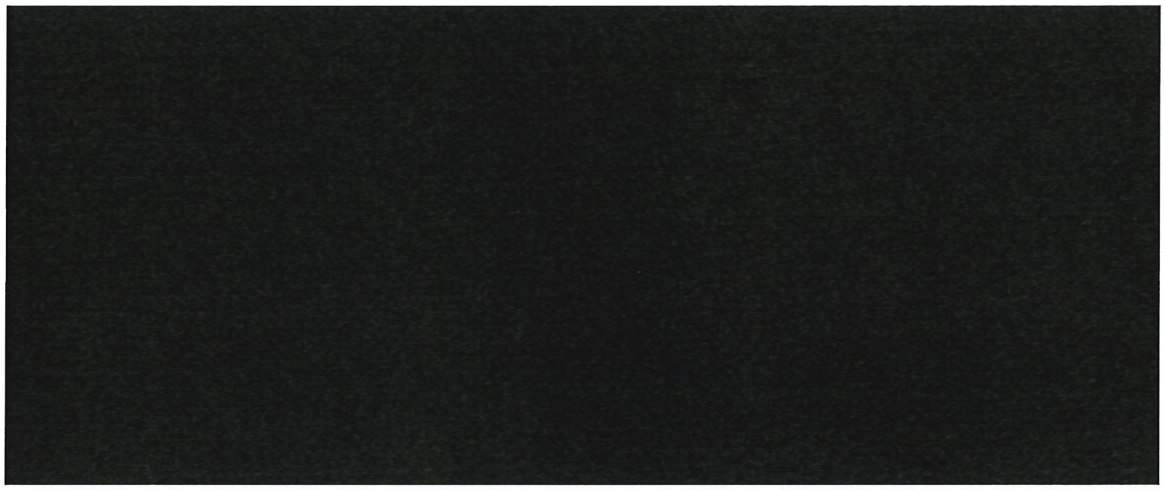


Figure 4-2: Summary of the manufacturing process steps that contain 4-tert-OPnEO

Each of the process steps has both inputs and outputs and the 4-tert-OPnEO-containing outputs have been summarised within Table 4-8.

Table 4-8: Overview of materials that may contain 4-tert-OPnEO that are removed from manufacturing process

Production step	**Material outputs that may contain 4-tert-OPnEO**
Production of lysis buffer	• Chemical waste (h , 100% 4-tert-OPnEO)
h	• Samples (250 mL, h 4-tert-OPnEO)
h	• Samples (500 mL, h 4-tert-OPnEO) • Hazardous waste (< 1L, h 4-tert-OPnEO)
h	• Samples • Hazardous waste • Liquid waste
h	• Samples • Hazardous waste • Liquid waste
h	• Hazardous waste • Liquid waste • Product

In summary, the material outputs from the applicant's manufacturing process that contain 4-tert-OPnEO are:

- Chemical waste
- Hazardous waste
- Liquid waste
- Samples
- Product

4.2.4. Annual tonnage of 4-tert-OPnEO used by the applicant

The applicant uses 4-tert-OPnEO as part of a batch manufacturing process, where 1 litre of the substance is used per batch. The maximum manufacturing capacity of the applicant's facility is g batches per year. Therefore, the annual volume of 4-tert-OPnEO estimated to be used by the applicant from a until a is <100kg (g,i) per year, based on a density of 1.07 g/cm^3. (24)

4.3. Remaining risk for the "applied for use" scenario

4.3.1. Overview

4-tert-OPnEO itself is not an endocrine disruptor but is considered as equivalent level of concern because it can break down into 4-tert-Octylphenol (EC 205-426-2, CAS 140-66-9). This degradation product has a harmonised classification of Aquatic Acute 1, Aquatic Chronic 1 and is an endocrine disruptor for the environment. (25)

4.3.2. Description of releases

While the applicant estimates that they will use up to g of 4-tert-OPnEO per year, most of the substance does not end up in the product and is diverted to a range of waste streams. Only one of these waste streams, liquid waste, results in a release to the environment which, in a worst-case scenario, is estimated to be <70g (g,i) of the substance per year.

Chemical waste

The applicant receives 4-tert-OPnEO from their supplier in 1L bottles. During the production run of a single batch, the applicant will use up to h of the substance and the remaining h of 4-tert-OPnEO is disposed of as chemical waste.

Chemical waste is moved through the applicant's facility in line with a Standard Operating Procedure (SOP). Ultimately, chemical waste is moved to storage and is moved off-site by a contractor every 1 or 2 weeks.

All chemical waste, including that which may contain 4-tert-OPnEO, is incinerated by the contractor.

Hazardous waste

The applicant uses Genetically Modified Organisms (GMO) in their manufacturing process, hazardous waste management is informed by The Genetically Modified Organisms (Contained Use) Regulations 2014.

All hazardous waste, including consumables and waste solids from the manufacturing process, is managed through the facility in line with a SOP. Solid hazardous waste is double bagged, moved through waste hatches to a storage area before it is collected by a contractor.

Additionally, liquid hazardous waste may be generated during the purification steps required to isolate the applicant's products. This is created from flow through, washing and strip of chromatography columns and contains detectable amounts of 4-tert-OPnEO.

All hazardous waste, including that which may contain 4-tert-OPnEO, is incinerated by the contractor in line with the Hazardous Waste (England and Wales) Regulations 2005, Environmental Permitting Regulations (England and Wales) 2010 as amended, and local authority requirements.

Liquid waste

During the filtration and purification processes, the applicant produces liquid waste that may contain 4-tert-OPnEO. Liquid waste is typically produced from the flow through, washing and strip of chromatography columns. Liquid waste is also produced from filter permeates.

All liquid waste is moved through the facility according to SOPs and ends up in the liquid waste room within a 200 L polyethylene drum. The liquid waste is treated with disinfectant for 24 hours, before it is pumped into the drain which flows into the London sewage system. This results in a release of 4-tert-OPnEO into the environment. The amount of liquid waste released to wastewater resulting from full production was calculated as g [redacted]. (24) Assuming a 12-hour production shift and a steady release of waste during production, this equates to a rate of g [redacted]. This is significantly lower than the permitted maximum discharge level stipulated in the discharge consent licence granted to the applicant by Thames Water, g [redacted] (26) which, assuming a density of 1.07 g/cm^3, equates to g [redacted]. In absolute daily amounts, the permitted maximum in the Thames Water licence is g [redacted]. (26) Conversion from the estimated actual daily maximum of g [redacted] gives a figure of g [redacted], again significantly lower than the permitted maximum. This is summarised in Table 4-9.

Table 4-9: Liquid waste released from the production process compared to the permitted maximum

Assessment by quantity		**Assessment by release rate**	
Liquid waste release, permitted amount (per day)	**Liquid waste release, actual amount (per day)[1]**	**Liquid waste release, permitted rate**	**Liquid waste release, actual rate**
g [redacted]	g [redacted]	g [redacted]	g [redacted]
		g [redacted]	g [redacted]

[1]Determined by dividing g [redacted] by 1.07 gm/^{3} density to give g [redacted], then converting to m^3.

Samples

The applicant may take small volumes of materials from all stages of the manufacturing process that contain 4-tert-OPnEO. These samples are moved around the facility according to SOPs. Samples can ultimately end up in long-term storage (freezer) and/or disposed of as hazardous waste.

Product

The applicant's products may contain trace amounts of 4-tert-OPnEO. The applicant considers this use out of scope of this authorisation application due to requirements under REACH Regulation, Article 2(5)(a).

4.3.3. Environmental concentrations

The exposure concentrations are reported in Table 4-10. The exposure estimates have been obtained with EUSES 2.2 unless stated otherwise.

Table 4-10: Exposure concentrations of the substance and risks for the environment (24)

Protection target	Exposure concentration – 4-tert-OP
Fresh water	Local PEC: 3.89 x 10-8 mg/L
Sediment (freshwater)	Local PEC: 2.34 x 10-6 mg/kg ww
Marine water	Local PEC: 5.43 x 10-9 mg/L
Sediment (marine water)	Local PEC: 3.27 x 10-7 mg/kg ww
Sewage Treatment Plant	Local PEC: 3.88 x 10-7 mg/L
Air	Local PEC: 4.72 x 10-10 mg m3
Agricultural soil	Local PEC: 4.53 x 10-6 mg/kg ww

4.3.4. Minimisation of releases

The applicant is following the hierarchy of control principles for controlling the risks from use of 4-tert-OPnEO.

- Substitution: the applicant has worked on identifying an alternative substance or technique to produce lysis buffer, as discussed in Section 5.1.
- Technical controls: three potential waste streams exist following the use of 4-tert-OPnEO in the manufacturing process, with excess substance and waste materials containing 4-tert-OPnEO being sent to either chemical, hazardous or liquid waste. In all instances, attempts are made by the applicant to prevent any excess release of 4-tert-OPnEO. Unused 4-tert-OPnEO is contained and stored before being collected by a contractor for off-sit incineration. The applicant has installed a system in which any hazardous waste containing 4-tert-OPnEO is double bagged, transferred from the room where production takes place into a waste room via material transfer hatches. This hazardous waste is collected by a contractor and taken offsite for incineration. Finally, liquid waste is collected, treated with the disinfectant Virkon, and resulting liquid is sent to drainage for treatment at a sewage treatment plant.
- Operational controls: The use of 4-tert-OPnEO takes place in an underground basement facility and is therefore used in an isolated environment, with the substance only being transferred (by trained personnel) between storage and the production room. The facility is built to industry best practices for sustainability. Material quantities, status and locations are controlled using a Quality System incorporating Good Manufacturing Practice (GMP). Employees are trained in company procedures on GMP. This includes storage, handling, cleaning, facility flow, production and disposal of hazardous and biohazardous substances. Operator training and certification is documented and maintained in an electronic training management system. Procedures are in place to respond to any potential spillage of 4-tert-OPnEO that may occur (both in storage and the production room).

The cost of chemical and hazardous waste disposal by contractor is approximately [redacted] per batch, including handling and transportation costs. Assuming [redacted] batches per year as the maximum production, the overall cost, including transportation and handling could be as high as [redacted] per year. This is [redacted] per kg of 4-tert-OPnEO used.

The emissions of 4-tert-OPnEO from the applicant's processes is as low as technically and practically possible. The applicant is committed to conducting its operations and managing its products in a manner protective of the environment and is committed to minimising the impact of their operations on the environment and the workplace. Considering the risk management measures described above that have been implemented and are on-going to capture the waste streams containing 4-tert-OPnEO, it can be concluded that the applicant is currently active in taking measures to minimise emissions of 4-tert-OPnEO to the environment to as low as technically and practically possible.

4.4. Human and environmental impacts of the "applied for use" scenario

4.4.1. Number of people exposed

4-tert-OPnEO poses no known risks to humans, therefore, there are no health impacts to people exposed to the substance.

4.4.2. Impact on the environment

4-tert-OPnEO has undergone assessment by ECHA (27) and was concluded to possess potential endocrine disrupting properties, due to degradation to 4-(1,1,3,3-tetramethylbutyl)phenol [4-tert-octylphenol; 4-tert-OP; EC 205-426-2, CAS 140-66-9).] (an identified endocrine disruptor) in wastewater, aquatic sediments and soils. Consequently, equivalent concern regarding endocrine disrupting properties is considered for 4-tert-OPnEO. Although ecotoxicity data are available for 4-tert-OPnEO, these are standard acute and chronic aquatic toxicity data and do not include endpoints for endocrine mediated effects.

There is evidence (28) that the degradation product 4-tert-OP is involved in endocrine activity affecting the reproductive behaviour of freshwater fish and amphibian species. It would be a reasonable assumption that prolonged exposure of aquatic species to 4-tert-OPnEO or similar substances or degradation products may have an adverse effect on population numbers of affected species. Furthermore, there is no threshold for 4-tert-OPnEO, so adverse effects may occur even at very low concentrations.

The 4-tert-OPnEO ECHA (27) assessment report summarises *in vitro* data on 4-tert-OPnEO and 4-nonylphenol ethoxylates [4-NPnEO] (which are considered close analogues to the corresponding octylphenol ethoxylates due to their similar chemical structure, the only difference being the alkyl group differing by one C-atom), and long-term fish toxicity data on 4-NPnEO. From these studies, it was concluded that the substances possess oestrogenic activity *in vitro* and may induce *in vivo* endocrine activity. Thresholds for such endocrine effects were not established in the *in vivo* studies. Both *in vitro* and *in vivo* information available for 4-nonylphenol and 4-tert-octylphenol show that these substances have very similar endocrine activity. It can therefore be assumed that the endocrine activity of 4-tert-OPnEO is like the activity of the corresponding 4-NPnEO.

Although measures are in place to minimise releases of 4-tert-OPnEO to the environment from the applicant's use (see Section 4.3.4), releases to wastewater may occur following the purification process. Therefore, freshwater aquatic organisms could be affected by the substance. As the main endocrine effects of 4-tert-OP are reproductive, it is likely that the populations of those species, mainly fish and benthic organisms, could be affected.

This can impact the overall balance of the receiving ecosystems, as predator / prey relationships could be disturbed by changes in the populations of species.

Description of receiving area

Wastewater from the manufacturing site is treated at Beckton Sewage Treatment Works (BSTW), located in Beckton, in the London Borough of Newham, East London, adjacent to the River Thames. It is the largest sewage treatment works in GB. (29) The outfall from BSTW is at Beckton.

BSTW is approximately 30 km upstream of the Thames Estuary where the Thames drains into the North Sea. The south-eastern edge of BSTW is the tidal confluence of the River Roding and the River Thames. The River Lea discharges into the Thames approximately 6 km upstream of BSTW, and the River Darent drains into the Thames approximately 17 km downstream of BSTW.

The surrounding catchment area is a mixture of residential, commercial and industrial. There are, however, no residential properties within 250m of the site hoarding. (30) Around 17% of the Thames river basin district as a whole is urbanised and the rural land is mainly arable, grassland and woodland. (31)

BSTW is located within the Beckton Lands South Site of Importance for Nature Conservation (SINC), however the habitat for which the SINC was designated is no longer present and it is therefore not considered to be an ecological resource. (29)

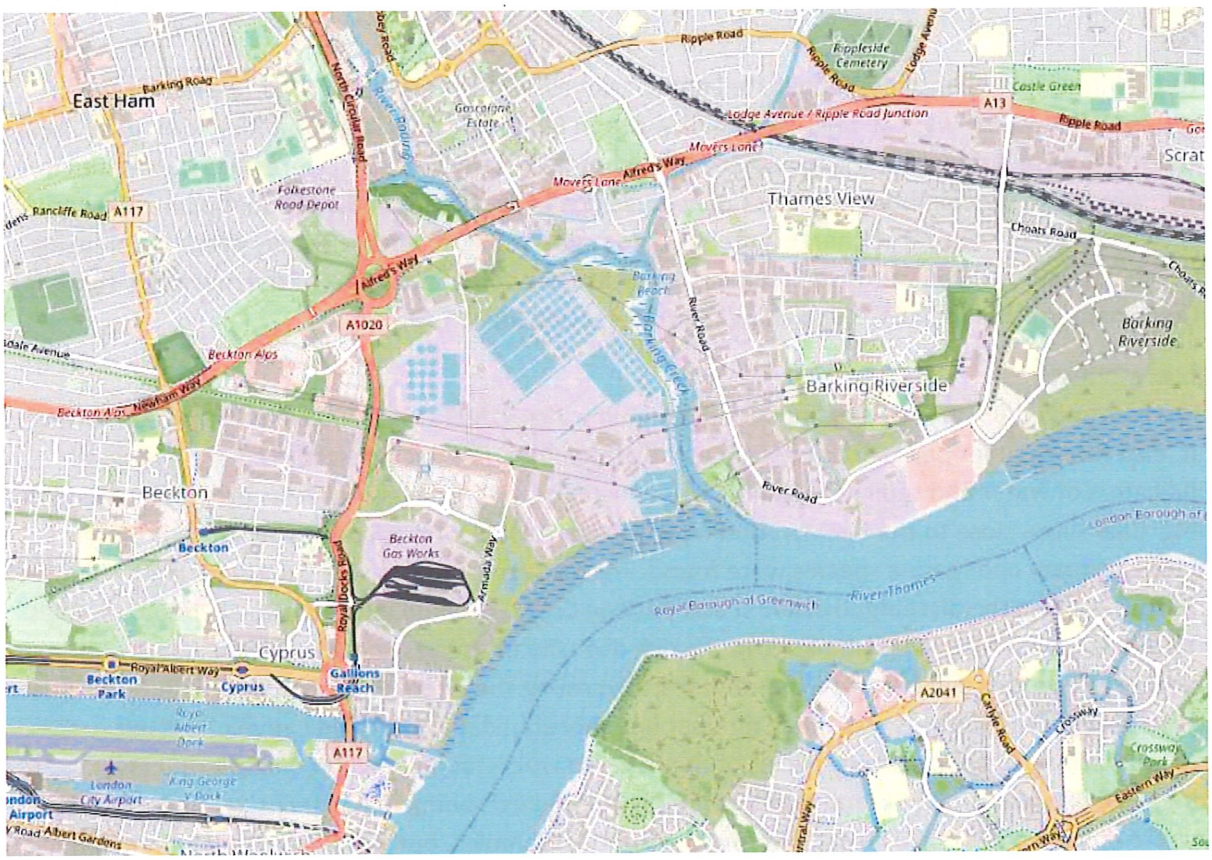


Figure 4-3: Location of Beckton Sewage Treatment Works (BSTW), London, United Kingdom (32)

The Old Ford Nature Reserve SINC also sits within the boundary of the site. The Tidal Tributaries SINC runs along the eastern and south sides of the site, with the Northern Settling Lagoon SINC to the north. (30)

The chemical and biological water quality of the Thames Estuary is monitored under the requirement of the Water Framework Directive (The EU Water Framework Directive 2000; Council Directive 2000/60/EC). Data in the Thames River Basin Management Plan suggested that the Thames

has a moderate ecological status but the chemical status of the river failed to meet the standards required by Water Framework Directive. (33)

Closer to the BSTW, the water is more saline and stressful, caused by wastewater release from BSTW, fluctuating tidal conditions and, in particular, sewage release from the surrounding areas during storm surges. (34) A major improvement to BSTW is underway and is expected to increase water quality; completion is anticipated in 2023. (35)
A substantial scour hole in the foreshore around the BSTW outfall point has developed as a result of treated effluent discharge, however the majority of the foreshore remains unaffected.

