SOCIO-ECONOMIC ANALYSIS

Legal name of Applicant(s): *Abbott Laboratories Limited*

Submitted by: *Abbott Laboratories Limited*

Substance: *4-(1,1,3,3-tetramethylbutyl) phenol, ethoxylated*

Use title: *Professional use as a surfactant in the final use of In-Vitro Diagnostic Devices (IVDs) for clinical testing using ARCHITECT, Alinity and ABBOTT PRISM automated analyser systems*

Use number: *1*

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List of Abbreviations

4-tert-OPnEO	4-(1,1,3,3-tetramethylbutyl) phenol, ethoxylated
4-tert-OP	4-(1,1,3,3-tetramethylbutyl) phenol
AfA	Application for Authorisation
AfU	Applied for Use
AoA	Analysis of Alternatives
CC	Clinical Chemistry
CKD	Chronic Kidney Disease
CLP	Classification, Labelling and Packaging
CMIA	Chemiluminescent Microparticle Immunoassay
CMV	Cytomegalovirus
CSR	Chemical Safety Report
ED / EDC	Endocrine Disruptor / Endocrine Disruptor Compound
EC	European Commission
ECHA	European Chemicals Agency
EEA	European Economic Area
EFPIA	European Federation of Pharmaceutical Industries and Associations
eGFR	Glomerular Filtration Rate
EQS	Environmental Quality Standard
ERR	Exposure-Response Relationship
EU	European Union
GGT	Gamma Glutamyl-Transferase
GB	Great Britain, made up of England, Scotland, and Wales
GFR	Glomerular Filtration Rate
HDL	High Density Lipoproteins
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
HIV	Human Immunodeficiency Virus
HTLV	Human T-cell Leukemia-Lymphoma Virus
IA	Immunoassay
IgG	Immunoglobulin G
IVD	*In-Vitro* Diagnostic Device
IVDD	*In-Vitro* Diagnostic Medical Device Directive
IVDR	*In-Vitro* Diagnostic Medical Device Regulation
kg	Kilogram
L	Litre

LAD	Latest Application Date
LDL	Low Density Lipoproteins
N/A	Not applicable
NPV	Net Present Value
NUS	Non-Use Scenario
OPE	Octylphenol Ethoxylate
PEC	Predicted Environmental Concentration
QC	Quality Control
R&D	Research and Development
RAC / SEAC	Committees for Risk Assessment /Socio-Economic Analysis
REACH	Regulation (EC) 1907/2006 on Registration, Evaluation, Authorisation and Restriction of Chemicals
RFP	Request for Proposal
RMM	Risk Management Measure
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2
SD	Sunset Date
SDS	Safety Data Sheet
SEA	Socio-Economic Analysis
SOP	Standard Operating Procedure
STP	Sewage Treatment Plant
SVHC	Substances of Very High Concern
t	Tonne
TSH	Thyroid Stimulating Hormone
TPM	Third Party Manufacturers
UK	United Kingdom, made up of England, Scotland, Wales and Northern Ireland
UVCB	Chemical Substances of Unknown or Variable Composition, Complex Reaction Products and Biological Materials
WHO	World Health Organisation
WDU	Wide Dispersive Use
WWTP	Wastewater Treatment Plant
yr	Year

Declaration

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

Also, we, Abbott Laboratories Limited, request that the information blanked out in the "public version" of the Socio-economic analysis is not disclosed. We hereby declare that, to the best of our knowledge as of today, **30th September 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:

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1. Executive summary of Socio-economic Analysis

1.1 Background

Abbott is a worldwide healthcare company and has a broad range of branded generic pharmaceuticals, medical devices, diagnostics, and nutrition products. The Company's diagnostics division provides immunoassays, including blood screening products, and clinical chemistry (CC) tests. Its medical tests and diagnostic instrument systems are used worldwide by hospitals, laboratories and blood banks for clinical diagnosis and monitoring diseases. The diagnostics division manufactures a broad range of tests, including SARS-CoV-2, HIV, hepatitis, thyroid function, fertility and pregnancy, cardiology, renal and metabolic markers, therapeutic drug monitoring, detection of drugs of abuse, clinical chemistry assays and other indicators of health.

4-(1,1,3,3-tetramethylbutyl)phenol, ethoxylated, covering well-defined substances and UVCB substances, polymers and homologues (hereafter "4-tert-OPnEO" or "the substance") is used to produce In-Vitro Diagnostic Medical Devices, which are distributed by Abbott Diagnostics GmbH, a distribution centre in Germany, for use by healthcare professionals in Great Britain (GB) and worldwide. Abbott Laboratories Limited is applying for a bridging application for the downstream use of IVD reagents and test kits containing 4-tert-OPnEO on behalf of its GB customers.

1.2 Discussion on the length of the review period in the AfA

A 5.5-year review period (through 4-Jan-2028) is requested for the Customer use of IVD reagent kits to align the authorisation of products supplied to customers in GB with the review period proposed by the ECHA Technical Committees (7-years ending 4-Jan-2028). The entire substitution process involves extensive testing with the substituted reagents, to verify performance of each individual assay, followed by submission to, and approval from, regulatory authorities prior to distribution in the individual countries globally. In addition, the Applicant's customers need time to perform cross-over studies as required per individual laboratory procedures using both versions of the reagents. Implementation of the IVDR (Regulation (EU) 2017/746) may cause delays as its requirements coincide with the Applicant's substitution project. Considering the need for complete internal validation of the alternatives within a broad range of approximately 200 IVD products and the lengthy global regulatory approval timeframes combined, substitution of the 4-tert-OPnEO in IVDs is not possible before the Sunset Date. Consequently, the Applicant requests approval for a bridging Authorisation with a review period of 5.5 years (through 4-Jan-2028).

1.3 Comparison of costs and benefits

The economic impacts from a refused authorisation affect the revenue and profit losses to the Applicant from GB. A refused authorisation would affect the Applicant's customers, who could face increased costs to find alternative suppliers of testing instruments and IVD kits. Over 150 employees could lose their jobs in the event of an authorisation being refused and the social cost of the unemployment would be considerable.

A granted authorisation would allow the Applicant to continue offering high-precision IVD tests to their customers to carry out tests necessary for the diagnosis of serious health conditions and for the required screening of life-saving blood donations. The Applicant will continue providing their more than 130

GB customers with IVD kits to run 100-1,000 (*i*) million clinical chemistry and 10-100 (*i*) million immunoassay tests. At the same time, their customers will continue testing 100% blood and plasma donations of GB. Due to the integral nature of the Applicant's instrument systems in laboratory testing, conversion to a replacement system would be a lengthy process for laboratory customers and could cause shortages in testing and in available blood components.

In the Non-Use Scenario, the Applicant's GB employees would lose their jobs, because the Applicant's operations would cease in GB. The unemployment created from a refused authorisation would have a considerable social cost to GB professionals and the GB society in general. Table 1-1 summarises the quantified costs and benefits from a refused authorisation for the applied for use, comparing prevented emissions with the expected negative economic impacts for the Applicant in Great Britain.

Table 1-1 Net profits lost per kg of 4-tert-OPnEO emissions prevented in the NUS

Impact over review period	Use 1
Review period	5.5 years
GB prevented emissions (kg)	227
GB economic impacts (£ million)	10-100 (*d*)
GB social costs of unemployment (£ million)	10-100 *i*
Impacts per kg 4-tert-OPnEO in GB (£/kg)	116,719

The cost of a refused authorisation per kg of prevented 4-tert-OPnEO emissions is over £116,000 per kg for GB impacts. The economic costs include the expected net profit losses for the Applicant as well as the social costs of unemployment for the Applicant's employees that would lose their jobs. In addition, the cost to replace the Applicant's instruments would be a significant economic impact.

The current substitution plan of the Applicant aims to remove 4-tert-OPnEO from reagent solutions. This would require only a small fraction of the cost of a refused authorisation. For comparison, the cost of the project for substitution in the reagents across the EU is £10-100 million (£ *f* million), equating to approximately £65,005 per kg 4-tert-OPnEO. With GB sales being 1-25% (*d*) of the Applicant's EU sales, the cost of substitution used for this analysis will be proportional or £1-10 million (£ *f* million), equating to approximately £6,566 per kg 4-tert-OPnEO. Compared to the Applicant's efforts, a refused authorisation is a less cost-effective option for the use applied for. A refused authorisation, as a measure to reduce emissions of 4-tert-OPnEO would bring diminishing returns and would be most effective during the first few years after the Sunset Date as a major portion of the Applicant's 4-tert-OPnEO usage would be substituted.

Overall, it is considered that a refused authorisation for the use examined in this SEA, would have a disproportionate impact to the Applicant, their customers, their employees and, most importantly, the lives of patients who are in need of blood transfusion and blood products (e.g. emergency or operations) and those who are being tested for serious diseases and conditions (e.g. SARS-CoV-2, thyroid or cancer) with the immunoassay and clinical chemistry IVD kits of the Applicant. This SEA shows that the benefits of authorisation for this use outweighs the risk to the environment.

2. Aims and Scope of the SEA

2.1 Aims and scope of the SEA

2.1.1 Regulatory background for 4-tert-OPnEO

IVD kits containing 4-tert-OPnEO are used by healthcare professionals in GB to analyse patient biological samples, to detect the presence of medical conditions (e.g. diabetes, HIV) and to screen blood samples intended for transfusion. Therefore, this substance is the focus of this socio-economic analysis.