Habitats and species

Aquatic

There is a limited number of habitats local to the BSTW. The waters surrounding BSTW's discharge point are slightly salty (or 'brackish'), meaning freshwater-tolerant marine species and salt-water tolerant freshwater species of fish and invertebrate predominate. In addition, flora and fauna need to be tolerant to variations in their physical environment caused by fluctuating tidal conditions in order to thrive in such habitats. The area surrounding BSTW forms an extensive intertidal mudflat and is identified as a UK Biodiversity Action Plan (BAP) priority 'mudflat' habitat. (30)

Fish

The Environment Agency (EA) conducted annual surveys of fish within the Tidal Thames between 1992-2010. Beckton was the nearest sampling site to BSTW. Records show that flounder, goby, bass and smelt were populous between 2002-2003, whereas bream and roach were each only found in one sample, suggesting freshwater fish may occasionally be present in the effluent plume. Sewer overflows and occasional discharges of untreated waste result in hypoxic water, which is damaging to fish populations. The water surrounding BSTW forms a component part of the migratory route for Tidal Thames fish populations, including the BAP species smelt. (30)

Invertebrates

The EA sampled BSTW over several periods spanning 1989-1993, 1995-2005 and 2008-2009, taking at least four samples per year using a variety of techniques. Benthic invertebrates are biological indicators of water and sediment quality. Upper estuary and freshwater species predominated in the intertidal shore close to the Beckton outfall, which contrasted with adjacent sites, where more middle estuary and marine species were found. The EA suggested this was due to the large volumes of freshwater in the discharged effluent and Barking Creek. Beckton intertidal and subtidal samples taken away from the outfall point showed a rich diversity of species, including *Oligochaeta* and *Polychaeta* worms, and bottom-living shrimps, suggesting the effect of the outfall is localised. The dominance of the samples by a small number but very abundant taxa is indicative of organic pollution. For example, certain species of *Oligochaeta* worm found at BSTW can tolerate low dissolved oxygen conditions and multiply rapidly in enriched sediments. *A. lacustre,* a species of high nature conservation importance, was found in subtidal samples, but also shown to be abundant in the Tidal Thames. The zebra mussel, a threat to native species, was also identified. Samples showed that the Brackish zone, in which BSTW sits, is less diverse than the freshwater zone. The relative levels of saline, as well as the degree of fluctuation, appear to be the determining factors of benthic diversity. (30)

Marine mammals

Between 2003-2011 the Zoological Society of London observed several species of marine mammals migrating through the Tideway, including the harbour porpoise (*Phocoena phocoena*), bottlenose dolphin (*Tursiops truncatus*), grey seal (*Halichoerus grypus*) and common seal (*Phoca vitulina*). Small

numbers of harbour porpoise and common seal were recorded near the Works, but the area is limited in habitats suitable for marine mammals. (30)

Algae

Pollution tolerant species predominate. The threat of eutrophication is considered low because of strong tidal flows. (30)

Terrestrial

A variety of grassland and shrubland habitats surround the site, along with scattered trees, standing and running water, and buildings. A habitat survey was conducted at the site, resulting in a notable species report.

During the survey 129 breeding territories with 21 breeding species were recorded, of which five are of nature conservation importance and on the Birds of Conservation Concern 3 Red or Amber List and/or London BAP. The habitats local to the site provided suitable nesting and foraging for 9 whitethroat breeding territories, as well as 2 linnet, 46 lesser black-backed gull, 18 herring gull and 1 dunnock breeding territory. Additionally, barn owls were reported to be breeding near BSTW. A small number of common bird species including feral pigeon, wren, robin and blackbird were recorded. 25 water bird species were observed on the intertidal mudflats, 20 of which are of nature conservation importance and on the Birds of Conservation Concern 3 Red or Amber List and/or London BAP. Shoveler, pochard, tufted duck, scaup and black-headed gull foraged around the scour pool of the sewer overflow. The intertidal mud along the foreshore surrounding the overflow was used for foraging by shelduck, gadwall, teal, mallard, black-tailed godwit, and redshank. (30)

Discussion on environmental impacts

Based on available acute and chronic aquatic toxicity data, 4-tert-OPnEO is considered acutely toxic to aquatic organisms and may cause long-term negative effects within the aquatic environment. (36) There is currently little information available on research that has been conducted and validated in accessing the impacts of 4-tert-OPnEO or its degradation products within such environments.

There may be potential risks from the use of 4-tert-OPnEO in lysis buffer production, primarily regarding emissions of liquid waste (following the purification process) to wastewater treatment plants, followed by indirect releases to the aquatic environment and terrestrial environment (via spreading of sewage sludge to agricultural land). However, more research is needed before realistic estimates can be concluded.

It is difficult to suggest the effects of the substance on the species listed above, as the effects will vary depending upon several factors. These include life stages, duration of exposure, amount and concentration of the substance and if any other chemicals are present. In particular, different life-cycle stages of various organisms can have very different levels of sensitivity to endocrine disrupting substances. (37) The substance may adversely affect aquatic species, but due to the current absence of research, it is not possible to make any definite estimates of effects.

4.4.3. Health impacts

Health impacts to workers using the substance

4-tert-OPnEO poses no know risks to humans, therefore, there are no health impacts to workers using the substance.

Health impacts to patients – primary market (Great Britain)

The applicant products are currently undergoing clinical trials and are intended to treat a range of diseases, as outlined in Table 4-11.

Table 4-11: Applicant's products and disease targeted, organised by group (2)

Applicant's Product	**Targeted Disease**	**Programme**
AAV-RPGR	X-Linked Retinitis Pigmentosa	Ocular
AAV-RPE65	Leber's Congenital Amaurosis / Early-Onset Severe Retinal Dystrophy	Ocular
AAV-CNGA3	Achromatopsia	Ocular
AAV-CNGB3	Achromatopsia	Ocular
AAV-GAD	Parkinson's	Neurodegenerative
AAV-AQP1	Xerostomia	Salivary Gland
AAV-AQP1	Sjögren's syndrome	Salivary Gland

For the purposes of identifying health impacts to patients with potential for treatment with the applicant's products, the impacts have been grouped by the applicant's separate development programmes: ocular, neurodegenerative and salivary gland.

Ocular Programme

XLRP

XLRP (X-linked retinitis pigmentosa) is an inherited disease that affects the retina, causing significant vision loss and potentially blindness. As an X-linked genetic condition this only affects males, with females being unaffected carriers. There is no effective treatment or cure on the market, with medical care consisting of vitamin therapy, light avoidance, treatment of associated symptoms and psychological and practical support for sight loss. (38)

RPE65 deficiency

RPE65 is a gene that codes for retinoid isomerohydrolase, a protein that is critical for normal retinal function. (39) Deficiency of this protein results in disease similar to retinitis pigmentosa, with prognosis and treatment as described above. (38)

The potential impacts on quality of life for the patient and family resulting from retinitis pigmentosa are summarised in Table 4-12.

Table 4-12: Impacts and outcomes for patients and carers/family resulting from retinitis pigmentosa (38)

Patient		**Carer/family**	
Impacts	**Outcomes**	**Impacts**	**Outcomes**
• Progressive loss of vision from childhood onwards • Poor night sight • Near-total blindness	• Increased use of mental health support • Use of vision aids / sunglasses • Loss of independence • Reliance on carers • Loss of earning potential • Social support • Educational support • Increased use of NHS for management of symptoms • Increased use of genetic testing for family planning • Disability Living Allowance (DLA) or Personal Independence Payment (PIP) • Cane / guide dog requirement • Increased likelihood of falls, lack of mobility, etc.	• Supportive care • Home modifications	• Loss of earning potential • Increased use of mental health support • Increased use of NHS

Achromatopsia

Achromatopsia, or total colour blindness, may be acquired or inherited via genetic mutation. There is a range of severity and symptoms, but there is typically a reduction in visual acuity associated with this condition, and an aversion to bright light. (20) There is no effective treatment or cure on the market. Management consists of measures such as coloured lens filters and treatment of any associated symptoms. (40)

The potential impacts on quality of life for the patient and family resulting from achromatopsia are summarised in Table 4-13. (20) (41)

Table 4-13: Impacts and outcomes for patients and carers/family resulting from achromatopsia (20) (41)

Patient		**Carer/family**	
Impacts	**Outcomes**	**Impacts**	**Outcomes**
• Colour blindness • Reduced visual acuity • Photophobia / day blindness	• Increased use of mental health support • Use of coloured filters • Potential for reduction of independence • Reliance on carers • Loss or reduction of earning potential • Social support • Educational support • Increased use of NHS for management of symptoms • Increased use of genetic testing for family planning • Disability Living Allowance (DLA) or Personal Independence Payment (PIP) • Increased likelihood of falls, lack of mobility, etc.	• Supportive care • Home modifications	• Loss or reduction of earning potential • Increased use of mental health support • Increased use of NHS

To illustrate the effects of these outcomes on quality of life (QoL), the charity Retina UK (42) conducted a survey of patients affected by inherited sight loss and their carers (n=916), the results of which were reported by NICE and are summarised below. (41) Note that these results are representative of the UK, and so include Northern Ireland, which is out of scope of the primary market; however these data remain illustrative of the QoL and would not be expected to significantly change if Northern Ireland was excluded from the results.

- Overall quality of life (QoL)
  - >50% of respondents reported a severe or very severe impact on their overall QoL
  - 36% reported a moderate impact on their QoL
- Mental health
  - 92% of respondents said their sight loss had an impact on their mental health:
    - 75% had experienced anxiety
    - 62% stress
    - 41% depression
    - 33% loneliness

    - Respondents reported that the progressive nature of such conditions leads to a continual series of losses, requiring patients and carers to constantly adapt to increasing disability.
- Social integrations
    - Social life
        - 97% reported that their sight loss affected their mobility
        - 95% reported that their condition impacted on their leisure time and hobbies
    - Education and employment
        - >50% reported some effect on their education
        - >75% reported an effect on their career and employment prospects.

There are currently no clearly defined clinical pathways for retinitis pigmentosa and achromatopsia. The current recommended treatment consists of supportive care and management options to ameliorate symptoms and their effects on quality of life. (41)

Management options are summarised in Table 4-14.

Table 4-14: Management options for retinitis pigmentosa and achromatopsia

Condition	**Management option**	**Commentary**
RP (retinitis pigmentosa)	Vitamin therapy	Effective only in a small proportion of patients, and only with certain types of RP (43)
	Light avoidance	Intended to prevent or slow further deterioration, rather than to relieve symptoms (44)
	Psychological support	Sight-loss charities such as RNIB provide support e.g. telephone advice and helplines. (45)
	Practical support	Range of products and technology, multimedia provision, and techniques such as bespoke display settings. Impossible to quantify as this should be individually tailored; however, it is clear that a significant degree of independence is possible. (46)
Achromatopsia	Coloured lens filters	Generally effective at managing light sensitivity to relieve symptoms (40)

For the purposes of quantification of costs, XLRP, RPE65 deficiency and achromatopsia are considered together as "other causes of vision loss" below.

The total estimated annual cost of all visual impairments in Great Britain is shown, alongside the proportion of this that represents other causes such as XLRP, RPE65 deficiency and Achromatopsia (4.7% of the total (41)). The remainder of the total represents more common conditions such as age-related macular degeneration (AMD), cataracts and refractive error.

Table 4-15: Total estimated annual costs of visual impairment in Great Britain (GB) and the proportionate figures representative of retinitis pigmentosa and achromatopsia

	Cost of visual impairment, all conditions (£billion / year) (GB) (47)	**Cost of visual impairment, other causes of vision loss (£billion / year) (GB) (4.7% of all conditions)** (47)
Direct costs	2.9092	0.1364
Indirect costs	5.5047	0.2587
Burden of disease costs	18.9870	0.8924
Total costs	287.4009	1.2878

Related to the applicant's Ocular Programme, the total estimated annual economic burden of these conditions in Great Britain is therefore £1.29 billion.

Neurodegenerative Programme

Parkinson's disease is a progressive neurodegenerative disease caused by the cell death of dopamine-producing nerve cells and the subsequent dopamine deficiency. (21) Dopamine is a neurotransmitter involved in the movement of signals between neurons, and is important for many bodily functions, such as fine movement and motor control. (48)

141,803 people in Great Britain are currently living with Parkinson's, with almost 1 million people indirectly affected as a spouse, family member, carer or friend of those individuals. (21) (49)

Symptoms can be broadly grouped into two categories: motor control symptoms, and non-motor symptoms. The effects of the disease are debilitating and life-changing for the individual, and ongoing care needs can have significant effects on the lives of their immediate family and/or carers. (21)

Table 4-16: Motor control symptoms and non-motor symptoms of Parkinson's disease (21)

Motor control symptoms	**Non-motor symptoms**
Tremors, shaking	Depression
Slowness of movement	Memory and cognitive problems
Rigidity, muscle stiffness	Sleep difficulties
	Associated pain

The effects of these progressive symptoms on the patient and immediate circle are summarised in Table 4-17.

Table 4-17: Impacts and outcomes for patients and carers/family resulting from Parkinson's disease (21)

Patient		**Carer/family**	
Impacts	**Outcomes**	**Impacts**	**Outcomes**
• Tremors, shaking • Slowness of movement • Rigidity, muscle stiffness • Depression • Memory and cognitive problems • Sleep difficulties • Associated pain • Side effects of medication (e.g. delusion, dyskinesia)	• Progressive and substantial loss of independence • Reliance on carers • Loss of earning potential • Social support • Increased use of NHS for management of symptoms • Increased use of mental health support • Disability Living Allowance (DLA) or Personal Independence Payment (PIP) • Increased likelihood of falls, lack of mobility, etc.	• Supportive care (progressive, leading to full-time care requirements) • Home modifications	• Loss of earning potential • Increased use of mental health support • Increased use of NHS

There is currently no cure for Parkinson's, with treatment consisting of medication and measures to alleviate symptoms. It is also critical that supportive measures are provided to assist with the degenerative effects and the ongoing needs of the patient and family/carers.

Treatment options are summarised in Table 4-18.

Table 4-18: Treatment options for Parkinson's disease

Medication (21)		**Supportive measures** (21)	
Class of drug	**Effects**	**Measure**	**Effects**
Levodopa	Increases the amount of dopamine (acts as a prodrug, converted into dopamine)	Physiotherapy	Assist with mobility, posture and balance
Dopamine agonists	Acts as a dopamine substitute	Speech and language therapy	Assist with communication, breathing, eating and swallowing
MAO-B inhibitors	Increases the amount of dopamine (inhibits an enzyme responsible for dopamine reuptake)	Occupational therapy	Advise on home/furniture setup, ergonomics for daily activities
COMT inhibitors (used alongside levodopa)	Increases the efficacy of levodopa (inhibits an enzyme that breaks down levodopa)	Exercise	General fitness and physical wellbeing; example Exercise Framework to be tailored to individual needs (50)
Anticholinergics	Blocks a chemical messenger (acetylcholine) and reduces tremors	Deep brain stimulation (DBS)	Surgical option for symptoms not adequately controlled by other therapies. Electrodes are placed in relevant areas of the brain, which are then stimulated. (51)
		Supportive equipment and technology	Assist with daily activities
		Home adaptations	Improve quality of life within the home
		Provision / funding of carer support	Retain some independence where possible, care in patient's own home

Direct and indirect costs of treatment and management of Parkinson's in the UK were calculated in a 2013 study to be £2 billion annually. (52) This includes direct medical costs as well as indirect costs such as lost productivity due to absence from work or early retirement.

An earlier study calculated a range of cost burden resulting from Parkinson's in the UK to be between £0.449 billion – £3.3 billion annually. (53) The £2 billion figure is close to the middle of this range, and is taken from a more recent study, and therefore can be taken as a representative figure

of the annual cost burden from this disease. Application of a calculation factor to remove Northern Ireland from this figure gives a final value of £1.94 billion.

Related to the applicant's Neurodegenerative Programme, the total estimated annual economic burden of Parkinson's disease in Great Britain is therefore £1.94 billion.

Salivary Gland Programme

Sjögren's syndrome is an autoimmune condition with an underlying genetic cause, often triggered by an environmental factor. The primary symptoms are xerostomia and dry eyes caused by improper function of the salivary and lacrimal glands, respectively. There is no effective cure on the market. Treatment consists of symptom management, with prescription drugs available to relieve the primary symptoms.

Xerostomia can also take the form of radiation-induced xerostomia (RIX), as a result of damage caused to the salivary glands by radiation therapy received in the treatment of head and neck cancer. Symptom management and medication would be similar in either case.

Sjögren's syndrome affects an estimated 0.6% of adults (23), giving a GB total of 389,418 individuals with the condition. (11)

The number of patients with RIX was estimated using the data in Table 4-19.

Table 4-19: Estimating the number of patients with radiation-induced xerostomia (RIX)

Number of survivors of head and neck cancer, UK (54)	62,500
Proportion of those treated with radiation therapy (mid-range of 64% used) (54)	40,000
Proportion of those that experience symptoms of RIX (90%) (55)	36,000
Adjusted to represent Great Britain (GB) figures (x 0.97)	34,920

Prescription drugs commonly used to treat the symptoms are eye drops ("fake tears" [for the eye-related symptoms of Sjögren's]) and cholinergic agonists such as cevimeline, for example (for both Sjögren's and RIX). (23)

Costs of annual treatment are estimated in Table 4-20 using the average monthly prescription cost and the cost of one annual medical check. (56) Note that the cost burden for NHS England is used as representative of Great Britain.

Table 4-20: Estimated annual treatment costs for Sjögren's syndrome and RIX in Great Britain

	Sjögren's syndrome		**Radiation-induced xerostomia (RIX)**	
	Monthly cost (per person) (£) (GB) (56)	**Annual cost (per person) (£) (GB)**	**Monthly cost (per person) (£) (GB)** (56)	**Annual cost (per person) (£) (GB)**
Eye drops	41.35	496.20	-	-
Cevimeline	41.35	496.20	41.35	496.20
Annual medical check	-	45 (56)	-	45 (56)
Annual cost GB (per person) (£)	-	1037.40	-	541.20
Annual cost GB (all affected individuals) (£)		403,998,233.20		18,898,704
Annual cost GB (all affected individuals, Sjögren's and RIX) (£)				422,896,937.20

The combined estimated annual economic burden of Sjögren's syndrome and RIX in Great Britain is therefore £0.42 billion.

The sum socioeconomic annual burden in Great Britain of the conditions considered under the Ocular, Neurodegenerative and Salivary Gland Programmes is given in Table 4-21.

Table 4-21: Total socioeconomic annual burden of ocular, neurodegenerative and salivary gland conditions (GB)

Diseases in scope of applicant's products	**Costs (£billion / year) (GB)**
Ocular	1.29
Neurodegenerative	1.94 (52)
Salivary Gland	0.42
Total	3.65

Related to the applicants Salivary Gland Programme, the estimated economic burden of these conditions in Great Britain totals £3.65 billion annually. The GB figures are used as this is intended to be the primary market for the applicant's products.

It is necessary to estimate the proportion of this figure that could reasonably be expected to be relieved via the use of the applicant's products. There are no equivalent in-market products or data

for the Neurodegenerative or Salivary Gland programs, so the focus will be on the Ocular program. As a first step a suitability factor was calculated using the example presented earlier (Section 4.1.2), Luxturna® (12) (13) (intended for use in the treatment of LCA). The prevalence of LCA in GB is cited as 1 in 100,000 population (57); this, combined with the population of GB, gives a number of 649.03 people affected by this disease in GB. In the example used, 86 patients were identified as suitable for treatment (12) (13), and this gives a suitability factor of 13.25%, as shown in Table 4-22.

Table 4-22: Calculation of the proportion of the total disease burden that could potentially be relieved by the applicant's products

Prevalence of LCA	1 / 100,000 (57)
GB population	64,903,140 (11)
Prevalence of LCA in GB	649.03
Patients identified as suitable for treatment	86 (12) (13)
% of patients suitable for treatment (suitability factor)	13.25

It can therefore be assumed, for the purposes of this assessment, that 13.25% of the total socioeconomic annual burden of the disease programmes could potentially be relieved by the applicant's products, dependent on efficacy. This gives an estimated total of £0.48 billion annually.

As a further step, an efficacy factor was calculated using data from the applicant's Phase I/II research on one of the products in the Ocular program, AAV-RPGR. In a cohort of 7 subjects given low or intermediate doses, significant improvements were observed in 6 subjects in visual mobility at low light levels (58). This gives an efficacy value of 85.71%. This can be factored into the calculation to give a truly representative figure of the burden of disease that could be expected to be relieved by the applicant's products. This is calculated in Table 4-23.

Table 4-23: Calculation of the proportion of the total disease burden to be relieved by the applicant's products

Prevalence of LCA	1 / 100,000 (57)
GB population	64,903,140 (11)
Prevalence of LCA in GB	649.03
Patients identified as suitable for treatment	86 (12) (13)
% of patients suitable for treatment (suitability factor)	13.25
Burden of disease with potential for relief (£billion / year)	0.48
Efficacy of applicant's product, used as demonstrative value (%)	85.71
Final estimated burden of disease relieved by the applicant's products (£billion / year)	0.41

Health impacts to patients – secondary markets

While this analysis will focus on the primary market, a view on the secondary markets is presented in this section only for information.

The primary market figure of £0.41 billion annually (proportionate) can be crudely extrapolated to other markets, based on population size. These figures are based on assumptions and should be taken as illustrative of the global socioeconomic burden. Secondary markets considered are the USA, Japan and the European Union. (4)

Population sizes for extrapolation:

- *Great Britain: 64,903,140* (11)
- *United States of America: 331,724,263* (59)
- *Japan: 126,307,469* (60)
- *European Union: 444,986,729 (note that this is the total for the 'EU27', and does not include the United Kingdom/Great Britain)* (61)

Table 4-24: Total socioeconomic annual burden of ocular, neurodegenerative and salivary gland conditions (specific secondary markets)

Diseases in scope of applicant's products	**Costs (£billion / year) (GB)**	**Costs (£billion / year) (USA)**	**Costs (£billion / year) (Japan)**	**Costs (£billion / year) (EU)**	**Costs (£billion / year) (Total, secondary markets)**	**Costs (£billion / year) (Total, primary and secondary markets)**
Ocular	1.29	-	-	-	-	-
Neurodegenerative	1.94 (52)	-	-	-	-	-
Salivary Gland	0.42	-	-	-	-	-
Total	3.65	-	-	-	-	-
Total (proportionate)	0.41	1.99	0.76	2.67	5.42	5.83

The estimated economic annual burden of these conditions in the USA, Japan and EU therefore totals £5.42 billion annually.

Combining the totals of primary and secondary markets gives a total of £5.83 billion annually.

4.5. Monetised damage of human health and environmental impacts

4.5.1. Environmental impacts

Quantifying the environmental impact of the applicant's use of 4-tert-OPnEO in the manufacturing of their products at the London facility is not straightforward, due to the nature of the variables and assumptions involved. For example:

- the London facility is assumed to run at maximum, producing g batches per year;

- it is assumed that <70g ([redacted]) of 4-tert-OPnEO will be released to wastewater per year – this is a worst-case assumption;
- it is not possible to predict exactly how much of the 4-tert-OPnEO released to wastewater will degrade to 4-tert-OP, therefore 100% is assumed to be conservative;
- although the degradation product 4-tert-OP is known to be an endocrine disruptor, it is not possible to predict the extent of any effect this might have on any exposed species.

By extension, it is therefore not possible to quantify the exposure effects without utilising generic values.

An OECD report conducted in 2016 (62) to investigate potential quantification methods for impacts on biodiversity and ecosystem services provides an economic valuation for various types of biomes, or ecosystems. By using these values in the context of the areas potentially exposed to the substance via wastewater release, an estimate can be arrived at. The relevant sites to include in the estimation are given in Table 4-25, along with the type of biome and the stated value.

Table 4-25: Affected sites, types of biome and values (62)

Site	**Type of biome**	**Value (USD/hectare/year)**
Beckton Lands South SINC	Grasslands	2,871
Old Ford Nature Reserve SINC	Grasslands	2,871
River Thames and Tidal Tributaries SINC	Coastal systems (inc. estuaries)	28,918

Note that from here Beckton Lands South SINC and Old Ford Nature Reserve SINC are combined in terms of area and biome type. Also note that although Beckton Lands South SINC is reported to be no longer of ecological interest, it is included here for the sake of thoroughness. Beckton Sewage Treatment Works Northern Settling Lagoon SINC, although mentioned in Section 4.4.2, is not included here as it has been earmarked to be built over and used for material storage warehousing. (63)

With this information the estimate of a monetised impact for environmental effects can now be built. Note that US dollars are converted to pounds sterling using currency conversion at the time of writing.

Table 4-26: Affected sites, types of biome and final estimated values (62)

Site	Area (hectares)	Biome	Value (USD / hectare / year)	Value (USD / year)	Value (GBP / year)
Beckton Lands South SINC	15.9 (30)	Grasslands	2,871	45,648.90	34,345.72
Old Ford Nature Reserve SINC					
River Thames and Tidal Tributaries SINC	2,314.93 (64)	Coastal systems (inc. estuaries)	28,918	66,943,145.70	50,367,275.37
Total				66,988,794.60	50,401,621.10

The estimated environmental impact in monetary terms calculated via this method is therefore £50.4 million annually. Note that this approach assumes the total loss of the environmental value of the biomes considered, when a release of <70g ([redacted]) per year into the Thames would have a negligible impact. There is not enough information on the effects of the substance to predict the actual cost impact on the environment resulting from its release. As a minimum, a dilution factor can be applied in order to reduce the estimated impact costs towards a more realistic level. A default dilution factor of x10 was assumed in the absence of site-specific data. Although the volume of the outflow at Beckton is large, the Thames at this point is of significant size (ca 550 m wide), tidal, with significant water volume and flow. An assumption of x10 dilution is therefore considered conservative.

Applying the x10 dilution factor to the total environmental value gives an adjusted estimated annual impact cost of £5,040,162.11.

4.5.2. Human health impacts

4-tert-OPnEO poses no know risks to humans, therefore, there are no health impacts to people exposed to the substance.

5. Selection of the "Non-Use" Scenario

5.1. Efforts made to identify alternatives

5.1.1. Research and development

The applicant's products are still in development and some clinical studies have already been conducted. Any change to the manufacturing process would create a significant delay to the marketing authorisation approval of all products and could require a repeat of some studies. Because the applicant has already spent a significant sum of money for development, additional costs for repeated studies may leave some of the applicant's products commercially unviable.

5.1.2. Data searches

The applicant used several methods in order to identify potential alternatives to 4-tert-OPnEO for their manufacturing process. These include, but are not limited to:

- Undertaking searches via various internet search engines for cell lysing detergents
- Contacting known manufacturers of cell lysing detergents
- Review of other applications for authorisation for 4-tert-OPnEO published on the European Chemicals Agency website (65)

5.2. Identification of known alternatives

5.2.1. Screening of potential alternatives

The applicant has identified the following potential alternatives to 4-tert-OPnEO as a cell lysing agent for their manufacturing process:

- Potential alternative 1, not using a detergent
- Potential alternative 2, sorbitan monolaurate, ethoxylated
- Potential alternative 3, sorbitan monooleate, ethoxylated
- Potential alternative 4, N,N-dimethyltetradecylamine N-oxide

Any alternative would need to match a set of essential criteria in order to be a viable substitution. These are outlined in Table 5-1.

Table 5-1: Essential criteria that must be demonstrated by potential alternatives to 4-tert-OPnEO

Criteria	**Reason the criteria are essential**
Cell lysing efficiency: - recovery / yield of AAV must be >90% compared to 4-tert-OPnEO - no negative impact on AAV recovery / yield in downstream unit operations compared to 4-tert-OPnEO	The applicant spends a significant sum on the cost of manufacturing each batch of their products. The amount of product recovered from each manufacturing batch must be maximised in order for the product to be competitively priced.
Good Manufacturing Practice (GMP): - manufactured and/or processed in accordance with GMP	To ensure the safety and quality of raw materials and the final product, and to provide a recognised system of documentary evidence and auditable processes.
No known incompatibility	Incompatibility/significant inefficiency of alternatives could prevent manufacturability of products and affect the applicant's ability to deliver product to patients.
No known impact on quality: - no effect on AAV stability or infectivity compared to 4-tert-OPnEO	Impact on quality of final product could prevent manufacturability of the product, impact patient safety and/or significantly reduce the efficacy of the product at the same dose.
Intrinsic hazards: - non-hazardous properties - no known toxicological concerns	A minimal amount of the cell lysing agent remains in the final product. The applicant does not want to undertake a regrettable substitution to an alternative that may be restricted by regulation in the future.

If a potential alternative was identified, then the applicant would perform a quality audit on the supplier and the use of that material would be risk assessed by the Impact Assessment Team.

5.3. Assessment of shortlisted alternatives

The applicant has assessed each of the short-listed alternatives against the essential criteria identified in Table 5-1 and the results are shown below. A status of *pass, does not pass* or *not concluded* has been attributed to every potential alternative's assessment against the essential criterion.

- *Pass* means that the alternative meets or surpasses the requirement set by that criterion;
- *Does not pass* means that the alternative does not meet the requirement set by that criterion;
- *Not concluded* means that the alternative has not been fully assessed against the requirement set by that criterion.

5.3.1. Alternative 1

Potential alternative 1 is to not use a detergent for cell lysing in the current manufacturing process. Alternative 1 was identified when the applicant found that AAV had been released from some transfected cells during production without provocation by a cell lysing agent.

Substance ID, properties and availability

Not applicable.

Technical feasibility of alternative 1

Table 5-2: Comparative assessment of alternative 1 against the essential criteria

Criteria	**Technical feasibility of alternative 1**
Cell lysing efficiency	Does not pass Some of the applicant's studies show an estimated <30% (h[redacted]) lysis and filtration efficiency compared to 4-tert-OPnEO
GMP	Not concluded
No known incompatibility	Not concluded
No known impact on quality	Not concluded
Intrinsic hazards	Not concluded

The mechanism for AAV release in the supernatant has not been investigated by the applicant but it is suspected as leaking of the virus outside the cell. It is apparent that some serotypes, such as AAV-RPGR, AAV-RPE65, AAV-GAD and AAV-AQP1, have a stronger affinity to host cell proteins and membrane receptors and others do not. The applicant suspects that serotypes with high affinity to cellular components tend to stay within the cells whilst another may leak out.