The substance was originally added onto Annex XIV of EU REACH (Authorisation list) because it breaks down to 4-tert-Octylphenol that has endocrine disrupting properties for the environment. Annex XIV of EU REACH was retained in UK REACH (The REACH etc. (Amendment etc.) (EU Exit) Regulations 2019; SI 2019 No. 758) with the same Latest Application Date (LAD) and Sunset Date (SD). In this instance the Applicant is able to benefit from transitional provisions introduced in The REACH etc. (Amendment etc.) (EU Exit) (No. 3) Regulations 2019; SI 2019 No. 1144, allowing for adjustment of the LAD and SD to 1st July 2022.

4-tert-OPnEO was included in the 5th ECHA recommendation of substances for inclusion in the Authorisation List, on 6 February 2014 [1] and was included in the Authorisation List on 4 July 2017. Table 2-1 shows the Annex XIV entry for the substance.

Table 2-1: Annex XIV substance details

Entry No	Substance	Intrinsic properties	Latest Application Date	Sunset Date
42	4-(1,1,3,3-Tetramethylbutyl) phenol, ethoxylated (covering well-defined substances and UVCB substances, polymers and homologues)	Endocrine disrupting properties (Article 57(f) - environment)	1st July 2022	1st July 2022

Abbott applied for authorisation to ECHA from its legal entities in Ireland and Germany prior to the Latest Application Date as per the EU REACH, with a final opinion by RAC/SEAC completed in December 2021. As a result of the UK exit from the EU, an authorisation package is required for GB. Therefore, this Socio-economic Analysis will focus on the impact on the GB downstream user only.

2.1.2 SEA requirements and aims

The purpose of this SEA is to demonstrate that the continued use of 4-tert-OPnEO in the following use outweighs the risk to the environment:

- USE 1. Professional use as a surfactant in the final use of In-Vitro Diagnostic Devices (IVDs) for clinical testing using ARCHITECT, Alinity and ABBOTT PRISM automated analyser systems.

The endocrine disruptive effects of the substance's breakdown products do not have an identified threshold. As it is not possible to show that risks from use of 4-tert-OPnEO are adequately controlled, this Application for Authorisation (AfA) will follow the socio-economic route. The SEA will demonstrate that the benefits of continued use of the substance for the use applied far outweighs the risks, according to articles 60(3) and 60(4) of REACH, during the requested review period of 5.5 years for the customer use of IVD reagent kits. As this is an endocrine disruptor for the environment, the SEA

will also show that a refused authorisation is not a cost-effective option for reducing emissions of 4-tert-OPnEO to the environment.

2.1.3 Temporal and geographical scope

Within this SEA, a review period of 5.5-years (through 4-Jan-2028) will be assessed, based on the time required to complete substitution based on the Applied for Use as follows:

- Customer use of IVD reagent kits will be examined over a 5.5-year review period, which will enable the Applicant to complete the extensive validation/verification activities and required regulatory approvals by multiple countries around the world, in order to substitute the 4-tert-OPnEO from the reagents. A 5.5 -year review period is required to bridge the gap to complete the substitution due to the large number of products affected, the complexities of the testing verification process, the regulatory requirements for IVD products and the alignment to the EU authorisation review period, as will be discussed in Section 2.5.

The Applicant maintains a diverse distribution network. This SEA will address the products associated with the Core Diagnostics at Abbott, which are an array of immunoassay and clinical chemistry instrument platforms, tests, and services. The individual IVD kits are distributed to GB customers. Therefore, this SEA will analyse the significant impact to the distribution of the products in GB countries in the event of a refused authorisation.

2.2 Information on the Applicant's operations and products

2.2.1 The Applicant

Abbott is a global healthcare company that supplies diagnostic products, medical devices, nutritionals and branded generic pharmaceuticals. It employs approximately 103,000 employees worldwide and in 2018 had a combined sales value of $30.6 billion [2]. The Core Diagnostics at Abbott which includes Core Laboratory and Transfusion Medicine, impacted by the authorisation of 4-tert-OPnEO, is a division of the Abbott Diagnostics Business.

Abbott Laboratories Limited is a legal entity of the Abbott Core Diagnostics Division which is applying for Authorisation on behalf of their professional downstream users in GB for the use of 4-tert-OPnEO in reagent solutions.

The Applicant distributes more than 600 different IVD kits to over 150 countries, including the United Kingdom, through a central distribution centre in Wiesbaden, Germany. This socio-economic package will focus on the impact to downstream users within GB.

2.2.2 The Applicant's assays and products

The Applicant manufactures *In-Vitro* Diagnostic Medical Devices (IVDs) that are used to diagnose and monitor a wide variety of diseases as well as other health indicators, with many of these devices depending on 4-tert-OPnEO.

The IVD business is highly regulated and requires approval by regulatory agencies prior to the product being placed on the market in that country. The approvals range from a notification to a government agency, to a full inspection of the regulatory submission with an onsite inspection. The approval duration is vastly different for the various countries, ranging from a few days to upwards of 18 months. Any change to an approved product requires an assessment of the additional regulatory approvals

required. The substitution of the 4-tert-OPnEO has been assessed and requires approval from numerous countries prior to placing the amended product on market in those countries.

The placing on the market and use of IVDs is regulated in the EU under Directive (EU) 98/79/EC on *in-vitro* diagnostic medical devices (IVDD) which is being repealed and replaced by the *In-Vitro* Diagnostic Regulation (EU 2017/746) (IVDR) by 2022. The regulation of IVDs aims to ensure that IVDs do not compromise the health and safety of patients, users and third parties and attain the performance levels specified by the manufacturer. As such, before a manufacturer can place an IVD product onto the market or make a change to an existing IVD product, they must meet a defined set of regulatory requirements and gain marketing approvals. The Applicant manufactures and supplies approximately 200 IVD products that would be required to complete regulatory approvals for any change resulting from the substitution of 4-tert-OPnEO. As such the Applicant must include the specific IVD regulatory requirements into their substitution plan for 4-tert-OPnEO. The EU IVDR did not take effect during the transition period and will not be transposed into law in GB. Therefore, registrations are required for IVDs being placed on the market and any changes to products will meet the requirements for law in GB.

During the review period for Professional use of IVD reagent kits, the Applicant will be substituting 4-tert-OPnEO from their products, where possible. At the same time, they will have to conform to the requirements of the IVDR and evaluate the products accordingly.

Definition of an IVD

According to the IVDR [3], an *in-vitro* diagnostic (IVD) medical device is:

> *"any medical device which is a reagent, reagent product, calibrator, control material, kit, instrument, apparatus, piece of equipment, software or system, whether used alone or in combination, intended by the manufacturer to be used in vitro for the examination of specimens, including blood and tissue donations, derived from the human body, solely or principally for the purpose of providing information on one or more of the following: (a) concerning a physiological or pathological process or state; (b) concerning congenital physical or mental impairments; (c) concerning the predisposition to a medical condition or a disease; (d) to determine the safety and compatibility with potential recipients; (e) to predict treatment response or reactions; (f) to define or monitoring therapeutic measures."*

The IVDR further provides a definition of an IVD kit (Article (2) (11)) as:

> *"a set of components that are packaged together and intended to be used to perform a specific in vitro diagnostic examination, or a part thereof;"*

The Applicant's products are a comprehensive array of immunoassay and clinical chemistry instrument platforms, tests, and services. These instrument platforms are then used with automation, analytics and informatics to drive greater efficiencies in diagnostic testing laboratories. The instrument systems are fully automated analysers operated by trained healthcare professionals in hospitals, reference labs, blood banks, physician offices and clinics. IVD reagent kits are exclusively designed for use on a particular instrument system to generate a test result associated with the test being performed. Many of the components of the IVD kit produced and distributed by the Applicant, including reagents, calibrators and controls, contain 4-tert-OPnEO.

The two main categories of IVD tests run on the Applicant's instrument systems are immunoassays and clinical chemistry and are described briefly below.

An **Immunoassay** (IA) is a test that uses antibody and antigen complexes as a means of generating a measurable result. The test utilises one or more select antibodies and/or antigens to detect analytes of interest. The analytes being measured may be those that are naturally present in the body (such as a thyroid hormone), those that the body produces but are not typically present (such as a cancer antigen), or those that do not naturally occur in the body (such as a medication or a substance of abuse). Immunoassays can also detect viruses and/or the body's immune response to infection, serving as the basis for tests serving the Transfusion (blood and plasma screening) market. The Applicant's immunoassay tests which are dependent on 4-tert-OPnEO are based on the CMIA (chemiluminescent microparticle immunoassay) technology. CMIA is a technology used to determine the presence of antigens, antibodies, and analytes in samples.

Clinical chemistry (CC) tests measure concentrations of biologically important ions (salts and minerals such as sodium and iron), small organic molecules (such as cholesterol, bilirubin, or certain substances of abuse), as well as large macromolecules (primarily enzymes or other proteins, such as lipases and high- or low-density lipoproteins) and therapeutic drugs. The Applicant's clinical chemistry tests, dependent on the use of a surfactant such as 4-tert-OPnEO, are based on the photometric method which is the process used by the Applicant's instrument systems to measure sample absorbance for the quantification of analyte concentration.