This means that the usability of alternative 1 during the manufacturing process may be dependent on the product that is being manufactured by the applicant.

Economic feasibility and economic impacts of alternative 1

While the implementation of alternative 1 would not incur a significant cost to the applicant, the lower yields produced by the alternative would mean that the cost per batch would be significantly more than using 4-tert-OPnEO.

Availability of alternative 1

Not applicable.

Hazard and risk of alternative 1

No known risks to human health and the environment.

Conclusions on suitability and availability of alternative 1

The applicant has disregarded alternative 1 because it does not pass the following essential criteria:

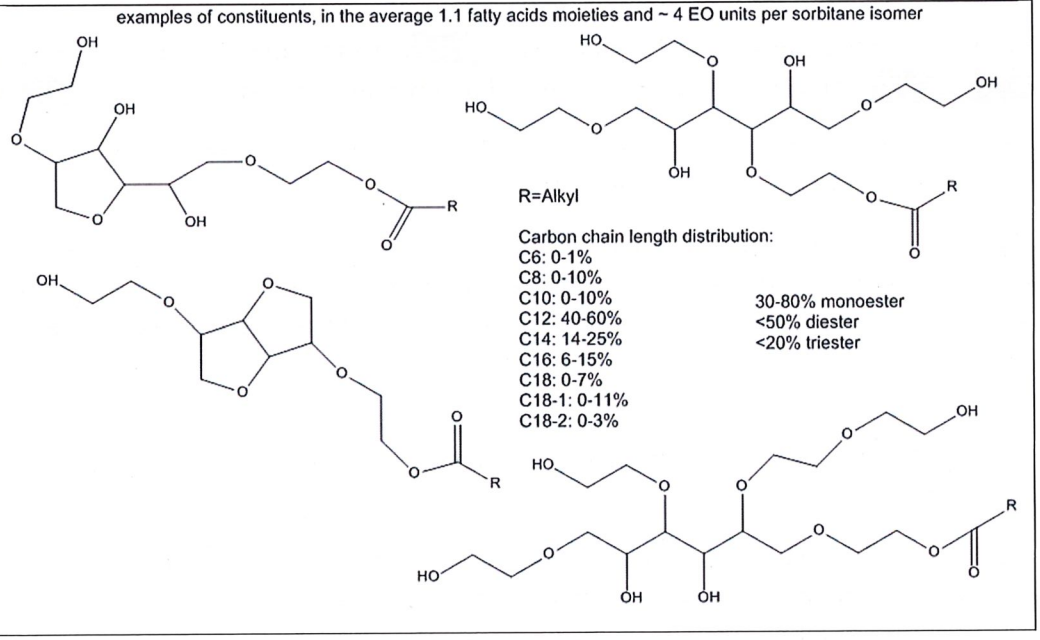
- Cell lysing efficiency

5.3.2. Alternative 2

Potential alternative 2 is intended to be used in the current manufacturing process as a drop-in replacement to 4-tert-OPnEO. Potential alternative 2 was identified when the applicant undertook a literature search for alternatives to 4-tert-OPnEO.

Substance ID, properties and availability

Table 5-3: Alternative 2 substance ID and properties

Substance name(s)	Sorbitan monolaurate, ethoxylated (1-6.5 moles ethoxylated) 2-[2-[3,4-bis(2-hydroxyethoxy)oxolan-2-yl]-2-(2-hydroxyethoxy)ethoxy]ethyl dodecanoate
Trade name(s)	Tween® 20
EC	500-018-3
CAS	9005-64-5
Molecular structure (66)	

Technical feasibility of alternative 2

Table 5-4: Comparative assessment of alternative 2 against the essential criteria

Criteria	Technical feasibility of Alternative 2
Cell lysing efficiency	Does not pass Testing by the applicant revealed the lysing efficiency to be insufficient. Specifically: • h alternative 2 o h lysis and filtration efficiency compared to 4-tert-OPnEO • Between h and h alternative 2 o h lysis and filtration efficiency compared to 4-tert-OPnEO • h alternative 2 o h lysis and filtration efficiency compared to 4-tert-OPnEO
GMP	Pass GMP grade is available on the Market
No known incompatibility	Not concluded
No known impact on quality	Not concluded
Intrinsic hazards	Pass No known risks to human health and the environment

Cell lysing efficiency was tested at small scale (h) at alternative 2 concentrations ranging from h , then evaluated the recovery of product after lysis and filtration at h .

Differences in performance were not explored from a mechanistic point of view and it seems that there is a relation between alternative 2 concentration and product recovery.

Higher amounts of alternative 2, compared to 4-tert-OPnEO, are required in order to achieve inferior product recovery, <70%, which suggests that alternative 2 is less efficient at lysing cellular material. This could also have an impact on downstream removal of alternative 2 from the applicant's products.

Economic feasibility and economic impacts of alternative 2

The applicant has discounted alternative 2 as a potential alternative based on its inadequate lysing and filtration efficiency.

However, if the applicant was able to accept a lower yield from a cell lysing detergent in their manufacturing process, then further research and development would be required before alternative 2 could be implemented. This would mean that the applicant would have to take time and pay for further studies to optimise concentration, improve removal of detergent from product, rule out any incompatibilities and ensure no impact on quality of final product.

Additionally, the manufacturing process would need to be modified before alternative 2 could be implemented. The lower yield leads to a higher risk of not achieving enough quantity of formulated drug product with the applicant's current batch size. Both the lysis and clarification unit operations would need to be further optimized and multiple batches would need to be combined prior to drug product formulation in order to make up for the lower recoveries.

Availability of alternative 2

The applicant has already identified a source of alternative 2 prior to undertaking testing of it within their facility. In addition, a search on the ChemExper database produced 107 results for suppliers of alternative 2 (67). This suggests that alternative 2 is readily available.

Hazard and risk of alternative 2

According to most notifications provided by EU REACH registrants to ECHA (68), no hazards have been classified for alternative 2. Alternative 2 is not a hazardous substance or mixture according to Regulation (EC) No. 1272/2008.

Table 5-5: Comparison of hazard classification and labelling of alternative 2

	Alternative 2	**4-tert-OPnEO**	**4-tert-Octylphenol**
EC	500-018-3	-	205-426-2
CAS	9005-64-5	9036-19-5	140-66-9
Physiochemical	None	None	None
Human health	None	H302 (Acute Oral Toxicity 4) H315 (Skin Irritant 2) H318 (Eye Irritant 1)	H315 (Skin Irritant 2) H318 (Eye Irritant 1)
Environmental	None	H410 (Aquatic chronic) [Endocrine disruptor, by degradation to octyl phenol] M factor = 10	H400 (Aquatic Acute 1) H410 (Aquatic chronic) [Endocrine disruptor] M factor = 10
Source(s)	European Chemicals Agency (69)	Supplier Safety Data Sheet (70)	European Chemicals Agency (25)

Based on the available data, this assessment shows that the hazardous properties of alternative 2 are less than compared to 4-tert-OPnEO. The conclusions of this assessment indicate that the adoption of alternative 2 would result in a lower risk to human health and the environment.

Conclusions on suitability and availability of alternative 2

The applicant has disregarded alternative 2 because it does not pass the following essential criteria:

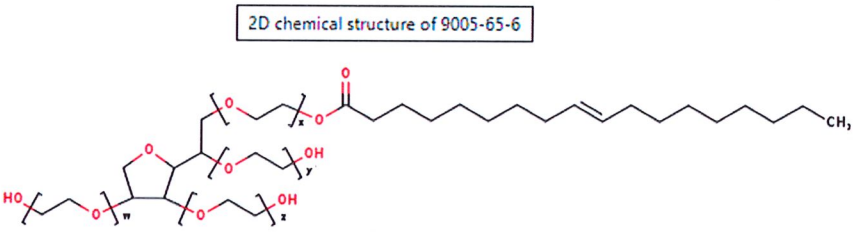
- Cell lysing efficiency

5.3.3. Alternative 3

Potential alternative 3 is intended to be used in the current manufacturing process as a drop-in replacement to 4-tert-OPnEO. Potential alternative 3 was identified when the applicant undertook a literature search for alternatives to 4-tert-OPnEO.

Substance ID, properties and availability

Table 5-6: Alternative 3 substance ID and properties

Substance name(s)	Sorbitan monooleate, ethoxylated (1-6.5 moles ethoxylated) 2-[2-[3,5-bis(2-hydroxyethoxy)oxolan-2-yl]-2-(2-hydroxyethoxy)ethoxy]ethyl (E)-octadec-9-enoate
Trade name(s)	Tween® 80
EC	500-019-9
CAS	9005-65-6
Molecular structure (71)	

Technical feasibility of alternative 3

Table 5-7: Comparative assessment of alternative 3 against the essential criteria

Criteria	Technical feasibility of alternative 3
Cell lysing efficiency	Does not pass Testing by the applicant revealed the lysing efficiency to be insufficient. Specifically: • h alternative 3 o h lysis and filtration efficiency compared to 4-tert-OPnEO • Between h and h alternative 3 o h lysis and filtration efficiency compared to 4-tert-OPnEO • h alternative 3 o h lysis and filtration efficiency compared to 4-tert-OPnEO
GMP	Pass GMP grade is available on the Market
No known incompatibility	Not concluded
No known impact on quality	Not concluded
Intrinsic hazards	Pass No known risks to human health and the environment

Cell lysing efficiency was tested at small scale (h) at Alternative 2 concentrations ranging from h , then evaluated the recovery of product after lysis and filtration at h . Lysing efficiency was <40% compared to 4-tert-OPnEO.

Economic feasibility and economic impacts of alternative 3

The applicant has discounted alternative 3 as a potential alternative based on its inadequate lysing and filtration efficiency.

Availability of alternative 3

The applicant has already identified a source of alternative 3 prior to undertaking testing of it within their facility. In addition, a search on the ChemExper database produced 145 results for suppliers of alternative 3 (67). This suggests that alternative 3 is readily available.

Hazard and risk of alternative 3

According to the supplier's Safety Data Sheet, no hazards have been classified for alternative 3. Alternative 3 is not a hazardous substance or mixture according to Regulation (EC) No. 1272/2008.

Table 5-8: Comparison of hazard classification and labelling of alternative 3

	Alternative 3	**4-tert-OPnEO**	**Octyl phenol**
EC	500-019-9	-	205-426-2
CAS	9005-65-6	9036-19-5	140-66-9
Physiochemical	None	None	None
Human health	None	H302 (Acute Oral Toxicity 4) H315 (Skin Irritant 2) H318 (Eye Irritant 1)	H315 (Skin Irritant 2) H318 (Eye Irritant 1)
Environmental	None	H410 (Aquatic chronic) [Endocrine disruptor, by degradation to octyl phenol] M factor = 10	H400 (Aquatic Acute 1) H410 (Aquatic chronic) [Endocrine disruptor] M factor = 10
Source(s)	Supplier Safety Data Sheet (72)	Supplier Safety Data Sheet (70)	European Chemicals Agency (25)

Based on the available data, this assessment shows that the hazardous properties of alternative 3 are less than compared to 4-tert-OPnEO. The conclusions of this assessment indicate that the adoption of alternative 3 would result in a lower risk to human health and the environment.

Conclusions on suitability and availability of alternative 3

The applicant has disregarded alternative 3 because it does not pass the following essential criteria:

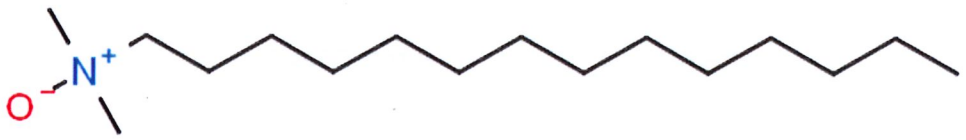
- Cell lysing efficiency

5.3.4. Alternative 4

Potential alternative 4 is intended to be used in the current manufacturing process as a drop-in replacement to 4-tert-OPnEO. Potential alternative 4 was identified when the applicant asked their suppliers for alternatives to 4-tert-OPnEO.

Substance ID, properties and availability

Table 5-9: Alternative 4 substance ID and properties

Substance name(s)	N,N-dimethyltetradecylamine N-oxide
Trade name(s)	Not applicable
EC	222-059-3
CAS	3332-27-2
Molecular structure	

Technical feasibility of alternative 4

Table 5-10: Comparative assessment of alternative 4 against the essential criteria

Criteria	Technical feasibility of alternative 4
Cell lysing efficiency	Pass Cell lysing efficiency was equivalent to 4-tert-OPnEO.
GMP	Does not pass The applicant's preferred manufacturer or supplier does not currently have GMP grade material
No known incompatibility	Not concluded
No known impact on quality	Not concluded
Intrinsic hazards	Does not pass Alternative 4 has similar hazardous concerns as 4-tert-OPnEO, Table 5-11

Economic feasibility and economic impacts of alternative 4

While GMP grade alternative 4 is not currently commercially available it is expected that the costs will not be economically prohibitive.

Availability of alternative 4

The applicant has already identified a source of alternative 4 prior to undertaking testing of it within their facility. This source is not GMP compliant, but it may become so in the future. In addition, a search on the ChemExper database produced 29 results for suppliers of alternative 4 (67). This suggests that alternative 4 is readily available.

Hazard and risk of alternative 4

According to the Classification & Labelling Inventory (Regulation (EC) No. 1272/2008), alternative 4 has a similar hazardous profile to 4-tert-OPnEO. While the identified classifications are not harmonised, they have been submitted to ECHA by most REACH registrants and CLP notifiers.

Table 5-11: Comparison of hazard classification and labelling of alternative 4

	Alternative 4	**4-tert-OPnEO**	**Octyl phenol**
EC	222-059-3	-	205-426-2
CAS	3332-27-2	9036-19-5	140-66-9
Physiochemical	None	None	None
Human health	H302 (Acute Oral Toxicity 4) H315 (Skin Irritant 2) H318 (Eye Irritant 1)	H302 (Acute Oral Toxicity 4) H315 (Skin Irritant 2) H318 (Eye Irritant 1)	H315 (Skin Irritant 2) H318 (Eye Irritant 1)
Environmental	H410 (Aquatic chronic)	H410 (Aquatic chronic) [Endocrine disruptor, by degradation to octyl phenol] M factor = 10	H400 (Aquatic Acute 1) H410 (Aquatic chronic) [Endocrine disruptor] M factor = 10
Source(s)	European Chemicals Agency (73)	Supplier Safety Data Sheet (70)	European Chemicals Agency (25)

Based on the available data, this assessment shows that the hazardous properties of alternative 4 are similar compared to 4-tert-OPnEO. Alternative 4 is classified for the environment on the basis of its aquatic toxicity and it has a PNEC of 33.5 ug/L (74) which is significantly higher than the PNEC of 0.122 ug/L proposed for 4-tert-OP, indicating that alternative 4 is less toxic to aquatic life. (75)

Additionally, it has not been identified that alternative 4 or its degradation products are endocrine disruptors to the environment. The hazardous properties do not raise a concern that the substance would meet the criteria set by REACH Article 57 so the applicant is not concerned that the substance would end up on Annex XIV.

However, the intrinsic hazards may have consequences for the applicant because trace amounts will be present in the final product.

Conclusions on suitability and availability of alternative 4

The applicant has paused testing on alternative 4 because it is currently not available as GMP grade. However, if this hurdle was overcome then the applicant would continue research and development on alternative 4 with the intention to use it as a substitute for 4-tert-OPnEO.

All of the essential criteria must be met by potential alternative 4 before it can be considered for substitution into the manufacturing process of the applicant's products. If all criteria were met, the applicant would have to undertake many studies to ensure that the substitute has no impact on the

final product nor have an impact on their market authorisation. The research and development of this potential alternative is still expected to take significant time and considerable investment.

5.4. The most likely Non-Use Scenario

5.4.1. Potential Non-Use Scenarios

The applicant is planning to use 4-tert-OPnEO for commercial production during a [redacted]. If authorisation was not granted for the substance, then the applicant has identified two options available to them:

- Option 1: delay schedule for commercial production and undertake further research and development and attempt to substitute to an acceptable alternative;
- Option 2: move production outside of Great Britain.

5.4.2. Likelihood of potential Non-Use Scenarios (NUS)

The applicant's manufacturing process is currently used to produce treatments that are undergoing clinical research, with the majority of products in Phase I or II (76).

If the applicant needed to identify and implement an alternative to 4-tert-OPnEO then the next phases of clinical research may be delayed. Additionally, in order to adapt an alternative, the previous phases of clinical research may need to be repeated so that the applicant's products could be granted a marketing authorisation.

Table 5-12: Phases of clinical research, average time and cost (77)

Phase	**Primary goal**	**Average time (years)**	**Average cost (£ billion)**
Preclinical	Drug is tested for safety and efficacy prior to testing in human subjects; testing is conducted in silico, in vitro and in vivo with animals / model organisms	5.5	0.53
Phase 0	Pharmacokinetics of the drug are tested, e.g. oral bioavailability and half-life; usually included as part of the Preclinical phase	Included in Preclinical	Included in Preclinical
Phase I	Drug is tested in healthy human subjects for safety	7.0	0.71
Phase II	Drug is tested for efficacy in participants with the relevant condition	8.5	0.92
Phase III	Drug is tested in a large sample population to generate data on safety, efficacy and therefore the overall risk/benefit of the treatment	11.0	1.10
Phase IV	Post-marketing surveillance once the drug is available for public use, to monitor long-term effects	Ongoing	Ongoing, difficult to estimate

Total *(not inc. Phase IV)*			3.26

The applicant estimates that the adoption of an alternative to 4-tert-OPnEO would mean that the marketing authorisation could be delayed by b years. With this delay, the applicant anticipates that other companies would be able to bring competing products to the market sooner, and because the market for some of the applicant's products is quite small, it is expected that the applicant would not be able to compete. Additionally, the applicant's products may be less competitively priced since they would have made additional investments for the research, development and implementation of an alternative to 4-tert-OPnEO.

For the reasons identified above, option 1 is highly unlikely. The applicant has already invested considerable resources to bring their products to market and are not able to lose their competitive advantage.

Regarding option 2, the applicant is currently funding the development of a new facility at the Shannon Free Zone in Co. Clare, Ireland. (7) The 94,000 sq. ft. facility will be fitted with a new manufacturing line which is intended to complement their London facility and to also increase manufacturing capacity. In addition, the facility will be used to manufacture plasmid DNA, which is one of the raw materials for their viral vector production.

In a NUS, it is more likely that the applicant would move all manufacturing to their Irish facility.

5.4.3. Description of most likely Non-Use Scenario (NUS) and impacts to stakeholders

Description of Non-Use Scenario

If an authorisation for 4-tert-OPnEO is not granted, then it is likely that the applicant would move the manufacture of their product to their facility in Ireland. While the facility is currently being developed, the applicant expects that the Irish facility will be manufacturing viral vectors by the end of a, in time for the commercial production to begin during a.

In a NUS, the applicant would plan for all commercial production to be undertaken in the Irish facility. This would mean that the London facility would never undertake commercial manufacture, but it may continue with a limited amount of research and development. If the applicant found that it was not viable to continue with research and development in GB, then the London facility would be closed down and decommissioned, with only separate office facilities remaining.

Impacts of Non-Use Scenario to Applicant

The applicant would have to undertake additional investment in order to transfer all manufacturing to its Irish facility. This operation may also have an impact on the schedule for commercial production and delaying time to market. While the investment into the creation of the London manufacturing facility would not be completely lost, it would yield a significantly lower return than originally expected by the applicant.

Impacts of Non-Use Scenario to suppliers of raw materials

The raw materials required for each production run are sourced from both within GB and from other Markets. The materials costs are estimated to be f per batch, with approximately f sourced from GB.

At full production, the applicant can manufacture g batches of product per year, which totals f for the cost of raw materials. Approximately >£5 million (f) is spent on sourcing from GB suppliers (see Table 4-7).

In a Non-Use Scenario where the applicant decommissions the London facility and either ceases production or moves production to Ireland, this represents a loss of >£5 million (f) per year to the GB raw materials suppliers.

Impacts of Non-Use Scenario to patients

In a Non-Use Scenario assuming that the applicant is able to move production to Ireland, this would lead to an estimated b delay in the applicant's products being available for the treatment of patients. The best-case outcome of this scenario is that the patients and their immediate families/carers continue to suffer from the effects of a number of incurable conditions (Table 2-2), and will also suffer b years of further deterioration in symptoms and a worsening prognosis. A further attendant consequence of this may be that delays in production and further investment costs raise the products' values beyond a financially viable price point (see NHS Budget Impact Test (16)), raising the possibility of the products not being available on the NHS at all. Also, in this scenario, it can be assumed that competitors are likely to enter the market during the delay period, potentially further compounding these effects.

6. Impacts of granting an authorisation

6.1. Human health or environmental impacts

4-tert-OPnEO poses no known risks to humans, therefore, there are no health impacts to workers using the substance.

6.1.1. Prevented environmental emissions in NUS

A refused authorisation would prevent annual emissions of <70g (i) of 4-tert-OPnEO to the environment in Great Britain. In a Non-Use Scenario, with the applicant decommissioning the London facility and moving production to a non-GB facility, there would be zero release to wastewaters in GB.

6.1.2. Conclusions on environmental impacts

4-tert-OPnEO is known to degrade in wastewater to 4-tert-OP, a substance that has potential endocrine disrupting properties. A worst-case assumption has been made here and in the Chemical Safety Report (CSR) for 4-tert-OPnEO that 100% of the 4-tert-OPnEO used in production is released to wastewater and converted to 4-tert-OP. In a real-world manufacturing scenario this will not be the case, and the environmental exposure is likely to be significantly lower.

Technical controls are in place at the applicant's manufacturing site which will minimise environmental exposure. The applicant is committed to conducting its operations and managing its products in a manner that is consistently protective of the environment via minimising the impact of their operations on the environment and the workplace.

A figure of £5.04 million annually (see Table 4-26) was calculated as an illustrative figure from OECD generic values (62) representing monetary impacts of environmental change in different biome types, and the areas potentially affected. This was calculated by using several worst-case assumptions, however, and adjusted with a x10 dilution factor; the genuine real-world impact of granting an authorisation is likely to be negligible.

6.2. Economic impacts

6.2.1. Description of impacts

If the authorisation was refused, the applicant would cease production of the products currently in development (see Table 2-1). The options then available to the applicant are summarised in

Table 6-1, along with the accompanying consequences.

Table 6-1: Post-refusal options and consequences for the applicant

Post-refusal option	**Immediate consequence**	**Long-term consequence**
Move manufacturing to a non-GB facility	Estimated b delay in commercial production	No product output during the delay
		No value generated during delay
		No recovery of investment during delay
		GB site permanently shut down, investment / funding lost
		Negative effect on share price / investment potential
		Lost business for upstream suppliers
		Delay in availability of products for patients
		No relief of socioeconomic burden during delay
		Competitors have access to market prior to the applicant's products being available
Use an alternative	Estimated b delay in commercial production	No product output during the delay
		No value generated during delay
		No recovery of investment during delay
		Potential negative effect on share price / investment potential
		Delay in availability of products for patients
		No relief of socioeconomic burden during delay
		Potential lack of viable replacement
		Competitors have access to market prior to the applicant's products being available

6.2.2. Economic impacts for the applicant

Lost revenue and profits

The applicant is currently in the production phase, and revenue will not be generated until sales commence in a [redacted]. An equivalent sales value, calculated from in-market figures from an equivalent gene therapy product to give a broadly illustrative figure for potential sales, was estimated to be >£15 billion (c [redacted]) over the 12-year review period (see Section 4.1.2). This figure represents the total potential revenue for the applicant. The potential net profit which would be lost in a non-use scenario was estimated as >£1 billion (c [redacted]) over the 12-year review period, or >£0.1 million (c [redacted]) per year.

The expected profits in a Non-Use Scenario (NUS) will take into consideration the delay of either moving the site to a non-GB facility or using an alternative product. It is anticipated that either NUS would cause a minimum e [redacted] delay in revenue being generated for the applicant. Using an assumed value of >£500 million (c [redacted]) for the estimated sales projections, assuming the price is not modified to account for the lost earnings due to delay, the expected lost revenue is estimated to be >£75 million (c [redacted]) for the non-use period.

As an additional point, it is expected that during any delay period experienced in a NUS, competitors of the applicant would enter the market and make alternative products and/or therapies available. In this event, the revenue subsequently available to the applicant is expected to be non-existent.

Process transfer costs

In a Non-Use Scenario where the applicant transfers production to a non-GB manufacturing facility, the applicant would be required to qualify and register that facility in line with cGMP, any local guidelines, and other regimes necessary to permit access to international markets. Specifically, the applicant would need to reapply for and gain marketing authorisations to the FDA and EMA, in order to market the products within the US and EU, respectively. It is likely that the new facility would require significant investment funding to comply, and also to provide suitable equipment for the complex manufacturing process. The total costs for transferring the manufacturing processes for the products to a non-GB facility are estimated to be approximately >£10 million (d [redacted]). This estimate includes:

- material costs to manufacture the qualification batches;
- equipment purchases;
- qualification and registration;
- technology transfers, including test method transfers;
- validations, including process validation and testing;
- labour costs;
- additional research and development and quality assurance work to show equivalence with previous processes, including characterisation data.

Decommissioning costs and lost investment

The estimated costs of decommissioning the London production facility are estimated to be d [redacted] and would take months to conduct.

The main lost investment in this scenario is the cost paid for the London facility. In December 2018 the applicant purchased a long leasehold interest in the site of the GB manufacturing facility in Britannia Walk, London, from Moorfields Eye Hospital NHS Foundation Trust for a figure of £5,250,000. (4)

6.2.3. Economic impacts for upstream suppliers

At full production, the applicant can manufacture g batches of product per year, which f for the cost of raw materials. Approximately >£5 million (f) is spent on sourcing from GB suppliers.

In the NUS, the suppliers would have reduced revenue for b as the applicant moved manufacturing to their Irish facility. It can be assumed that when the applicant restarts manufacturing in Ireland, they could use the same suppliers or switch to local sources.

6.2.4. Economic impacts for downstream users

Development of the applicant's products has a long investment cycle, requiring large investment in the initial stages of the development process. No profits are expected to be generated until a , a years after the initial investment. Any delays to the manufacturing process and eventual release to market will reduce the timeframe for the applicant's return on investment. As a result, the cost of the product is likely to be impacted and may need to be higher than defined in the initial business and investment strategies.

6.2.5. Summary and discussion on economic impacts

The economic impacts of a non-use scenario are wide and would negatively affect the entire chain of supply. At the beginning of the chain, suppliers of raw materials would experience a significant loss of income. For the applicant the costs would be so large as to threaten the viability of the business in an investment context, and from a strategic perspective. The loss of investment added to the need for decommissioning and moving production essentially amounts to a business restructuring; the costs of these, combined with the loss of sales value for the GB market, would severely impact the applicant's prospects. Further, any significant delay in production would likely have the dual impact of adversely affecting the investment return plan, and giving competitors the opportunity to enter the market and capitalise on the market share; the end result of these would be a higher price for the end product (the treatments), and this would in turn affect their availability on NHS treatment plans. Most importantly, the last stage of the supply chain would be the patients themselves, who would be negatively affected by either an absence of these treatments, or reduced availability due to higher costs.

6.3. Social impacts

6.3.1. Description of impacts

In a non-use scenario where the GB facility ceases production, there would be economic consequences in addition to those affecting the applicant, their suppliers and the afflicted patients. The immediate consequence of unemployment for a large proportion of the applicant's London workforce would be compounded by the effects on the local economy, potential burden on the welfare system and mental health issues resulting from unexpected loss of income and career.

6.3.2. Job losses

Direct job losses

The immediate outcomes of direct job losses resulting from this non-use scenario are summarised in Table 6-2.

Table 6-2: Effects and outcomes of direct job losses

Effect of direct job losses	**Potential outcome**

Loss of salary	Financial burden to the state of unemployment support
Unable to make rent/mortgage payments	Financial burden on immediate family or the state
Requirement to relocate	Disruption to family / lifestyle
Unable to contribute to local economy	Loss of income for local businesses
Increased stress / mental health issues	Increased burden of health (e.g. medical appointments, medication)
Difficulty finding alternative employment	Some or all of the above may be compounded

Indirect job losses

In such a scenario, the effects would not be localised to the immediate employees of the applicant. There would be wider, indirect effects, and these are summarised in Table 6-3.

Table 6-3: Potential indirect effects arising from direct job losses

Outcome of direct job losses	**Potential indirect effects**
Financial burden of unemployment support	Psychological effects on the individual
Financial burden on immediate family	Spouse/partner required to alter work plans, associated stress
Disruption to family / lifestyle	Relocation away from settled area; Children's schooling disrupted
Loss of income for local businesses	Local cleaners, cafes, restaurants, snack bars/fast food, small stores and providers of leisure activities would lose income; potential indirect loss of jobs
Increased burden of health (e.g. medical appointments, medication)	Further adverse effects on mental health, associated stress for individual and immediate family
Difficulty finding alternative employment	Some or all of the above may be compounded

6.3.3. Cost of unemployment

If the applicant was unsuccessful in the authorisation, the most likely non-use scenario would be for production to move to Ireland, with the London manufacturing facility either closing or being converted to research and development or office space. In this scenario the applicant estimates that e of the London workforce would either be retained or would transfer to Ireland, with the remaining number e (approximately e employees) being made redundant. These employees are highly skilled specialist scientists who have gained a vast amount of experience in the processes for generating the applicant's eight products. This focussed experience will make it very difficult to find alternative, suitable employment which meets their skillsets.

Lost output from salaries (78) (79)

Due to the employees being highly skilled and their experience being focussed on the process for the applicant's products, it would be extremely unlikely that they would be engaged in suitable alternative employment straight away. Using the methodology from the ECHA guidance document, the average duration of unemployment in the UK was calculated to be 9.09 months. (80) The calculations and data are shown in Table 6-4. Note that these figures are derived from information on the United Kingdom; this data was representative of the primary target market of Great Britain and would not be expected to change in any meaningful way by adjustment to exclude Northern Ireland data.

Table 6-4: Data on duration of unemployment in the UK (representative of Great Britain) (81)

UK unemployment duration	Assumed duration	Mean number of unemployed	% of unemployed	Cumulative months
Less than 1 month	0.5	221.6	17.64%	0.09
From 1 to 3 months	1.5	332.5	26.47%	0.40
From 3 to 5 months	4	237.9	18.93%	0.76
From 6 to 11 months	8.5	186.7	14.86%	1.26
From 12 to 17 months	14.5	91.8	7.31%	1.06
From 18 to 23 months	20.5	37.3	2.97%	0.61
From 24 to 47 months	35.5	76.1	6.06%	2.15
48 months and over	48	72.4	5.76%	2.77
Total		**1256.2**		**9.09**

The salaries of these employees are between e [redacted] per year with a mean of >£50,000 (e [redacted]) (these values take into consideration employer tax contributions). Considering the mean salary value is used, the output cost of unemployment for the duration of 9.09 months in lost salaries will be >£25,000 (e [redacted]) For all employees made redundant, this would relate to lost wages of >£2.5 million (e [redacted]) (including employer's tax contributions).

Scarring costs

If the London manufacturing facility were to close, an assumption can be made that employees will either relocate to an alternate site, relocate for alternative work, or will experience a loss of earnings. Due to the level of available opportunities for employees, it is expected that a decrease of 20% in the acceptable wage will be assumed. This number is mostly illustrative, as estimating the wages of highly skilled professionals in London is not possible.

Using the lower end range for the employees' salaries gives a gross wage of >£50,000 (e [redacted]). The scarring costs for the employees can be estimated by using the assumption that in searching for alternative employment, an employee would accept the reservation wage, i.e. the lowest wage that is financially viable for that employee. ECHA have suggested 80% as a reasonable prediction for the reservation wage, (82) therefore the assumed salary would be subject to a 20% reduction.

The scarring costs are estimated in Table 6-5, allowing for a six-year period following re-employment.