2.2.3 IVD kit components

An IVD kit consists of a number of components, each with a specific role in the analysis of patient or blood samples. In addition to the IVD kit components, the instrument system requires use of system solutions. These test components fall within three main categories:

- Reagent kits and their subsequent components
- Calibrators and controls
- System solutions, called "onboard solutions" in clinical chemistry kits and "bulk solutions" in immunoassay and blood screening kits

Figure 2-1 IVD kits and bottles manufactured by the Applicant (credit: Abbott)

Reagents, calibrators, controls and system solutions are reactants in the immunoassay/clinical chemistry processing steps and are manufactured for use exclusively with the Applicant's automated instrument systems. Each assay has a specific reagent kit with components for the analyte being measured. The components generate the signal to be measured within the instrument.

Reagent kits and components

An immunoassay reagent kit contains a minimum of two components: a solid phase or 'capture' component to bind the analyte in question, and a detection moiety. Paramagnetic microparticles are coated with a capture molecule (antigen, antibody, or viral particle), which is specific for the analyte being measured. The detection component is an acridinium-labelled conjugate that is used to generate the assay signal. An immunoassay reagent kit may also contain additional components, such as pre-treatment or assay specific diluents, depending on the specific analyte assay design.

Clinical chemistry reagent kits are one or more cartridges that contain all the necessary chemicals and/or enzymes needed to perform the analysis. 4-tert-OPnEO is used in many of the reagent kit components and is a constituent of the final formulations.

Calibrators and Controls

Calibrators are solutions with known values to establish the relationship between the amount of signal produced in the assay and the analyte concentration.

Controls are samples that contain known concentrations of analyte and are used to monitor the accuracy and precision performance of an assay and an instrument system.

These test components generally do not contain 4-tert-OPnEO, but a few do contain the substance. Essentially all immunoassay and clinical chemistry IVD kits utilise calibrators and controls.

System Solutions

Onboard solutions are used on the clinical chemistry analysers to wash the sample and reagent probes, mixers, and reaction cuvettes. Onboard solutions do not contain 4-tert-OPnEO.

Bulk solutions are liquid solutions provided in large quantities that are used in sample processing on the Applicant's immunoassay systems. They are an essential part of the functioning of each immunoassay run on the analyser. Three bulk solutions are loaded onto the processing module or instrument:

- Pre-Trigger Solution is a hydrogen peroxide solution used to split the acridinium dye off the conjugate bound to the microparticle complex. This process prepares the acridinium dye for the addition of Trigger Solution. A surfactant is essential for the proper functioning of this solution, which is required for use with every immunoassay. The Pre-Trigger Solution does not contain 4-tert-OPnEO.
- Trigger Solution is a sodium hydroxide solution used to produce the chemiluminescent reaction that provides the final read. A surfactant is essential for the proper functioning of this solution, which is required for use with every immunoassay. The Trigger Solution does not contain 4-tert-OPnEO.
- Concentrated Wash Buffer is a solution containing phosphate buffered saline. Wash buffer is used throughout assay processing and is pumped to the sample and reagent pipetting assemblies and the two wash zones. The wash buffer does not contain 4-tert-OPnEO.

The performance of an IVD assay is dependent upon the use of reagents, calibrators and controls designed for the particular analyte and the system solutions when performed on the associated instrument system. The presence of Pre-Trigger and Trigger solutions on the function of an immunoassay is critical, as a measurable signal cannot be generated without these solutions. The reagents are designed for use on a particular instrument and are not interchangeable with reagents for another system.

Figure 2-2: System Solution bottles for ARCHITECT (left) and Alinity (right) (credit: Abbott)

2.2.4 Instrument systems

The Applicant manufactures instrument systems that serve the Clinical Chemistry, Immunoassay Core Laboratory and Transfusion (blood and plasma screening) markets. The Applicant has three different instrument systems in use in GB, namely ARCHITECT, Alinity and ABBOTT PRISM. These instruments are used by hospitals, reference laboratories, blood banks, physician offices and clinics. Different models of these systems are available to customers, depending on the throughput required for the laboratory test load.

The following types of dedicated instrument systems are currently marketed by the Applicant.

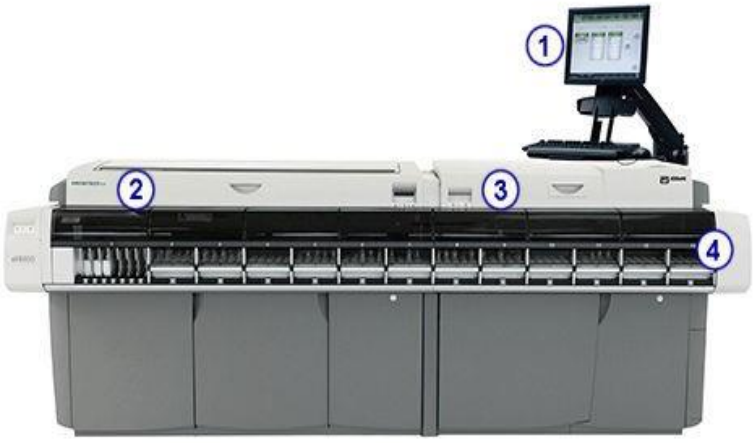
- Immunoassay analysers, i.e., analysers performing the full suite of immunoassay and/or blood and plasma screening tests.
- Clinical chemistry analysers, i.e., analysers performing clinical chemistry tests and homogenous immunochemistry tests. These analysers are capable of running third party manufacturer reagents.
- Integrated analysers, i.e., analysers physically joined to form a single processing unit. This can include linking a clinical chemistry and immunoassay analyser to increase laboratory efficiency.

ARCHITECT systems

The ARCHITECT system is currently the Applicant's most widely distributed system within GB. Individual modules are designed for clinical chemistry (*c* series) and immunoassay (*i* series), with different models allowing for different high-volume throughputs. The modular design of the ARCHITECT family of analysers allows multiple processing modules to be physically joined to form a single, integrated workstation or system. The processing modules joined determines the system configuration.

When integrated, ARCHITECT systems can run both clinical chemistry and immunoassay tests. They are used in hospital and clinical laboratories to run in-house patient sample tests, by blood banks, which screen donated blood samples, and by independent reference laboratories offering testing services to patients and healthcare professionals. The *i* series analyser is designed to use assays developed by the Applicant only, while the *c* series analyser allows testing of third-party reagents on the instrument when validated by the instrument user per laboratory procedures. A standard core laboratory immunoassay analyser will generate approximately 5.5 L of liquid waste per hour, while a clinical chemistry analyser will produce between 15 – 53 L per hour depending on the system and throughput.

Figure 2-3 below depicts the primary components of an ARCHITECT integrated system.



1. System control center: Computer system that provides user control of the processing module(s) and related components through a centralized interface. The computer may be located on a stand or inside the right-side cover of the *i* System processing module.

2. *Processing module (c System)*: Diagnostic module that performs sample processing using photometric methods.

3. *Processing modules (i System)*: Diagnostic module with priority processing capability that performs sample processing using the CMIA (chemiluminescent microparticle immunoassay) method.

4. RSH - robotic sample handler: Transport module that presents samples to the processing module(s) for analysis and retest

Figure 2-3: Primary components of an integrated ARCHITECT system (credit: Abbott)

Alinity systems

The Alinity ci System is a harmonised family of fully automated analysers, that offers modules for clinical chemistry and immunoassay analyses. The system is scalable allowing multiple analysers to be joined based on the needs of a particular test laboratory. This includes joining up to four immunoassay and/or clinical chemistry modules to create a fully integrated test system with a single user-friendly interface. Like the ARCHITECT, the Alinity i series analyser is designed to use reagents developed by the Applicant only, while the c series analyser allows limited testing of third-party reagents on the instrument when validated by the instrument user per laboratory procedures.

The Alinity s System is a high-volume, automated, blood-screening analyser that is designed to determine the presence of specific antigens and antibodies by using chemiluminescent microparticle immunoassay (CMIA) detection technology. The system performs high-throughput routine and priority processing that features continuous access and automated retesting. The Alinity s System is intended to produce donor specific and other routine specimen results based on the available menu. The Alinity s System offers infectious disease immunoassay test panels exclusively, such as HIV, Hepatitis B and Hepatitis C. It is intended to be used in donor screening, plasma and plasmapheresis screening, at organ donor centres, hospitals, and reference laboratories. The Alinity instruments generate a liquid waste volume of 8-18 L per hour immunoassay analysers, and up to 30 L per hour for the clinical chemistry analyser depending on the throughput.

ABBOTT PRISM systems

The ABBOTT PRISM System is a high-volume, fully automated immunoassay analyser designed to enhance the safety of blood and plasma donations. It was developed by Abbott in 1995 and has been used by customers continuously since then [4]. This instrument consolidates much of the manual testing of the blood and plasma donation screening process into a single system. The analyser is designed to detect the presence of specific antigens and antibodies - with a focus on HIV, Hepatitis B, Hepatitis C and other blood borne pathogens - by using chemiluminescent immunoassay technology. The system performs batch/continuous access and STAT (immediate) processing. The ABBOTT PRISM system is used by blood banks, hospitals, organ donor centres and blood banking reference laboratories worldwide to screen donor blood and plasma samples for transfusion.