Table 6-5: Calculation of scarring costs

Gross Salary (including employer tax contribution) (£)	>50,000 (e [redacted])

Scarring wage (£)	>25,000 ([redacted])
Scarring cost, annual, per employee (£)	>10,000 ([redacted])
Scarring cost, 6-year period, per employee (£)	>50,000 ([redacted])
Scarring cost, 6-year period, all ([redacted]) employees (£)	>5 million ([redacted])

The total scarring costs in this scenario would therefore be >£5 million ([redacted]).

Leisure time

When working, an employee is compensated for their time by their salary. To calculate the relevant trade off value for the employee of whether to work or not, a reservation wage of 80% of the expected post-tax wage is used. Table 6-6 contains the identified reservation wage, adjusted for scarring.

Table 6-6: Calculation of leisure benefit

Gross Salary (£)	>50,000 ([redacted])
Scarring wage (£)	>25,000 ([redacted])
Adjusted for employee tax and National Insurance (£)	>25,000 ([redacted])
Adjusted for Reservation wage (£)	>25,000 ([redacted])
Hourly rate (£) (Assumed 40-hour week)	>10 ([redacted])
Mean duration of unemployment (months)	>9 ([redacted])
Benefit for employees additional time (£)	>10,000 ([redacted])
Benefit for all ([redacted]) employees additional time (£)	>1 million ([redacted])

The total leisure benefit in this scenario for the employees to be made redundant is >£1 million [redacted]). This value will be considered as a cost loss (treated as a negative value for the total costs of the lost jobs).

The typical household expenditure on leisure time and recreational activities will therefore no longer be available as income for the relevant local businesses. The lost revenue for the economy in the surrounding area is estimated in Table 6-7, using the values for London to be representative of the location of the facility and the employees' home lives. (83) The calculations are conducted on the assumption that the economic contribution from [redacted] employees ([redacted] of the workforce) would no longer be available to the local economy, and the average number of people per household in London as 2.6, (83) giving a total of [redacted] affected households.

Table 6-7: Average annual loss resulting from closing the applicant's London facility

	Average weekly household expenditure (London) (£)	**Average annual household expenditure (London) (£)**	**Average total annual loss to local economy (£)**

Recreation and culture	64.60	3,359.20	>100,000 ([redacted])
Restaurants and hotels	63.00	3,276.00	>100,000 ([redacted])
Total	127.60	6,635.20	>200,000 ([redacted])

The local leisure and recreation economy would therefore suffer an average annual loss of >£200,000 ([redacted]) in the event of the applicant closing the London manufacturing facility.

Job search and recruitment costs

During the period of unemployment, it is assumed that time will be spent seeking new employment. The average figure of 2.5 hours per week (82) spent on this can be applied to the average unemployment period of 9.09 months to give an estimate of the costs of seeking a new job.

Table 6-8: Cost of seeking employment

Time spent (hours/week)	2.5
Period of unemployment (months)	9.09
Total time spent (hours)	98.48
Hourly rate (adjusted for scarring costs) (£)	12.25
Cost per person (adjusted for scarring costs) (£)	1206.38
Total cost for all ([redacted]) employees (adjusted for scarring costs) (£)	>75,000 ([redacted])

The total cost of seeking employment for all [redacted] affected employees is therefore >75,000 ([redacted]). Note that these costs relate solely to the time impact, and costs relating to travel and other expenses have been excluded.

Recruitment costs will only be required for the applicant's employees on the basis of this authorisation. The assumed costs for an individual to be recruited is determined by 0.3 years (based on the future wage cost).

Table 6-9: Costs of recruitment

Salary (adjusted for scarring costs) (£)	>25,000 ([redacted])
Recruitment cost factor	30%
Recruitment costs	>10,000 ([redacted])
Total cost for (50-100 [redacted]) all employees (£)	>1 million ([redacted])

The total cost to recruit all staff made redundant from the non-use scenario is therefore >£1 million ([redacted]).

Total unemployment costs

For clarity the costs of unemployment are collated and summed in Table 6-10.

Table 6-10: Total unemployment costs

Loss of output	>£75 million (£[redacted])
Scarring effects	>£5 million (£[redacted])
Leisure benefit	>£1 million (£[redacted])
Leisure cost	>£200,000 (£[redacted])
Costs of seeking employment	>£1 million (£[redacted])
Total	>£100 million (£[redacted])

Note that the loss of output includes:

- the assumed loss of revenue
- the assumed process transfer costs
- the assumed decommissioning costs
- the lost output from salaries.

The total costs for the Non-Use Scenario in which half the workforce in London would lose their jobs will be >£100 million (£[redacted]) over the 12-year review period.

6.4. Wider economic impacts

Table 6-11: Socio-economic benefits of continued use

Description of major impacts	Quantification of impacts [annualised to £ million per year]
1. Benefits to the applicant(s) and/or their supply chain	
1.1 Avoided profit loss due to investment and/or production costs related to the adoption of an alternative	>7.5 (d [redacted])
1.2 Avoided profit loss due to ceasing the use applied for[1]	>1,500 (c [redacted])
1.3 Avoided relocation or closure cost (one-off cost within the first 12 months following authorisation refusal, spread over 12-year review period)	>0.1 (d [redacted])
1.4 Avoided residual value of capital (one-off cost of site purchase, spread over 12-year review period)	>0.25 (d [redacted])
1.5 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 (d [redacted])
Sum of benefits to the applicant(s) and / or their supply chain	**>1,500 (j [redacted])**
2. Quantified impacts of the continuation of the SVHC use applied for on other actors	
2.1 Avoided net job loss in the affected industry[2]	>0.25 (e [redacted])
2.2 Foregone spill-over impact on surplus of alternative producers	>5 (f [redacted])
2.3 Avoided consumer surplus loss (e.g. because of inferior quality, higher price, reduced quantity, etc.)	n/a
2.4 Avoided other societal impacts (e.g. avoided CO_2 emissions or securing the production of drugs)	410.00
Sum of impacts of continuation of the use applied for	**>400 (j [redacted])**
3. Aggregated socio-economic benefits (1+2)	>2,000 (J [redacted])

6.4.1. GB competitiveness

The applicant's products will be used to offer a therapeutic benefit in patients with diseases which result from mutations in a single gene in a patient's genome. There are currently no other products currently on the market which offer the same level of treatment for the following diseases:

- Achromatopsia
- Parkinson's disease
- Xerostomia

1 Profit losses to be counted in only for the first [x] years, see SEAC note on economic surplus changes (not yet available).

2 Job losses to be accounted for only for the arithmetic mean period of unemployment in the concerned region/country as outlined in the SEAC paper on the valuation of job losses. (82) (80)

- Sjögren's syndrome.

The products are being developed in Great Britain (GB) and, if the authorisation is granted, this would put the applicant at the cutting edge of manufacturing in this therapeutic area. If the use of the substance is not authorised for these products, the manufacturing would be moved to a non-GB facility, reducing the competitiveness for Great Britain.

6.4.2. Local area development

The applicant's GB manufacturing facility is located in Britannia Walk, London. The local area of Britannia and Shoreditch, within the London Borough of Hackney, is undergoing a phase of improvement and redevelopment with completion estimated during 2021. This includes a secondary school, a leisure centre, and hundreds of new homes, including affordable housing. There are also plans for a public square and space for community events, walking and cycling routes, and nature-friendly wildlife habitats (84) (85). The applicant's facility, and its employees, could form an important part of this local community as it develops and improves.

6.5. Combined assessment of impacts

6.5.1. Comparison of impacts

A refused authorisation would prevent annual emissions of <70g ([redacted]) of 4-tert-OPnEO to the environment in Great Britain. In a Non-Use Scenario, with the applicant moving manufacturing to a non-GB facility, there would be zero release in GB.

The cost of a refused authorisation is approximately >£100 million ([redacted]). This cost can be broken down into:

- lost profits for the applicant due to delaying marketing of the products
- cost for transferring the manufacturing process to a non-GB facility
- decommissioning the London based site
- unemployment cost for the applicant's assumed [redacted] employees that would be made redundant after the Sunset Date.

If the applicant's products are removed from the global and GB markets, patients suffering from a suite of otherwise incurable conditions (Table 2-2) will continue to experience the debilitating and progressive effects of those conditions, and all the attendant negative consequences for themselves and their families. The socioeconomic effects of these conditions are significant, as summarised in Table 4-21. There is also an ethical element to the consideration of making these treatments available to patients. A core value of medical ethics is ensuring that patients have access to drugs and other treatment methodologies with curative or preventative effects on diseases with life-altering effects, (86) and this is enshrined in the National Health Service (NHS) Constitution, (87) as shown below.

Table 6-12: Ethical statements within the NHS Constitution (87)

Principles:	3. The NHS aspires to the highest standards of excellence and professionalism – in the provision of high-quality care that is safe, effective and focused on patient experience; and through its commitment to innovation and to the promotion, conduct and use of research to improve the current and future health and care of the population.
	4. The patient will be at the heart of everything the NHS does.
Values:	Commitment to quality of care
	Compassion
	Improving lives
	Everyone counts
Rights:	You have the right to receive care and treatment that is appropriate to you, and meets your needs.
	You have the right to expect decisions on funding of other drugs and treatments to be made rationally following a proper consideration of the evidence.
Pledges:	To identify and share best practice in quality of care and treatments.

Table 6-13: Comparison of socio-economic benefits and risks of continued use

Socio-economic benefits of continued use		**Monetised excess risks associated with continued use**	
Benefits to the applicant(s) and/or their supply chain [annualised to £ million per year]	>1,500 (c [redacted])	Monetised excess risks to workers directly exposed in the use applied for [annualised to £ million per year]	0
Quantified impacts of the continuation of the SVHC use applied for on other actors	0	Monetised excess risks to the general population and indirectly exposed workers [annualised to £ million per year]	0
Additional qualitatively assessed impacts	0	Additional qualitatively assessed risks [annualised to £ million per year]	5.04
Aggregated socio-economic benefits [annualised to £ million per year]	>1,500 (j [redacted])	Aggregated monetised excess risk [annualised to £ million per year]	5.04

Table 6-14: Benefit / risk summary

Net benefits [annualised to £ million per year]	>1,500 (c,j [redacted])
Benefit/monetised risk ratio	>300 (c,j [redacted])

Table 6-15: Cost of non-use per kg and year (for PBT/vPvB substances and endocrine disruptors)

	Per year
Total cost [annualised to £ million per year]	5.04
Total emissions (kg/year)	j [redacted]
Ratio (£mill/kg/year)	>50 (j [redacted])

Notes:

1. "Total cost" (of non-authorisation) = Benefit of authorisation

2. "Total emissions" (if authorisation is granted) = Estimated emissions to the environment, kg per year from Section 10.2 of the CSR
3. "Ratio" = Total cost/Total emissions

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

Combined impacts

The impacts of a refused authorisation have been considered throughout this analysis and allocated a monetary value as far as possible given the context and the available data. For clarity the monetary impacts are collated and summed in Table 6-16.

Table 6-16: Combined impacts of a refused authorisation

Impact	**Monetary cost [annualised to £ million per year]**
Costs of investment and/or production costs related to the adoption of an alternative (not inc. clinical trials)	>7.5 ([a])
Avoided profit loss due to ceasing the use applied for	>1,000 ([c])
Cost of decommissioning and moving production (one-off cost within the first 12 months following authorisation refusal, spread over 12-year review period)	>0.1 ([b,d])
Lost investment of London facility (one-off cost of site purchase, spread over 12-year review period)	>0.25 ([d])
Avoided additional cost for transportation, quality testing, etc.	>0.75 ([d])
Health burden remaining, as treatment not available	410
Costs of unemployment	>0.25 ([d,e])
Lost income for suppliers	>5 ([f])
Total	>1,500 ([a,b,c,d,e,f])

6.5.2. Distributional impacts

Table 6-17: Distributional impacts

Affected group[1]	**Economic impact [annualised to £ million per year]**	**Health and environmental impact [annualised to £ million per year]**
Economic operator		
Applicant	>1,000 ([redacted])	n/a
Suppliers of alternatives in GB	n/a	n/a
Suppliers of alternatives outside GB	n/a	n/a
Competitors in GB	n/a	n/a
Competitors outside GB	n/a	n/a
Customer group 1[2]: patients with conditions covered under Ocular Programme	1,290.00	+++
Customer group 2: patients with conditions covered under Neurodegenerative Programme	1,940.00	+++
Customer group 3: patients with conditions covered under Salivary Gland Programme	400.00	++
Total, Customer groups 1, 2 & 3, adjusted for prevalence and proportionate patient numbers (see Table 4-23)	410.00	
Public at large in the GB	n/a	5.04
Geographical scope		
Great Britain	>400 ([redacted])	5.04
Within the applicant's business		
Employers/Owners	>1,000 ([redacted])	n/a
Exposed workers	8.35	n/a
Non-exposed employees	8.35	n/a

Notes:

[1] Adapt the groups as relevant for your application.

[2] Identify group or groups as relevant. These may comprise the downstream or end users of the substance or the final customers of the products.

Severity of impacts: either monetary [annualised to £ million per year] or using scale high (+++ or ---), medium (++ or --), low (+ or -) or not applicable (n/a)

The impacts of a refused authorisation have been considered throughout this analysis and allocated a monetary value as far as possible given the context and the available data.

6.6. Uncertainty analysis

6.6.1. Assumptions and uncertainties

Several assumptions have been necessary in consideration of all the estimated effect values relating to use of the substance, the value of the applicant's products, benefits to patients and cost burden, and the eventualities in a No-Use Scenario. A degree of uncertainty is therefore unavoidable. To counter this, a conservative approach has been used, with 'worst-case' values or reliable equivalence data used wherever possible.

Table 6-18: Assumptions used and uncertainties

Uncertainty	**Assumption**	**Approach taken**
Exact costs of decommissioning not known	Costs would be within the range estimated by the applicant	Mid-range value taken for cost burden estimates
Exact costs of transferring production not known	Costs would be within the range estimated by the applicant	Mid-range value taken for cost burden estimates
Unknown if max. production capacity will be maintained	g batches per year produced	Worst-case: calculate from the maximum
Unknown if max. amount of substance will be released	<70g (i)/year of the substance released to wastewater	Worst-case: calculate from the maximum
Unknown % of substance actually converted to degradation product in a real-world scenario	100% of the substance converted to degradation product	Worst-case: calculate from the maximum
Degradation product is a known endocrine disruptor, extent of effect is not known	100% of the degradation product is in scope for environmental considerations	Worst-case: calculate from the maximum
Extent of environmental effects of the substance / degradation product are not known	Environmental effects of the substance's release can be quantified using reliable generic values	Reliable values sought and used; OECD-defined values (62) for different biomes combined with exact size values for affected areas; adjusted for dilution factor
Projected range of sales value is very broad; Products are novel to the applicant and to the market	Sales value of the applicant's products can be quantified	Best-match equivalent values sought and used for calculations
Total cost burden of the various conditions can be calculated; unknown how much of this burden would be relieved by the applicant's products	Total cost burden can be adjusted proportionately to provide a more representative estimate	Prevalence data and in-market patient information for an equivalent product used to provide an adjusted figure

% unemployment of London facility employees is not known	In a non-use scenario, e[redacted] of London workforce would be unemployed	Applicant's best estimate of a reasonable figure used

6.6.2. Sensitivity analysis

Impact of profits from sales of Product 1 and Product 2

The potential sales value resulting from the applicant's products was estimated to be >£15 billion (c[redacted]) over the 12-year requested review period of the products. This was calculated based on equivalence values from a similar product as shown in Table 4-2.

Impact of assumed release factor

A figure of £50.4 million annually (see Table 4-26) was calculated as an illustrative figure from OECD generic values (62) representing monetary impacts of environmental change in different biome types, and the areas potentially affected. This was calculated by using several worst-case assumptions, however, and the genuine real-world impact of granting an authorisation is likely to be negligible. Also note that the uncertainty of the relevance of one area, Beckton Sewage Treatment Works Northern Settling Lagoon SINC, was considered and excluded from calculations due to its planned use as material storage warehousing. (63)

Uncertainty reduction

Although uncertainties and assumptions have been acknowledged, it is good practice to identify those inputs that cause the most significant uncertainty, and where uncertainty could be reduced.