Similar to the immunoassays as stated above, individual assays have been developed to measure the relevant analytes. Some of the components of the ABBOTT PRISM assays contain 4-tert-OPnEO.

The ABBOTT PRISM System is in the process of being replaced in the market by the Alinity s System. The reagents utilizing 4-tert-OPnEO will be discontinued during the review period, therefore, substitution efforts will be focused on the reagents associated with the Alinity s system.

Applicant's systems' overview

Table 2-2 shows an overview of the Applicant's instrument systems, their applications and relevant IVD kit components which may contain 4-tert-OPnEO.

Table 2-2: Applicant's IVD kit assays relevant to the AfA

Relevant instrument families	Assay type	Assays relevant to AfA	IVD components with 4-tert-OPnEO
ARCHITECT *i*	Immunoassay core laboratory	Tumour Markers, Thyroid Function Hormones, Fertility/Pregnancy Hormones/Proteins, Individual and Specified Hormones/Proteins, Anaemia Related/Vitamin Tests, Therapeutic Drug Monitoring, Auto-Immune Diseases, Cardiac Markers, SARS-CoV-2	Reagents Calibrators Controls
Alinity i			
ARCHITECT *c*	Clinical chemistry	Enzymes, Substrates, Electrolytes, Specific Proteins, Therapeutic Drug Monitoring, Drugs of Abuse/Toxicology, Rheumatoid-Inflammatory Diseases Markers, Cardiac Markers	Reagents Calibrators Controls
Alinity c			
ABBOTT PRISM	Transfusion	Hepatitis Viruses, Retrovirus, Parasitology	Reagents
Alinity s		Bacteriology, Hepatitis Viruses, Retrovirus, Other Virology, Parasitology	Reagents

2.2.5 Importance of IVD kits for human health

Benefits of IVDs over traditional lab methods

The IVD products available provide information to doctors and patients on a wide range of conditions. They measure markers for inorganic chemistry (electrolytes, toxins and ions), markers for organic chemistry/biochemistry (proteins, lipids, and carbohydrates), as well as indicators for diseases, such as Hepatitis, HIV, cancer, and diabetes.

IVDs are widely used to diagnose, monitor, and assess medical conditions, diseases, or infections, providing outcomes for earlier and more targeted treatment [5, 6]. In addition, IVD tests can be used to assess the potential risk of developing a disease or disorder, to guide patient management and to monitor the progression of a disease or the effectiveness of a therapy.

The tests are carried out on human biological samples, including blood, tissues and other specimens (e.g. urine, spinal fluid) and the results are used in combination with clinical examinations to deliver high quality and accurate medical outcomes [7]. When used in testing of a human sample, IVDs allow for faster testing and for running a larger number of different tests than with traditional manual laboratory methods. Therefore, more patients can be tested with greater speed and accuracy than in the past.

The Applicant's instrument systems have been designed to fully automate the diagnostic testing laboratory by harmonizing the instrument systems and assays with informatics and automation to streamline laboratory operations.

Applicant's IVD assays reliant on 4-tert-OPnEO

The Applicant's IVD products within the scope of this AfA are used in clinical chemistry and immunoassay analyses. Over 600 assays are offered by the Applicant, covering a wide range of conditions, including SARS-CoV-2, HIV, hepatitis, thyroid function, fertility and pregnancy, cardiology, renal and metabolic markers, therapeutic drug monitoring, detection of drugs of abuse and clinical chemistry assays and other indicators of health.

Immunoassays use targeted antibodies to identify enzymes, drugs, hormones and other substances to diagnose a variety of medical problems. Certain immunoassays are used specifically for testing blood and blood products for transfusion. The Applicant's Transfusion business supplies these highly specific assays for detecting transfusion transmitted diseases such as HIV, Hepatitis B and C, Human T-Lymphotropic Virus (HTLV), Syphilis, Chagas and Cytomegalovirus (CMV).

Clinical chemistry assays measure important substances in biological samples including substrates, metabolites, electrolytes, blood gases, etc, to help doctors understand the performance of basic bodily functions. Many of these tests are used in routine medical check-ups to monitor routine body function and provide an overall appraisal of a patient's wellness. Abnormal values in any of the routine tests would signal further investigation, as a result, clinical chemistry is still one of the most important areas for diagnostic testing.

Important sectors using Applicant's IVD assays reliant on 4-tert-OPnEO

Immunoassay tests

The Applicant's immunoassay IVD kits have a variety of applications, including oncology, transplant, cardiovascular and endocrinology applications to name a few. A sampling of some of the disease states evaluated by the Applicant's products are provided below.

Oncology deals with the diagnosis, monitoring and treatment of cancers. The Applicant is a leading manufacturer of IVD assays for prostate, liver and lung cancer monitoring and treatment for patients worldwide. In GB, the Applicant provides approximately [redacted] % of the total oncology assays used by in-vitro laboratory testing facilities. When monitoring patients using oncology assays, common practice is to obtain an initial baseline result reading and then monitor the patient for any changes in the results over time, spanning from weeks to annually depending upon the type of cancer and the treatment plan recommended.

Transplant: Solid organ transplant recipients are placed on immunosuppressant drugs such as Tacrolimus, Cyclosporine or Sirolimus, which suppress the patient's immune system and prevent organ rejection post-surgery. Some of the drugs are used in combination with each other or with other drugs to optimise therapy. Due to the very narrow therapeutic range for the drugs to be effective, careful monitoring of the concentration of the drug within the patient is critical. If too much of a drug is administered, the final concentrations could be toxic for the patient. On the other hand, if the level of the drug is too low, there is increased risk of organ rejection and additional complications including additional surgery or even death. Therefore, a sufficiently sensitive, reliable and consistent method is required. The Applicant is a leading provider of Cyclosporine assays with approximately [redacted] market share in GB.

Cardiovascular: Managing the acute care setting is critical, as emergency services are part of hospital and medical centre offerings. Cardiovascular events are a leading cause of death globally, so being able to accurately and reliably detect biomarkers which help to identify risk in pre-screening and in the critical care areas in case of suspected heart attacks is critical to ensure immediate treatment. The Applicant supplies a highly sensitive Troponin I assay available in GB. This assay is critical for the acute care setting and Emergency Departments for patient cardiovascular event diagnosis. Additionally, the Applicant provides a total of 6 biomarkers which are used for cardiovascular testing and are critical for managing acute care patients and monitoring.

Endocrinology is the study of hormone related diseases and includes many different types of hormones produced from the adrenal glands, hypothalamus, ovaries and testicles, pancreas, parathyroid glands, pineal gland, pituitary gland, thymus and the thyroid gland. These hormones help to regulate many body functions from the immune response to respiration, heart rate, reproductive systems, sleep, temperature, blood sugar and blood pressure. The Applicant is among the global market leaders with best-in-class thyroid function testing. In some areas of the world, the Abbott Thyroid Stimulating Hormone (TSH) assay market share is >[redacted] . Monitoring of TSH is critical to ensure that the thyroid gland is functioning in its purpose of stimulating the production of T3 And T4 hormones. The Applicant's TSH assay is a market leading third generation assay and is useful in the discrimination of patients with true hyperthyroidism and some non-thyroidal illnesses. Furthermore, other thyroid tests offered by the Applicant (Free T4 estimate, Total T4, T-Uptake, and Total T3), combined with the ability to accurately measure low levels of TSH, improve the efficiency of thyroid diagnosis.

Transfusion assays

A subset of the Applicant's immunoassay IVD kits are used specifically in screening donated blood and plasma units for certain infectious diseases to prevent the transmission of these diseases to recipients of blood, blood components, cells, tissues and organs. These do not differ in principle from the core laboratory immunoassays. However, due to their intended use and high volume for critical applications, these are discussed separately. Abbott's Transfusion business supplies these highly specific assays for detecting transfusion transmitted diseases, such as HIV, Hepatitis B and C, Human T-lymphotropic virus (HTLV), Syphilis, Chagas and Cytomegalovirus (CMV).

Blood services and blood banks collect, and store donated blood and blood components before they are distributed to hospitals and clinics through a dedicated network. Donated blood and plasma must be tested for these infectious agents before they can be used in transfusions and the production of other blood products. Therefore, the blood screening products are critical to the availability of safe blood and blood components in GB.

EU Directive 2002/98/EC, as implemented by Directive 2004/33/EC, sets technical requirements for blood and blood components intended for transfusion [8]. Article 4 and Annex III of the Implementation Directive (2004/33/EC) set deferral criteria for medical conditions and infections for potential blood donors. The deferral criteria require the potential blood donor to test negative for a number of infectious diseases such as Hepatitis B and C, HIV-1/2, HTLV I/II and Trypanosomiasis cruzi (Chagas disease) before the donated blood can be used for transfusions. Other criteria include negative results for other infectious diseases, such as syphilis.

In today's medical treatment, patients may be given whole blood or specific blood components required for their condition. The components are red blood cells, white blood cells, platelets and plasma. Whole blood is rarely used for transfusion. Blood component therapy makes clinical sense as most patients require a specific component of blood, such as red cells or platelets, and the dose can then be optimised. Each donation is manufactured into a different component and stored under different conditions

allowing a single donation to benefit several patients. Worldwide standards allow donated blood to be kept for up to 42 days, therefore highly specific assays with a high throughput are necessary to meet the requirements of blood banks. Table 2-3 shows the most common uses of blood and blood components.

Table 2-3: Uses of whole blood and blood components in healthcare

Blood / blood component	Uses
Whole blood	Rapid and massive blood loss cases e.g. during surgery or for accident victims (trauma)
Red blood cells	- Treatment of anaemia. - Replacing lost red blood cells in accidents or during surgery or childbirth - When a genetic condition prevents proper red cell formation by the body. - If the body loses the ability to produce enough of its own red blood cells when undergoing chemotherapy for cancer.
Platelets	- Patients who receive chemotherapy for cancer may need platelet transfusions to help their blood clot effectively. - Patients undergoing stem cell transplant and have not yet engrafted to produce platelets. - Heart surgery patients and victims of serious trauma may need platelet transfusions.
Fresh frozen plasma	- Replace clotting factors which may be depleted in bleeding or infection. - Replace proteins where they are lost due to a large blood loss from trauma and during surgery. - Plasma is used to make purified concentrates. For example: patients often receive treatment with cryoprecipitate immunoglobulin concentrates or albumin made from plasma.
Sources: http://www.hsa.gov.sg/content/hsa/en/Blood_Services/Blood_Donation/Why_Should_I_Donate/Blood_Components_and_Their_Uses.html https://www.nhlbi.nih.gov/health-topics/blood-transfusion https://www.giveblood.ie/Learn-About-Blood/How_Blood_is_Used/	

The Applicant's blood and plasma screening assays are designed to be highly sensitive and highly specific based on design requirements for each assay. Highly specific assays are required to minimize false-positive results (causing unnecessary loss of blood units and donor deferrals) and false-negative results (causing potentially infectious blood to be given to patients). In addition to analytical performance, ABBOTT PRISM and Alinity s deliver the processing speed capable of addressing the throughput and turnaround times in many high-volume laboratories. A high throughput is essential to ensure safety and availability of blood and plasma donations.

The Applicant manufactures IVD assays in the EU, which are distributed to blood banks both in and outside GB. [redacted]

Blood and plasma services across the world depend on the Applicant to supply systems and assays to screen blood and blood products for infectious diseases, such as HIV and Hepatitis, to protect blood supply by ensuring it is safe from bloodborne pathogens. The Applicant offers multiple systems and assays for blood and plasma screening: ABBOTT PRISM, ARCHITECT, Alinity s and Alinity i can be used by blood and plasma services in government, non-profit, and private industries. The primary purpose of the products is to ensure an adequate supply of safe, life-saving blood, plasma, and organs.

Clinical chemistry tests

Clinical chemistry tests measure concentrations of biologically important ions (salts and minerals such as sodium and iron), small organic molecules (such as cholesterol, bilirubin, or certain substances of abuse), as well as large macromolecules (primarily enzymes or other proteins, such as lipases and lipoproteins (HDL or LDL). The Applicant's clinical chemistry tests, dependent on the use of a surfactant such as 4-tert-OPnEO, are based on the photometric method which is the process used by the Applicant's instrument systems to measure sample absorbance for the quantification of analyte concentration.

Use of clinical laboratory test results in diagnostic decision making is integral to clinical medicine. The Applicant offers IVD tests for clinical chemistry analyses that can be used to inform doctors' diagnosis. The analytes detected in those tests reflect many different organs and diseases. Table 2-4 presents some common clinical chemistry analytes offered by the Applicant and what insights they can offer to doctors.

Table 2-4: Common clinical chemistry analytes

Analyte	Type of analyte	Associated conditions and diseases
Calcium (Ca^{2+})	Ion	Wide range of metabolic problems, e.g. vitamin D metabolism, hyperparathyroidism, pancreatitis
Phosphorus (P)	Ion	Increased levels of P in serum may occur in hypervitaminosis D, hypoparathyroidism and renal failure. Reduced levels of P in serum may indicate vitamin D deficiency, hyperparathyroidism and Fanconi's syndrome.
Uric acid	Small molecule (waste products)	Gout, kidney disease, leukaemia. Also used to monitor patients undergoing radiation treatment or chemotherapy
Creatinine	Small molecule (waste products)	Various causes of kidney dysfunction
Albumin	Protein	General indicator of health and nutritional status
Bilirubin	Protein	Increased levels of total bilirubin are indication of liver disorders, such as hepatitis, cirrhosis, haemolytic disorders, several inherited enzyme deficiencies and conditions causing hepatic obstruction.
Gamma Glutamyl-transferase (GGT)	Enzyme	Measured to assess liver disease or damage. It is a very sensitive indicator of any liver disorder. Increased values are indication of biliary obstruction and alcoholic liver disease.
Immunoglobulin G (IgG)	Protein	Quantitation of IgG can be used to evaluate humoral immunity, establish diagnosis and monitor therapy in IgG myeloma, and evaluate patients (adults and children) and those with lymphoma with propensity to infections. Decreased levels are associated with several conditions, including pemphigus, pregnancy, myotonic dystrophy, non-IgG lymphomas or immunosuppressive therapy. IgG values in AIDS patients can range from extremely low to extremely high, depending on clinical stage and disease stage. Elevated levels of IgG are associated with autoimmune diseases, sarcoidosis, chronic liver disease, multiple myelomas and leukaemia.
Immunoglobulin M	Protein	Increased levels may indicate a viral infection, such as viral hepatitis, or conditions such as rheumatoid arthritis, and other chronic disorders. They are also associated with active sarcoidosis, nephrotic syndrome and other conditions.

High Density Lipoprotein (HDL) – Low Density Lipoprotein (LDL) cholesterol	Lipoprotein	Part of cardiovascular risk profile
Phenytoin	Therapeutic drug	The assay is used to monitor levels of the drug, which is used to treat ventricular arrhythmias and seizures.
Theophylline	Therapeutic drug	The assay is used to monitor levels of the drug, which is used to treat acute and chronic asthma symptoms.
Sources: · Abbott Diagnostics, Learning Guide Series: Clinical Chemistry, available online at: https://www.corelaboratory.abbott/sal/learningGuide/ADD-00061345_ClinChem_Learning_Guide.pdf · Package inserts for Clinical Chemistry IVD kits		

The Applicant's clinical chemistry IVD assays are used to assist doctors in making well-informed medical decisions in various situations:

- **Monitor the patient's condition over time**. The Applicant's clinical chemistry tests are a reliable method for monitoring certain markers for a person's nutritional condition and to identify risks of developing chronic conditions, such as diabetes or heart and circulatory problems, in the future. Cholesterol, triglycerides and ions are such examples.
- **Identify the presence of a chronic condition**. The Applicant's clinical chemistry IVD assays are used in measuring concentrations of proteins or enzymes which are indicators of underlying conditions such as liver or kidney diseases.
- **Quickly understand if there is risk** of an acute condition or in emergencies, such as during surgeries. Some of the Applicant's IVD kits are indicators of a condition that could be life-threatening in the short term. For example, elevated levels of D-dimer, a clotting protein, can be an indicator of inappropriately high clotting levels, which may be indicative of deep vein thrombosis or pulmonary embolism.
- **Monitor the levels of drugs administered to patients**. Some drugs have a very narrow window of efficiency, outside of which they are either ineffective or toxic. The Applicant's CC assays provide vital information to doctors to adjust the dosage of the drug accordingly.

2.3 Definition of the "Applied-for Use" Scenario

2.3.1 Introduction

The Applied for Use scenario describes the impacts associated with the continued use of 4-tert-OPnEO during the requested review period, while activities associated with substitution of 4-tert-OPnEO out of the products within the scope of this AfA are completed.

2.3.2 Relevant supply chains

Use of 4-tert-OPnEO by the Applicant to manufacture IVD kits outside GB

The Applicant manufactures IVD kits, which include 4-tert-OPnEO in many of the components, in the manufacturing sites located outside of GB. 4-tert-OPnEO is used to manufacture several components of the IVD kits:

- Reagents, calibrators and controls formulation: Several components of the IVD kits contain 4-tert-OPnEO. Concentration of 4-tert-OPnEO in the reagent solution varies, depending on the assay.

The Applicant manufactures more than 150 IVD kits for use in immunoassay (core laboratory and transfusion) instruments. Approximately 68% of these contain 4-tert-OPnEO in the reagents, calibrators and/or controls. An additional 85 immunoassays are manufactured by Third Party Manufacturers with approximately 60% containing 4-tert-OPnEO. The clinical chemistry IVD kits are formulated by Third Party Manufacturers. Approximately 17% of clinical chemistry IVD kits distributed in GB contain 4-tert-OPnEO.

Applicant's ancillary operations affected by use of 4-tert-OPnEO

Instrument platform manufacturing

The reagents containing 4-tert-OPnEO were exclusively designed for use on instrument platforms provided by the Applicant. To utilise the reagents, an end user procures an instrument from the Applicant, which is installed into the testing laboratory. The IVD kits for use on the instrument are purchased from the Applicant. The assays are designed to run on the instrument system. Instruments are an integral part of generating a result for each IVD kit.

Manufacturing of the instrument systems is performed by non-GB manufacturers. Abbott manufactures diagnostic instruments at a plant in the United States.

Reagents and process solutions formulation without 4-tert-OPnEO

Many products distributed by the Applicant do not contain 4-tert-OPnEO in their formulations. Some are free of the substance and therefore, do not need an authorisation to be marketed in GB.