Table 6-19: Potential for uncertainty reduction

Assumption	Approach taken	Uncertainty	Potential for uncertainty reduction
Decommissioning costs would be within the range estimated by the applicant	Mid-range value taken for cost burden estimates	Minimal	Acquire refined estimates; negligible effect on final figures
Costs of production transfer would be within the range estimated by the applicant	Mid-range value taken for cost burden estimates	Minimal	Acquire refined estimates; negligible effect on final figures
g batches per year produced	Worst-case: calculate from the maximum	Minimal	Unlikely until production is ongoing; any correction would deviate from the worst-case estimates
<70 g ( )/year of the substance released to wastewater	Worst-case: calculate from the maximum	Minimal	Unlikely until production is ongoing; any correction would deviate from the worst-case estimates
100% of the substance converted to degradation product	Worst-case: calculate from the maximum	Minimal	Not possible to refine; any correction would deviate from the worst-case estimates
100% of the degradation product is in scope for environmental considerations	Worst-case: calculate from the maximum	Minimal	Not possible to refine; any correction would deviate from the worst-case estimates
Environmental effects of the substance's release can be quantified using reliable generic values	Reliable values sought and used; OECD-defined values (62) for different biomes combined with exact size values for affected areas; adjusted for dilution factor	Large	Unlikely that alternative values could provide more refined and/or reliable figures
Sales value of the applicant's products can be quantified	Best-match equivalent values sought and used for calculations	Large	Refined sales projections could be provided
Total cost burden can be adjusted proportionately to provide a more representative estimate	Prevalence data and in-market patient information for an equivalent product used to provide an adjusted figure	Medium	If in-market data for equivalent treatments for Neurodegenerative and Salivary Gland programmes were available, these could be used to adjust further
In a non-use scenario, e of London workforce would be unemployed	Applicant's best estimate of a reasonable figure used	Minimal	Reasonable assumption used; small effect on final figures

6.6.3. Conclusion on uncertainty in the SEA

The most significant sources of uncertainty in the estimates used are:

- quantifying the environmental effects of the release of this specific substance to wastewater is not possible without using assumptions and generic values;
- further adjustment of the proportionate cost burden of diseases is not possible without further in-market data being available;
- refined projections of the sales value of the applicant's products are not available.

Uncertainty could be reduced if more detailed sales projections were available. Other uncertainties are acceptable given the context of the assessment.

6.7. Information for the length of the review period

The applicant requests a 12-year review period to allow use of 4-tert-OPnEO for continued manufacture of their gene therapies. While a potential alternative has been identified by the applicant, several challenges need to be overcome before it could be adapted as an alternative and it is not guaranteed that these issues can be addressed.

The development of the applicant's products started in a [redacted] and it is anticipated that the first will be commercialised in a [redacted], giving a development timeline of at least a [redacted] years. The manufacturing process that is established during development needs to be representative of the process used for commercial production. The same requirement applies to the formulation that is used during clinical trials and post-authorisation. If the manufacturing process or formulation was modified to change the final product then this would require a full evaluation with supporting studies to demonstrate that the modification does not have any detrimental effect on that product.

The steps required and estimated time to implement the potential alternative for each of the applicant's products are:

- Procuring GMP grade potential alternative – if possible, could be confirmed within 6 months
- Optimising potential alternative concentration within buffer solution – 6 months
- Scale up of potential alternative – 6 months
- Run through of downstream process with potential alternative – 1 month
- Characterisation of product manufactured with potential alternative – 12 months
- Set up and manufacture a commercial scale batch – 12 months

While the applicant has a strong understanding of the steps required to test and implement an alternative cell lysing agent, there is no guarantee that the potentials will pass all the essential criteria. If the potential alternative fails, then the applicant needs to restart their substitution from the beginning.

6.8. Substitution effort taken by the Applicant if an authorisation is granted

The applicant will continue to undertake research and development of the potential alternative in an effort to substitute 4-tert-OPnEO. The applicant aims to use an alternative that is both technically and commercially viable while also being as safe for human health and safer for the environment.

7. Conclusions

7.1. Conclusions of analysis of alternatives

The AoA has demonstrated that there are currently no available alternative substances that could replace 4-tert-OPnEO in the manufacturing of the applicant's products. Of the 4 potential alternatives that were evaluated, only one (N,N-dimethyltetradecylamine N-oxide) shows future potential due to its cell lysing efficiency. If this potential alternative becomes available in GMP grade, then the applicant would resume testing. However, it must be noted that this potential alternative has intrinsic hazards and a significant amount of testing would be required before it could be considered safe for manufacturing the applicant's products.

Therefore, there are no currently available alternatives to 4-tert-OPnEO. Further, the use of any alternative may require significant research and development investment to ensure stability, suitability, economic viability and continuity of supply. Nevertheless, the applicant undertakes to continue seeking and evaluating potential alternatives for the course of the review period.

7.2. Conclusions of socio-economic analysis

The SEA has demonstrated that the benefits from the applicant's use of 4-tert-OPnEO in the manufacturing of their products significantly outweigh any costs arising from risk to the environment in Great Britain (GB).

As these novel products and treatments are still being developed by the applicant, several reasonable assumptions have been made in order to quantify the benefits arising from the use of the substance, including use of data resulting to a similar product. For clarity, these assumptions are discussed in the uncertainty analysis. For all elements factored into the analysis, monetised impacts were able to be calculated and provided a quantitative approach throughout. Qualitative aspects are discussed where this is useful in providing context, for example the impact on quality of life for patients with the diseases targeted by the applicant's products.

In a non-use scenario following a refused authorisation, the release to wastewater of <70g ([redacted]) annually in GB would be prevented; the attendant cost burden resulting from this environmental exposure was estimated as £5.04 million annually. The most likely scenario following a refusal of authorisation would be for the applicant to decommission the London, GB, manufacturing facility and either cease activity or move production to a facility in the Republic of Ireland. The costs of this are included in the calculation of combined monetary impacts, which totals an estimated >£1,500 million ([redacted]) annually. This total figure also includes lost relief of disease burden, lost sales value for the applicant, lost salaries and impact for employees, and lost business for suppliers.

While the relief of burden of disease can, and indeed has, been quantified in terms of monetary impact, it is vital to remember the ultimate 'end user' of the products, and the potential for radical, life-changing positive effects resulting from use of the applicant's products in treatment regimens. The three categories of disease (Ocular, Neurodegenerative and Salivary gland – described in detail throughout) together affect many people in GB and, ultimately, globally, and the effects can be devastating. Currently no curative or restorative treatments are available for the patients suffering long-term with these diseases, and the applicant's products represent a landmark opportunity to change the medical approach to their treatment and prognosis – in short, to make a life-changing impact to the lives of a great many people.

In summary, a refusal of authorisation would have a disproportionate impact to the applicant, their employees, the patients and society at large. The quantities of the substance released to wastewater

resulting from the applicant's use would be low, and the applicant would continue to take all possible measures to reduce release going forward. The benefits of granting an authorisation far outweigh any cost arising from risk to the environment over the requested review period of 12 years.

Glossary

4-tert-OP....4-(1,1,3,3-tetramethylbutyl)phenol
4-tert-OPnEO....4-(1,1,3,3-tetramethylbutyl)phenol, ethoxylated, covering well-defined substances and UVCB substances, polymers and homologues
AAV....Adeno-Associated Virus
ACHM....achromatopsia
AMD....Age-related Macular Degeneration
AoA....Analysis of Alternatives
ATMP....Advanced Therapy Medicinal Products
BAP....Biodiversity Action Plan
BSTW....Beckton Sewage Treatment Works
CAS....Chemical Abstracts Service
cGMP....current Good Manufacturing Practice
CLP....European Regulation (EC) No 1272/2008 on classification, labelling and packaging of substances and mixtures
CMOs....Contract Manufacturing Organisations
CNGA3....Cyclic Nucleotide Gated Channel Alpha 3
CSR....Chemical Safety Report
DLA....Disability Living Allowance
EA....Environment Agency
EC....European Community Number
ECHA....European Chemicals Agency
EMA....European Medicines Agency
EU....European Union
EUSES....European Union System for the Evaluation of Substances
FDA....Food and Drug Administration
GAD....Glutamic Acid Decarboxylase
GB....Great Britain
GMP....Good Manufacturing Practice
HLB....Hydrophile-Lipophile Balance
HPV....Human Papillomavirus
IRD....Inherited Retinal Dystrophies
LCA....Leber's Congenital Amaurosis
MHRA....Medicines and Healthcare products Regulatory Agency
NASDAQ....National Association of Securities Dealers Automated Quotations
NHS....National Health Service
NICE....National Institute for Health and Care Excellence
NUS....Non-Use Scenario
OECD....Organisation for Economic Co-operation and Development
PBT....Persistent, Bioaccumulative and Toxic
PEC:....Predicted Environmental Concentration
PIP....Personal Independence Payment
PNEC....Predicted No-Effect Concentration
ppm....parts per million
PRIME....Priority Medicines scheme
QoL....Quality of Life

REACH.....REGULATION (EC) No 1907/2006 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 18 December 2006 concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH)
RIX.....Radiation-Induced Xerostomia
RP.....Retinitis Pigmentosa
RPE65.....Retinal pigment epithelium-specific 65 kDa protein, also known as retinoid isomerohydrolase
RPGR.....Retinitis Pigmentosa GTPase Regulator
SEA.....Socio-Economic Analysis
SINC.....Site of Importance for Nature Conservation
SOP.....Standard Operating Procedure
SVHC.....Substance of Very High Concern
UK.....United Kingdom
USA.....United States of America
USD.....US dollars
UVCB.....Unknown or Variable composition, Complex reaction products or Biological material
vPvB.....very Persistent and very Bioaccumulative
XLRP.....X-Linked Retinitis Pigmentosa

References

1. European Chemicals Agency. SETTING THE REVIEW PERIOD WHEN RAC AND SEA GIVE OPINIONS ON AN APPLICATION FOR AUTHORISATION. *European Chemicals Agency.* [Online] 13 Septermber 2013. [Cited: 15 December 2020.] https://echa.europa.eu/documents/10162/13580/seac_rac_review_period_authorisation_en.pdf#:~:text=It%20is%20recognised%20that%20the%20preparation%20of%20the,length%20of%20the%20review%20period%20of%20seven%20years..

2. MeiraGTx. Research & Development. *MeiraGTx.* [Online] 2020. [Cited: 9 November 2020.] https://meiragtx.com/research-development/clinical-trials/.

3. —. Our Company. *MeiraGTx.* [Online] 2018. [Cited: 9 November 2020.] https://meiragtx.com/company/about-us/.

4. 2018 Annual Report. *MeiraGTx.* [Online] 2018. [Cited: 9 November 2020.] https://investors.meiragtx.com/static-files/830b3941-feb2-4c28-b6b2-f54c984b72a9.

5. MeiraGTx. Scientific Platform. *MeiraGTx.* [Online] MeiraGTx. [Cited: 11 November 2020.] https://meiragtx.com/our-strategy/scientific-platform/.

6. MeiraGTx Holdings plc. Form S-1 Registration Statement MeiraGTx Holdings plc. *MeiraGTx.* [Online] 14 May 2018. [Cited: 21 December 2020.] https://investors.meiragtx.com/static-files/40362049-65da-4810-bda9-f19e12b747d9 .

7. RTE. [Online] [Cited: 13 November 2020.] https://www.rte.ie/news/business/2020/0807/1157887-meiragtx-announces-expansion-at-shannon-facility/.

8. Companies Registration Office. Company Details. *Companies Registration Office.* [Online] 17 June 2020. [Cited: 13 November 2020.] https://search.cro.ie/company/CompanyDetails.aspx?id=672472&type=C.

9. Nuffield Department of Clinical Neurosciences. Gene Therapy for X-Linked Retinitis Pigmentosa. *Nuffield Department of Clinical Neurosciences.* [Online] 2020. [Cited: 2 December 2020.] https://www.ndcn.ox.ac.uk/research/clinical-ophthalmology-research-group/trials/xlrp-gene-therapy.

10. UCL Institute of Ophthalmology. New gene therapy approach may offer a new treatment for retinitis pigmentosa (RP). *UCL Institute of Ophthalmology.* [Online] 16 June 2020. [Cited: 2 December 2020.] https://www.ucl.ac.uk/ioo/news/2020/jun/new-gene-therapy-approach-may-offer-new-treatment-retinitis-pigmentosa-rp.

11. Office for National Statistics. Population estimates for the UK, England and Wales, Scotland and Northern Ireland: mid-2019. *Office for National Statistics.* [Online] 24 June 2020. [Cited: 17 November 2020.] https://www.ons.gov.uk/peoplepopulationandcommunity/populationandmigration/populationestimates/bulletins/annualmidyearpopulationestimates/mid2019estimates.

12. NHS England. First patients begin gene therapy treatment for blindness as part of NHS Long Term Plan. *NHS England.* [Online] 17 February 2020. [Cited: 19 November 2020.] https://www.england.nhs.uk/2020/02/first-patients-begin-gene-therapy-treatment-for-blindness/.

13. National Institute for Health and Care Excellence (NICE). NICE recommends novel gene therapy treatment for rare inherited eye disorder. *National Institute for Health and Care Excellence (NICE).* [Online] 4 September 2019. [Cited: 19 November 2020.] https://www.nice.org.uk/news/article/nice-recommends-novel-gene-therapy-treatment-for-rare-inherited-eye-disorder.

14. Fundament, T., et al. Deep Brain Stimulation for Parkinson's Disease with Early Motor Complications: A UK Cost-Effectiveness Analysis. *Plos One.* [Online] 21 July 2016. [Cited: 14 January 2021.] https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0159340#pone.0159340.s003.

15. MeiraGTx. MeiraGTx To Present Clinical Program Update for AAV-hAQP1 Treatment of Radiation-Induced Xerostomia. *MeiraGTx.* [Online] 16 December 2020. [Cited: 21 December 2020.] https://investors.meiragtx.com/news-releases/news-release-details/meiragtx-present-clinical-program-update-aav-haqp1-treatment.

16. Ogden, J. How will NICE's budget impact test affect new drug availability? *Prescriber.* [Online] August 2017. [Cited: 19 November 2020.] https://www.prescriber.co.uk/wp-content/uploads/sites/23/2017/08/NICE-budget-impact-EB-edit-lsw.pdf.

17. Macrotrends LLC. Novartis AG Net Income 2006-2020. *Macrotrends.* [Online] 30 Septermber 2020. [Cited: 21 December 2020.] https://www.macrotrends.net/stocks/charts/NVS/novartis-ag/net-income.

18. Merck Millipore. Triton™ X-100. *Merck Millipore.* [Online] [Cited: 17 December 2020.] https://www.merckmillipore.com/GB/en/product/Triton-X-100,MDA_CHEM-108643.

19. MeiraGTx Holdings plc. Form S-1 Registration Statement. *MeiraGTx.* [Online] 14 5 2018. [Cited: 9 November 2020.] https://investors.meiragtx.com/node/6476/html.

20. RNIB. Achromatopsia: Life in black and white. *RNIB.* [Online] 23 November 2016. [Cited: 30 October 2020.] https://www.rnib.org.uk/nb-online/life-in-black-and-white.

21. Parkinson's UK. What is Parkinson's? *Parkinson's UK.* [Online] n.d. [Cited: 5 November 2020.] https://www.parkinsons.org.uk/information-and-support/what-parkinsons .

22. Parkinson's UK Scotland. Incidence of Parkinson's is increasing. *Parkinson's UK Scotland.* [Online] 8 January 2018. [Cited: 11 November 2020.] https://www.edinburghparkinsons.org/incidence-parkinsons-increasing/#:~:text=The%20number%20of%20people%20diagnosed%20and%20living%20with,The%20estimated%20incidence%20for%202018%20is%20around%2018%2C000..

23. *Estimating the prevalence among Caucasian women of primary Sjögren's Syndrome in two general practices in Birmingham.* Bowman, S. and al, et. 1, s.l. : UK Scandinavian Journal of Rheumatology, 2004, Vol. 33.

24. TSG Consulting. *Chemical Safety Report: 4-(1,1,3,3-tetramethylbutyl) phenol, ethoxylated (4-tertOPnEO).* s.l. : TSG Consulting, 2021.

25. Agency, European Chemcials. Brief Profile, 4-(1,1,3,3-tetramethylbutyl)phenol. *European Chemcials Agency.* [Online] European Chemcials Agency. [Cited: 12 November 2020.] https://echa.europa.eu/brief-profile/-/briefprofile/100.004.934.