However, these products, which do not contain 4-tert-OPnEO, would also be affected by a refused authorisation. IVD products from a single manufacturer are usually offered as panels or portfolios (e.g. thyroid panel). Results from a panel offer the necessary information to physicians to make a medical decision. If a panel is incomplete, a physician would not have sufficient information to make a diagnosis. If some of these products become unavailable, the laboratories may opt for an alternative supplier that can provide the entire panel of assays. Having a single platform for running a panel of related tests allows for training and setup efficiency in the clinical laboratory, as a laboratory technician can be trained on a single instrument system.

Maintaining multiple instrument systems to run a panel is inefficient. ARCHITECT and Alinity systems are designed for a single interface for multiple instruments, which can include both immunoassay and clinical chemistry capability. Laboratories usually have limited floor space and may not be able to accommodate multiple instrument systems as the instruments require access to utilities, such as power, water, waste handling.

Commercial offices and ancillary operations

The Applicant operates commercial offices in GB. There are more than 150 [redacted] employees that support the commercial, finance, R&D and quality of IVD products in GB.

Upstream supply chain

The Applicant's GB sales account for 1-10% [redacted]) of their Global Sales. In the event of a refused authorisation, it is not anticipated that upstream, raw material suppliers would be impacted.

Downstream customers: clinics, hospitals, health practitioners, blood banks, etc.

The Applicant's customers are healthcare professionals that analyse patient samples daily, often across multiple shifts. More specifically, the main customers for the Applicant's IVD kits are:

- Core laboratories, based in or outside of hospitals, providing full day services to both adult and pediatric patients. The test menu includes SARS-CoV-2, general chemistries, therapeutic drug testing, endocrine testing (including thyroid monitoring), cardiovascular, and comprehensive emergency toxicology and psychotropic drug testing services, to name a few.
- Blood, plasma and organ banks, which obtain and test blood for transfusion/transplant with the need to test each blood donation for transmissible medical conditions before it is used in transfusion or transplant. The blood is sent to hospitals through dedicated distribution channels.
- Other customers, such as physicians' offices, government agencies, alternate care testing sites and plasma protein therapeutic companies.

The Applicant has supplied laboratories in GB with over 500 instrument systems for use in testing patient samples using the Applicant's IVD kits in 2021.

Table 2-5 shows the expected use of 4-tert-OPnEO by the Applicant's customers in GB until 2028.

Table 2-5: Customer use of 4-tert-OPnEO (kg) through the review period in GB

Year	Use 1 Reagent Releases (kg) prior to Sunset Date	Use 1 Reagent Releases (kg) after the Sunset Date	Pre-Trigger & Trigger Releases (kg) prior to Sunset Date	Total Downstream Releases (kg)
2021	93	0	192	286
2022	44	44	0	88
2023	0	81	0	81
2024	0	57	0	57
2025	0	21	0	21
2026	0	15	0	15
2027	0	10	0	10
2028	0	0	0	0

The reduction in annual usage of 4-tert-OPnEO observed in 2022 is due to the completed substitution of 4-tert-OPnEO in the Pre-Trigger and Trigger System Solutions prior to the Sunset Date. As discussed in Section 2.5.1 below, usage of 4-tert-OPnEO by the Applicant's customers will be reduced as a result of the Applicant's substitution project.

Patients

As mentioned above, 4-tert-OPnEO is used in immunoassay and clinical chemistry IVD kits. Immunoassays are further divided into core laboratory, infectious diseases and blood screening products. In 2018, the Applicant shipped core laboratory and transfusion immunoassay IVD kits sufficient for 10-100 million [redacted] million) individual immunoassay and 100-1,000 million [redacted] million) clinical chemistry tests to customers in GB.

The IVD kits supplied by the Applicant are used to detect and/or monitor a wide range of conditions through the lifecycle of various diseases, as discussed in section 2.2.5. They are used for:

- Screening of donated blood and blood components (e.g. plasma) for presence of infectious agents, such as hepatitis, HIV and syphilis.
- Qualitative IVD test to aid in the diagnosis of SARS-CoV-2 IgG antibody detection
- Diagnosis of disease indicators, such as e.g. tumour markers, inflammatory disease markers, etc.
- Detection of infectious elements, e.g. bacteria, hepatitis viruses, retroviruses, etc.
- Monitoring of molecules critical for health, e.g. electrolytes, urea, etc.
- Monitoring of a patient's condition and of effectiveness of therapy and drugs

Doctors are increasingly using results from IVD testing to support care decisions regarding diagnosis of a patient and selection of a drug.

2.3.3 Key economic figures

Market outlook

The IVD market is dominated by a small number of large companies, including the Applicant. These companies combined supply more than 80% of the IVD kits in GB. These large players aim to offer comprehensive services to their customers, covering all their testing needs with a wide portfolio of assays. The tests are offered as portfolios or arrays and are normally used with each supplier's instrument system(s). Customers of these suppliers do not normally purchase individual assays, but award contracts for services, which include supply of the analytical instrument(s) and assays as required to cover each customer's needs.

The IVD market is supplemented by a larger number of niche IVD manufacturers. These companies offer specialised assays and instruments, which target a very narrow set of analytes and diseases.

The IVD market is well established in the UK, with revenues reaching £819 million in 2017. Overall, the market seems to be experiencing slow growth with an increase of 2% in 2017, according to MedTech Europe [9]. The UK is one of the larger IVD markets, with IVD expenditure averaging approximately 0.4% of total health expenses in the UK and cost approximately £36.9 per citizen.

According to aggregated information collected by the association of IVD manufacturers, MedTech Europe, it was concluded that 4-tert-OPnEO is widely used across all categories of IVDs. However, the report did not state which assays are impacted within each category.

Applicant's sales value

The Applicant's UK sales of blood and plasma screening, core laboratory immunoassay and clinical chemistry IVD kits, instruments and services were £10-100 ([redacted] million in 2018. As this SEA is addressing the impact for GB, the sales related to Northern Ireland will be removed. [redacted] With the removal of Northern Ireland, the Applicant's GB sales of IVD kits, instruments and services is £10-100 (£[redacted] million in 2018.

The Applicant's sales include three elements: instruments; solutions (reagents, system solutions); and services. These are all part of the sales packages offered to customers. The Applicant is supplying the instruments needed to run the assays, along with the reagent kits for particular tests, according to each customer's needs. Finally, there are supporting services, such as e.g. training, maintenance and consulting that are offered as part of the overall package.

Table 2-6 shows an estimation of the Applicant's revenue and profits from sales of IVD kits within GB during the review period. The sales include the costs of the instrument platforms used for carrying out

the tests with the IVD kits. As the instruments were specifically designed for use with the Applicant's IVD kits, loss of market for the kits would lead to loss of market for the instruments as well. In a typical contract between the Applicant and a customer, the Applicant supplies both the testing instrument platform and the IVD kits. Profits are calculated using a 1-10% (*h* net profit margin. The Applicant expects that sales will increase at a rate of 1-10% (*h* through the review period).

Table 2-6: Revenue and net profits from sales of the Applicant's IVD kits in GB for the AfU Scenario (in £ million)

Year	GB			
	Revenue	Profits	Revenue (2021 prices)	Profits (2021 prices)
2021	*d*			
2022				
2023				
2024				
2025				
2026				
2027				
Total to 2027				

Notes:

These values were calculated from the 2018 values from the Applicant's sales, assuming a *h* annual increase in consumption, driven by increased demand.

Over the period (2021-2027), GB sales account for £100-1,000 million (£*d* million) of revenue and £10-100 million (*d* million) of profits. All values are discounted to 2021 year-end prices, using a 4% discount factor, per ECHA's guidance on SEA for authorisation.

IVD marketing and use constraints

IVD kits are mainly sold through mid- to long-term contracts which typically have a duration ranging between 3-5 years and occasionally 5.5 years but may be as short as a year depending on the contract. Once a contract is nearing its end, the customers renew a contract with the existing supplier or re-tender for potentially finding a new supplier.

The standard practice in IVD laboratories is to purchase or lease an instrument which runs the required tests within a panel or portfolio (fertility panel, thyroid panel, etc). Panel are groups of tests that are run together to provide a comprehensive result for the physician. It is more efficient to run these tests as a panel from the same supplier because it is easier to ensure consistency among the individual test results. They also reduce the laboratory complexity and costs since a single platform could be used within the laboratory and separate instrument systems with contracts would not be needed. This also allows the customer to utilise lab floor space efficiently as multiple instrument platforms would not be needed. As these are bulky and expensive instruments, the customers would rather avoid purchasing or leasing an additional instrument to run a limited number of tests, when there could be available other instruments which can offer the full portfolio of assays.

The Applicant's instruments for core laboratory immunoassay and blood screening only utilise IVD kits manufactured by the Applicant. The clinical chemistry instrument systems can run assays designed by a third party for the instrument system with validation activities required by the laboratory.

2.3.4 Environmental impacts in the Applied for Use Scenario

4-tert-OPnEO is considered as being of equivalent concern to an endocrine disruptor substance, according to Article 57(f) of the REACH Regulation, because it degrades to 4-tert-OP, which is a known environmental pollutant and an endocrine disruptor for the environment. The degradation product has a CLP classification as Aquatic acute 1 and Aquatic chronic 1 and usually adsorbs to sediment from where it is slowly released to the aquatic environment.

If Authorisation is granted, GB professional users will continue processing patient samples using IVD kits containing 4-tert-OPnEO through the review period resulting in releases of 4-tert-OPnEO to the environment, through municipal Sewage Treatment Plants (STPs) in various locations across GB. Emissions to the environment will be proportional to the quantity of 4-tert-OPnEO used, with the environmental concentration varying among the regions due to the number of tests per capita, the variable 4-tert-OPnEO content in the solutions and the dilution factor before and after the STP.

Description of releases

Customer use of IVD reagent kits

The users of the clinical chemistry and immunoassay IVD kits are hospitals, clinics, medical labs and blood banks. The tests using the reagents are carried out in the automated instrument systems provided by the Applicant. The bottles or cartridges containing the reagents with 4-tert-OPnEO are loaded and unloaded manually on the instrument, with all other operations carried out automatically by the instrument, including mixing of reagent with samples. Once processing is complete and the sample has been analysed, the contents of the reaction vessel/cuvette are discarded. A continuous discharge of small volumes of reagents occurs throughout the sample processing steps and mixes with large volumes of wash solutions. ARCHITECT and Alinity systems discharge the solutions to liquid waste streams.

The ABBOTT PRISM does not have a liquid waste stream. Used ABBOTT PRISM sample and reagents are retained in a reaction tray which contains an absorbent filter material and the tray is disposed of as solid biohazardous waste, which is treated by incineration in GB. In addition, for ABBOTT PRISM, residual reagent remaining in reagent bottles is collected and treated as clinical waste which is incinerated.

The Applicant evaluated the fate of waste generated at customer sites from testing with the reagent solutions. It was established that liquid discharge from the ARCHITECT and Alinity systems is directed to drain to be treated in the local STP. The release factor to the environment is assumed to be 100%, all of which is released to wastewater.

The quantity of 4-tert-OPnEO used by downstream users in the UK was calculated from the use quantity for the entire EEA (which includes the UK). The UK use quantity was initially calculated from the EEA downstream professional use quantity identified in the Applicant's EU REACH application 0167-02, which included customers in the UK. The use quantity was extracted based on the number of the Applicant's tests distributed in the UK relative to that for the entire EEA. Number of tests is relevant as the EEA use quantity in the Applicant's EU REACH application was based on the average amount of 4-tert-OPnEO per test. The GB use quantity was estimated from the UK use quantity calculated above. The conversion from UK to GB use quantity was made using an adjustment for the percentage of the Applicant's analysers (excluding ABBOTT PRISM quantities) that are used in GB vs total UK

j percent) which are not included in this assessment. See section 9.0.1 of the CSR for the calculations performed.

In 2021, less than 300 kg *c* kg) of 4-tert-OPnEO were consumed in immunoassay and clinical chemistry IVD kits by customers in GB, including 4-tert-OPnEO Pre-Trigger and Trigger quantities.

Table 2-7 shows the quantities of 4-tert-OPnEO estimated to be released by the Applicant's customers in GB from reagents **after** the Sunset Date with a decrease through the review period.

Table 2-7: 4-tert-OPnEO releases by the Applicant's GB customers

Year	Use 1 Reagent Releases (kg) after the Sunset Date
2022	44
2023	81
2024	57
2025	21
2026	15
2027	10
2028	0
Total	227

Over 5.5 years, emissions of 4-tert-OPnEO from the use of the Applicant's IVD kits in GB customer laboratories are projected to be 227 kg.

The Applicant's customers are very diverse and consist of small, local analytical laboratories, small and large diagnostic laboratories in clinics, hospitals and blood banks. The customer testing load ranges from a few tests each day up to several thousand individual immunoassay and clinical chemistry tests each day, in some of the largest customers. The Applicant has customers in all countries within GB.

Used containers / kits containing reagents and/or system solutions, from the ARCHITECT and Alinity instrument systems are disposed as solid waste. Based on information collected on some of the Applicant's customers, the fate of residual waste 4-tert-OPnEO in these containers and vessels varies, but, as a worst-case approach, it is assumed that they are discharged to wastewater. Accordingly, the releases shown in Table 2-7 are likely over-estimated.

Environmental concentrations

Customer use of reagent solutions in IVD kits

Releases from the downstream use of the Applicant's IVD reagents occur through the discharge of the IVD analyser liquid waste to the local area wastewater treatment plants (WWTP). Use of the IVD reagents is widely distributed in hospitals, clinical labs, and blood screening centres across GB. As this is considered a widespread use, the Applicant examined a wide dispersive use calculation and verified this value against four example exposure scenarios. The widespread use assessment was carried out, as described in 9.1 of the CSR, and resulted in a predicted environmental concentration (PEC) of 4.74E-7 OP mg/L for the freshwater compartment, and 4.77E-8 OP mg/L for the marine compartment.

To review this situation, the Applicant evaluated a subset of their downstream user profiles (very high, high, medium, low emissions), receiving STPs and different environmental compartments. The range of these four examples resulted in a lowest predicted concentration of 2.64E-7 OP mg/L for freshwater

(local area #4), 1.68E-8 OP mg/L for marine water (local area #3), and highest predicted concentration of 2.46E-6 OP mg/L for freshwater (local area #1).

As can be observed by the information in Table 2-8 the resulting local concentrations and PECs for fresh and marine water are very low, in the range of ng/l or below.

Table 2-8: Clocal and PEC emission concentrations for emission categories within local areas and the wide dispersive use (WDU) assessment.

Table 2-8: Clocal and PEC emission concentrations for emission categories within local areas and the wide dispersive use assessment										
Assessment	WDU		1		2		3		4	
Emission category	NA		Very high		High		Medium		Low	
Exposure assessment	Clocal	PEC	Clocal	PEC	Clocal	PEC	Clocal	PEC	Clocal	PEC
Freshwater mg/L	4.54E-07	4.74E-07	2.44E-06	2.46E-06	1.72E-06	1.74E-06	NA	NA	2.45E-07	2.64E-07
Sediment (freshwater) mg/kg dw*		4.76E-04		2.47E-03		1.75E-03		NA		2.65E-04
Marine water mg/L	4.54E-08	4.77E-08	NA	NA	NA	NA	1.46E-08	1.68E-08	NA	NA
Sediment (marine water) mg/kg/dw*		4.79E-05		NA		NA		1.69E-05		NA
Sewage treatment plant mg/L		4.61E-06		3.23E-05		3.34E-05		1.48E-06		8.47E-07
Air mg/m^3	2.86E-10	3.12E-09	5.78E-06	5.78E-06	2.24E-06	2.24E-06	8.68E-08	8.97E-08	8.28E-10	3.69E-09
Agricultural soil mg/m^3	1.44E-04	1.44E-04	1.07E-03	1.07E-03	1.07E-03	1.07E-03	4.70E-05	4.71E-05	2.64E-05	2.66E-05

*For sediments, EUSES does not return a local concentration (without regional contribution) and thus no estimate is available (Guidance Chesar 2, Section 25.3)

The four local areas assessed illustrate the range of release rates expected for the downstream use where. Resulting Clocal and PEC across GB would be expected to vary depending on the particulars of individual STPs and receiving bodies of water. The highest concentrations of emissions can be expected to be seen in areas that have higher usage such as large capital cities, with receiving water bodies that may not have high dilution rates (moderately flowing rivers). Higher concentrations could also be expected in medium usage local areas where waste is received by a small STP that discharges to rivers with low flow rates (low dilution). It should be noted that, in selecting these local areas and the parameters to use for the calculation of the environmental concentrations, conservative approaches were used. More specifically, a single STP was used for the very high-volume local area (local area #1), where it is more reasonable to assume that treatment of waste is spread over several STPs. A single STP was selected as a worst-case assumption, as it leads to lower dilution and higher environmental concentrations.

Through both methods of calculations, local areas with specific individual data, or through wide dispersive use calculation, the predicated environmental concentrations are either within the same order of magnitude (Local areas #3 & #4 and WDU measuring E-7 OP mg/L), or one order of magnitude higher (Local areas #1 & #2 measuring E-6 OP mg/L). As a result of this assessment, it can be assumed that the predicated environmental concentrations reflected through the wide dispersive use assessment exposure scenario for ES1 are broadly accurate, given the variation in the Applicant's downstream user profiles and therefore was considered to be an appropriate value for use in overall exposure assessment.

Conclusion on risk characterisation:

Based on hierarchy of control principle the following risk management measures were considered, as shown in Section 9.2.1.3 of the CSR.

Substitution plan:

The Applicant, as described in the Applicant's Analysis of Alternatives, is carrying out a large R&D project, aiming at full substitution of 4-tert-OPnEO from all reagents in immunoassay and clinical chemistry IVD kits.

Due to the large number of affected IVD assays and the requirement to receive regulatory approval for each individual product, it is not possible to substitute 4-tert-OPnEO in all reagents by the Sunset Date. The Applicant prioritised substitution of the product that accounted for 90% of the total 4-tert-OPnEO releases. This product (Trigger) launched in GB in 2020 and is therefore not included in the exposure assessment. The Applicant has a staggered substitution plan for the remaining assays, which will gradually reduce the number of IVD kits that contain 4-tert-OPnEO and the releases of the substance to the environment in GB.