26. Thames Water Utilities Ltd. *Consent to the discharge of trade effluent.* London : Thames Water Utilities Ltd., 2019. TBEC1VW7.

27. ECHA. SUPPORT DOCUMENT FOR IDENTIFICATION OF 4-(1,1,3,3-TETRAMETHYLBUTYL)PHENOL, ETHOXYLATED. *European Chemicals Agency.* [Online] 12 12 2012. [Cited: 30 October 2020.] https://www.echa.europa.eu/documents/10162/c4634d14-bd48-42da-add8-dc02568bb27c.

28. Environment Agency. Environmental Risk Evaluation Report: 4-tert-Octylphenol. *Environment Agency.* [Online] April 2005. [Cited: 24 November 2020.] https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/290844/scho0405biyz-e-e.pdf.

29. Thames Water Utilities Limited. Thames Tideway Tunnel Planning Statement Appendix Y: Beckton Sewage Treatment Works. *Tideway London.* [Online] January 2013. [Cited: 30 October 2020.] https://www.tideway.london/media/1160/planning-statement_beckton-sewage-treatment-works.pdf.

30. —. Environmental Statement Volume 26: Beckton Sewage Treatment Works site assessment. *National Infrastructure Planning.* [Online] January 2013. [Cited: 30 October 2020.] https://infrastructure.planninginspectorate.gov.uk/wp-content/ipc/uploads/projects/WW010001/WW010001-000958-6.2.26_Environmental_Statement_Volume_26_Beckton_Sewage_Treatment_Works_Site_Assessment_Sections_1_to_15.pdf.

31. Environment Agency. Thames - Summary: River Basin District. *Environment Agency.* [Online] 17 September 2020. [Cited: 30 October 2020.]

32. Greenspace Information for Greater London. Discover London. *Greenspace Information for Greater London.* [Online] October 2020. [Cited: 2020 October 30.] http://discover-london.gigl.org.uk/?theme=DEFAULT.

33. Transport for London. Silvertown Tunnel Preliminary Environmental Information Report: Chapter 16 Water Environment . *Transport for London.* [Online] October 2015. [Cited: 9 November 2020.] http://content.tfl.gov.uk/peir-ch16-water-environment.pdf.

34. Environment Agency. Water for life and livelihoods Part 1: Thames river basin district - River basin management plan. *Environment Agency.* [Online] December 2015. [Cited: 30 October 2020.] https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/718342/Thames_RBD_Part_1_river_basin_management_plan.pdf.

35. Tideway London. Tideway is building the Thames Tideway tunnel - London's new super sewer. *Tideway London.* [Online] October 2020. [Cited: 6 11 2020.] https://www.tideway.london/the-tunnel/.

36. Merck Millipore. Safety Data Sheet for Triton® X-100 108643. *Merck Millipore.* [Online] 8 May 2020. [Cited: 9 November 2020.] https://www.merckmillipore.com/GB/en/product/msds/MDA_CHEM-108643?Origin=PDP .

37. Environmental Protection Agency. Endocrine Disruptors in the Irish Aquatic Environment (2000-MS-2-M1) Synthesis Report. *Environmental Protection Agency.* [Online] 2005. [Cited: 2 November 2020.] https://epa.ie/pubs/reports/research/water/EPA_endocrine disruptors_ERTDI32_synthesis.pdf.

38. Science Education. A surprising number of carrier females are affected by x-linked retinitis pigmentosa. *Foundation Fighting Blindness.* [Online] 4 August 2015. [Cited: 20 October 2020.]

https://www.fightingblindness.org/research/a-surprising-number-of-carrier-females-are-affected-by-x-linked-retinitis-pigmentosa-4601 .

39. RPE65 retinoid isomerohydrolase RPE65. *NCBI.* [Online] 11 October 2020. [Cited: 30 October 2020.] https://www.ncbi.nlm.nih.gov/gene?Db=gene&Cmd=ShowDetailView&TermToSearch=6121.

40. *Foundations of low vision: clinical and functional perspectives.* Corn, A.N. and al, et. Arlington : AFB Press, 2010. 9780891288831.

41. National Institute for Health and Care Excellence. *Voretigene neparvovec for treating inherited retinal dystrophies caused by RPE65 gene mutations [ID1054].* s.l. : NICE, 2019.

42. Retina UK. Homepage. *Retina UK.* [Online] 2018. [Cited: 2 November 2020.] https://retinauk.org.uk/ .

43. Garg, S. Retinitis pigmentosa: Treatment. *Uptodate.* [Online] 16 June 2020. [Cited: 30 October 2020.] https://www.uptodate.com/contents/retinitis-pigmentosa-treatment#:~:text=Vitamin%20and%20nutritional%20supplementation%20therapy%20is%20beneficial%20only,treatments%20include%20gene%20therapy%20and%20retinal%20cell%20transplantation..

44. Lions Eye Institute. Retinal Dystrophy. *Lions Eye Institute.* [Online] 2020. [Cited: 30 October 2020.] https://www.lei.org.au/services/eye-health-information/retinal-dystrophy/#:~:text=Light%20avoidance%20%E2%80%93%20the%20use%20of%20sunglasses%20have,with%20RP%20but%20no%20strong%20evidence%20currently%20exists..

45. RNIB. Sight Loss Advice Service. *RNIB.* [Online] 2014. [Cited: 2 November 2020.] https://www.rnib.org.uk/advice.

46. —. Making the most of your sight. *RNIB.* [Online] January 2019. [Cited: 4 November 2020.] https://www.rnib.org.uk/sites/default/files/SO_Making_the_most_of_your_sight_2019.pdf . 9781444501445.

47. Access Economics. The economic impact of sight loss and blindness in the UK adult population, 2013. *RNIB.* [Online] 2019. [Cited: 17 November 2020.] https://www.rnib.org.uk/professionals/knowledge-and-research-hub/research-reports/general-research/economic-impact-sight-loss.

48. Psychology Today. Dopamine. *Psychology Today.* [Online] 2020. [Cited: 5 November 2020.] https://www.psychologytoday.com/gb/basics/dopamine .

49. Parkinson's UK. The Incidence and Prevalance of Parkinson's in the UK. *Parkinson's UK.* [Online] 2018. [Cited: 17 11 2020.] https://www.parkinsons.org.uk/sites/default/files/2018-01/CS2960%20Incidence%20and%20prevalence%20report%20branding%20summary%20report.pdf.

50. —. Exercise framework for professionals. *Parkinson's UK.* [Online] 2020. [Cited: 5 November 2020.] https://www.parkinsons.org.uk/professionals/resources/exercise-framework-professionals .

51. —. Deep brain stimuation. *Parkinson's UK.* [Online] January 2020. [Cited: 11 November 2020.] https://www.parkinsons.org.uk/information-and-support/deep-brain-stimulation.

52. *The Size, Burden and Cost of Disorders of the Brain in the UK.* Fineberg, N.A. and al, et. s.l. : Journal of Psychopharmacology, 2013.

53. *The economic impact of Parkinson's disease.* Findley, L.J. Suppl:S8-S12, s.l. : Parkinsonism & Related Disorders, 2007.

54. Cancer Research UK. Head and neck cancers statistics. *Cancer Research UK.* [Online] 2010. [Cited: 16 December 2020.] https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/head-and-neck-cancers#heading-Zero.

55. Olver, I. N. Xerostomia: a common adverse effect of drugs and radiation. *CORE.* [Online] August 2006. [Cited: 16 December 2020.] https://core.ac.uk/reader/204814560.

56. NetDoctor. New interactive tool works out how much you've cost the NHS. *NetDoctor.* [Online] 11 December 2017. [Cited: 30 October 2020.] https://www.netdoctor.co.uk/healthy-living/wellbeing/news/a29286/how-much-youve-cost-nhs-tool/ .

57. Lowrth, M. Hereditary Retinal Dystrophies. *Patient Info.* [Online] 11 March 2016. [Cited: 30 November 2020.] https://patient.info/doctor/hereditary-retinal-dystrophies#nav-5.

58. al, Michaelides et. AAV5-RPGR Gene Therapy for RPGR-Associated X-Linked Retinitis Pigmentosa: 12-month Results From a Phase 1/2 Clinical Trial. *MeiraGTx.* [Online] 13 November 2020. [Cited: 14 December 2020.] https://meiragtx.com/wp-content/uploads/2020/11/AAO_2020_RPGR_12_month.pdf.

59. Worldometer. United States Population (Live). *Worldometer.* [Online] 12 November 2020. [Cited: 12 November 2020.] https://www.worldometers.info/world-population/us-population/.

60. —. Japan Population. *Worldometer.* [Online] 1 July 2020. [Cited: 8 December 2020.] https://www.worldometers.info/world-population/japan-population/.

61. —. Countries in the EU by population (2020). *Worldometer.* [Online] 12 November 2020. [Cited: 12 November 2020.] https://www.worldometers.info/population/countries-in-the-eu-by-population/.

62. Markandya, A. OECD Environment Working Papers No. 101: Cost benefit analysis and the environment: How to best cover impacts on biodiversity and ecosystem services. *OECD.* [Online] 3 March 2016. [Cited: 23 November 2020.] https://www.oecd-ilibrary.org/docserver/5jm2f6w8b25l-en.pdf?expires=1606130708&id=id&accname=guest&checksum=357288DCF6FE081F92BF4FFD4A8BB350.

63. Thames Water . Lee Tunnel and Beckton Sewage Treatment Works Extension. *Thames Water .* [Online] May 2008. [Cited: 23 November 2020.] https://www.eib.org/attachments/pipeline/20110483_eia_en.pdf.

64. London Borough of Bexley. SITES OF IMPORTANCE FOR NATURE CONSERVATION REPORT. *London Borough of Bexley.* [Online] December 2016. [Cited: 23 November 2020.] https://www.bexley.gov.uk/sites/default/files/2020-05/Sites-of-Importance-for-Nature-Conservation-SINC-Report-2016C.pdf.

65. Agency, European Chemicals. Adopted opinions and previous consultations on applications for authorisation. *European Chemicals Agency.* [Online] European Chemicals Agency. [Cited: 11 November 2020.] https://echa.europa.eu/applications-for-authorisation-previous-consultations?diss=true&search_criteria_ecnumber=923-960-0&search_criteria_casnumber=-&search_criteria_name=4-%281%2C1%2C3%2C3-Tetramethylbutyl%29phenol%2C+ethoxylated.

66. —. Sorbitan monolaurate, ethoxylated. *European Chemicals Agency.* [Online] [Cited: 13 November 2020.] https://echa.europa.eu/registration-dossier/-/registered-dossier/13525.

67. Chemexper. Chemexper. *Chemexper.* [Online] [Cited: 12 November 2020.] https://www.chemexper.com/.

68. Agency, European Chemicals. [Online] [Cited: 12 November 2020.] https://echa.europa.eu/brief-profile/-/briefprofile/100.105.528.

69. Sorbitan monolaurate, ethoxylated, Brief Profile. *European Chemicals Agency.* [Online] European Chemicals Agency. [Cited: 11 November 2020.] https://echa.europa.eu/brief-profile/-/briefprofile/100.105.528.

70. Millipore, Merck. Merck Millipore. *Merck Millipore.* [Online] [Cited: 12 November 2020.] https://www.merckmillipore.com/GB/en/product/Tween-20,MDA_CHEM-822184.

71. U.S. National Library of Medicine. ChemIDplus: Substance Name: Polysorbate 80. *U.S. National Library of Medicine.* [Online] n.d. [Cited: 24 November 2020.] https://chem.nlm.nih.gov/chemidplus/rn/9005-65-6.

72. Millipore, Merk. Merk Millipore. *Merk Millipore.* [Online] Merk Millipore. [Cited: 12 November 2020.] https://www.merckmillipore.com/GB/en/product/msds/MDA_CHEM-822187.

73. Agency, European Chemicals. Brief Profile - N,N-dimethyltetradecylamine N-oxide. *European Chemicals Agency.* [Online] [Cited: 20 November 2020.] https://echa.europa.eu/brief-profile/-/briefprofile/100.020.055.

74. N,N-dimethyltetradecylamine N-oxide. *European Chemicals Agency.* [Online] European Chemicals Agency. [Cited: 23 November 2020.] https://echa.europa.eu/registration-dossier/-/registered-dossier/14677/6/1.

75. Brooke, D., Johnson, I., Mitchell, R. & Watts. C. *Environmental Eisk Evaluation Report: 4-tert-Octylphenol.* Bristol : Environment Agency, 2005. 1844324109.

76. MeiraGTx. [Online] [Cited: 13 November 2020.] https://meiragtx.com/research-development/pipeline/.

77. Torjesen, I. Drug development: the journey of a medicine from lab to shelf. *Tomorrow's Pharmacist.* [Online] 12 May 2015. [Cited: 13 November 2020.] https://www.pharmaceutical-journal.com/publications/tomorrows-pharmacist/drug-development-the-journey-of-a-medicine-from-lab-to-shelf/20068196.article?firstPass=false.

78. Office for National Statistics. Length of time spent in unemployment. *Office for National Statistics.* [Online] 16 October 2019. [Cited: 13 11 2019.] https://www.ethnicity-facts-figures.service.gov.uk/work-pay-and-benefits/unemployment-and-economic-inactivity/length-of-time-spent-in-unemployment/latest#download-the-data.

79. —. United Kingdom population mid-year estimate. *Office for National Statistics.* [Online] 24 June 2020. [Cited: 13 November 2020.] https://www.ons.gov.uk/peoplepopulationandcommunity/populationandmigration/populationestimates/timeseries/ukpop/pop.

80. The Economics Interface. Valuing the social costs of job losses in applications for authorisation . *The Economics Interface.* [Online] September 2016. [Cited: 9 November 2020.]

https://echa.europa.eu/documents/10162/13555/unemployment_report_en.pdf/e0e5b4c2-66e9-4bb8-b125-29a460720554.

81. Eurostat. Eurostat. *Unemployment by sex, age, duration of unemployment and distinction registration/benefits (%).* [Online] 11 November 2020. [Cited: 17 November 2020.] http://appsso.eurostat.ec.europa.eu/nui/show.do?dataset=lfsa_ugadra&lang=en.

82. European Chemicals Agency. The social cost of unemployment SEAC/32/2016/04. *European Chemicals Agency.* [Online] 20 September 2016. [Cited: 9 November 2020.] https://echa.europa.eu/documents/10162/13555/seac_unemployment_evaluation_en.pdf/af3a487e-65e5-49bb-84a3-2c1bcbc35d25.

83. Office for National Statistics. Table A35: Detailed household expenditure by countries and regions. *Office for National Statistics.* [Online] 24 January 2019. [Cited: 17 November 2020.] https://www.ons.gov.uk/peoplepopulationandcommunity/personalandhouseholdfinances/expenditure/datasets/detailedhouseholdexpenditurebycountriesandregionsuktablea35.

84. Hackney.gov. Britannia site. *Hackney.* [Online] 21 October 2020. [Cited: 11 December 2020.] https://hackney.gov.uk/britannia-site.

85. Morgan Sindall. Britannia Newsletter October 2020. *Hackney.* [Online] October 2020. [Cited: 11 December 220.] https://drive.google.com/file/d/1ukB7JlTNGWHI-pVopCUg4eItvYQpzkro/view.

86. Rodriguez-Monguio, R., Spargo, T. & Seoane-Vazquez, E. Ethical imperatives of timely access to orphan drugs: is possible to reconcile economic incentives and patients' health needs? *Orphanet Journal of Rare Diseases.* [Online] 5 January 2017. [Cited: 19 November 2020.] https://ojrd.biomedcentral.com/articles/10.1186/s13023-016-0551-7#:~:text=Most%20modern%20societies%20consider%20an%20ethical%20imperative%20to,focused%20on%20the%20most%20prevalent%20diseases%20and%20conditions..

87. Department of Health. NHS Constitution. *NHS England.* [Online] 27 July 2015. [Cited: 19 November 2020.] https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/480482/NHS_Constitution_WEB.pdf.

88. Patel, U., Boucher, M., de Leseleuc, L. & Visintini, S. Voretigene Neparvovec: An Emerging Gene Therapy for the Treatment of Inherited Blindness. *PubMed.* [Online] 1 March 2018. [Cited: 20 November 2020.] https://pubmed.ncbi.nlm.nih.gov/30855774/.