Considerable resources have been allocated to REACH remediation activities by the Applicant, with funding of £10-100 (£*f* million. This is the cost associated with the substitution activities required for approximately 200 products. As discussed in this SEA, the substitution effort was initiated due to the EU REACH regulation. As the GB sales are 1-25% (*d* of the Applicant's EU sales, the cost of substitution used for this analysis will be proportional or £1-10 million (£*f* million). The Applicant is applying appropriate resources to prioritize and expedite substitution of 4-tert OPnEO and other SVHCs in all products.

Minimization of releases and feasibility:

Based on available technology, collection and incineration of waste is the only treatment method available to eliminate releases of 4-tert-OPnEO from the instrument effluent. However, prevention of release to the environment through collection and incineration is not possible at hospital, blood screening and clinical laboratories due to space and infrastructure limitations. It is important to note when considering the feasibility of controlling releases of 4-tert-OPnEO from IVD kit reagent usage at downstream user sites that concentrations in liquid waste are very low (maximum of 0.0001 – 0.001 (0.0004) % directly at the outflow of the analyser in 2021). Therefore, the volume of wastewater will be extremely high relative to the quantity of 4-tert-OPnEO. As a result, local regulations governing disposal generally allow the instrument effluent to be disposed of as non-hazardous wastewater. A standard core laboratory immunoassay analyser will generate approximately 5.5 L of liquid waste per hour, while a clinical chemistry analyser will produce between 15 – 53 L per hour depending on the system and throughput. Given this high volume of liquid waste generated, the analysers in place at downstream user sites are generally plumbed directly to the wastewater drain.

A typical customer will have several such devices that are plumbed directly to drain. Extensive infrastructural upgrades would be required to re-route drainage systems and divert the analyser waste from other facility wastewater. This could involve internal excavation work and navigation through wards, cleanrooms, and other controlled areas. Even if separate drainage systems could be established, in reasonable time and at reasonable cost (which in general we believe is not possible), then it would require large scale collection tanks to be installed externally, with secondary containment and enough room for a tanker lorry to maneuver to make regular wastewater collections. External space considerations would then come into play which again shows the practical infeasibility of waste collection. Hospitals are often limited in external (as well as internal) space.

Some larger customers may have waste treatment incineration facilities on site; however, the capacity of local liquid waste treatment is generally 200kg/d to 1t/d at the very maximum [10]. A single large-scale analyser would therefore generate more waste than the incineration capacity available at even the larger customer sites.

The Applicant is implementing comparable analyser waste containment projects at EU manufacturing sites which will result in temporary disruption to QC testing activities. While this can be accommodated at a manufacturing facility, for example by proactively building inventory to bridge the shutdown period, it is not possible for a clinical laboratory to cease testing without jeopardizing patient care and safety. Downstream users within scope of authorisation cumulatively perform 10-100 million (*i* million) individual immunoassay and 100-1,000 million (*i* million) clinical chemistry tests annually across GB using the Applicant's immunoassay and clinical chemistry systems. Workflow disruption during facility modifications would lead to a delay in generating and reporting test results, which in turn would lead to delayed diagnosis and adverse patient outcomes.

Technical Feasibility of Alternatives to Collection and Incineration:

The logistical aspects of collection and incineration demonstrate the infeasibility of these measures. Accordingly, the Applicant has evaluated the technical feasibility of various treatment technologies that might be deployed at customer sites as an alternative to collection and incineration.

There are no commercially available treatment technologies with proven efficacy in reducing/preventing 4-tert-OPnEO from the liquid waste stream. The Applicant has evaluated two technologies to determine their capability and determined they are not practical/feasible.

Advanced Oxidation Processes: *b*

b

b

Activated Carbon Filtration: *b*

b

None of these alternatives have proven to be viable alternative to incineration. Therefore, the entire quantity of >12,000,000 litres of wastewater would have to be collected and incinerated annually to prevent 4-tert-OPnEO releases from Use 1.

Economic feasibility: As shown in Table 2-9 over 10-100 ([redacted] million litres of wastewater would have to be collected and incinerated annually to prevent 4-tert-OPnEO releases from Use 1. The cost effectiveness would decrease significantly over time. Analyser liquid waste volume will remain constant, whereas the 4-tert-OPnEO concentration will reduce over time as individual products are substituted. The net result is that the incineration cost to prevent 1 kg 4-tert-OPnEO release rises over the review period, exceeding 1-10 ([redacted]) million-pound sterling per kg in 2027. These figures exclude facility modification costs which are expected to far exceed the annual incineration costs.

Table 2-9: Annual cost to incinerate liquid waste to prevent 1 kg 4-tert-OPnEO release from downstream users

Year	kg 4-tert-OPnEO per year	Liquid waste volume (L)	Volume of waste to prevent 1 kg 4-tert-OPnEO release (L)	Incineration cost to prevent 1 kg 4-tert-OPnEO release (£)	Incineration cost discounted to 2021 prices (£)
2022	44	[redacted]	[redacted]	[redacted]	[redacted]
2023	81				
2024	57				
2025	21				
2026	15				
2027	10				
2028	0				

Notes
A 1-10% ([redacted]) annual increase in liquid waste volume, driven by increased demand is
Cost values are discounted to 2021 year-end price, using a 4% discount factor.

Environmental Considerations:

CO_2 emissions from incineration of downstream user waste containing 4-tert-OPnEO is significant and would partially offset the potential environmental benefit of prevented releases of 4-tert-OPnEO. The waste is a very dilute solution, consisting almost entirely of water. The quantities of waste that would be incinerated annually are conservatively estimated to be 10-100 ([redacted]) million litres. It is possible to calculate the CO_2 emissions from the incineration given the following reasoning.

The water in the liquid waste must be vaporized before the 4-tert-OPnEO can be burned in the incinerator, which requires energy. There is energy needed to heat the water from 15 to 100°C. Since the energy required to raise the temperature of one gram of water 1°C (the calorie) is 4.1855 joules [11], the energy required to heat [redacted] m^3 (tonnes) by 85 degrees is [redacted] x 85 x 4.1855 = [redacted] GJ. Secondly, there is energy required for the vaporization, known, as the heat of vaporization, which is a physical property of a substance. It is defined as the heat required to change one mole of liquid at its boiling point under standard atmospheric pressure, expressed as kg/mol or kJ/kg. When a material in liquid state is given energy, it changes its phase from liquid to vapor (the energy absorbed in this process, the heat of vaporization). The heat of vaporization of water is about 2,260 kJ/kg [12]. The energy required to vaporize the wastewater can be calculated as [redacted] x 2,260 = [redacted] GJ.

The total energy to incinerate the wastewater is therefore [redacted] GJ + [redacted] GJ = [redacted] GJ. Assuming that the required energy would be generated using natural gas, the most efficient of the fossil fuels, the CO_2 released by burning enough natural gas to produce [redacted] GJ can be calculated from the specific carbon dioxide emission factor for natural gas, 56.1 kg CO_2/GJ [13]. The carbon dioxide released from the incineration of the [redacted] m^3 (tonnes) of wastewater would therefore be 1,000- 10,000 ([redacted]

tonnes ([redacted] x 56.1). This is for this Applicant only. Adding other IVD manufacturers with high throughput analysers would significantly increase the overall burden at a time when GB is working to reduce greenhouse gas emissions.

Conclusion on liquid waste collection by downstream users:

Given the unique considerations for high throughput, fully automated analyser systems Abbott requests that Authorization is granted to Downstream Users for Use 1 without a condition to segregate the waste streams. It should be considered instead to commit the Applicant to the elimination of the emissions within 5.5 years as documented in the Substitution Plan.

Organisational RMMs: The Applicant has ensured that the system operations manuals provide recommendations for waste handling, stating that each facility is responsible for labelling all waste containers and characterizing its waste stream to ensure waste is disposed of in accordance with the appropriate local, state, and national regulations.

It can be concluded that the Applicant has taken appropriate measures to minimise emissions of 4-tert-OPnEO to the environment to the degree that is technically and practically possible.

2.4 Definition of Non-use Scenarios

2.4.1 Potential Non-Use Scenarios

The Applicant evaluated the possible Non-Use Scenarios (NUS) associated with the Professional use of IVD reagent kits containing 4-tert-OPnEO. In the event of a refused application, the use of 4-tert-OPnEO would no longer be allowed beyond the Sunset Date.

The potential NUS are presented below:

1. **Use 1 – Customer use of IVD reagent kits**: GB customers would no longer be able to utilise the Applicant's reagent kits.
   a. Option A – Reagent substitution prior to the Sunset Date: Substitute 4-tert-OPnEO out of the reagent solutions with sufficient time for the GB downstream users to consume existing reagent inventory containing 4-tert-OPnEO before the Sunset Date.
   b. Option B – Cease GB Reagent Distribution: Cease distribution of IVD kits containing 4-tert-OPnEO to GB downstream users.

2.4.2 Likelihood of potential Non-Use Scenarios

This section will discuss each of the NUS identified above to determine the most likely scenario to move forward for further discussion within this SEA.

Non-Use Scenarios to be examined in the SEA

The NUS below are considered the most likely for the applied for use and will be examined further:

- **Use 1: Customer use of IVD reagent kits**
  - ***Option B - Cease GB Reagent Distribution***
    Distribution of the Applicant's IVD kits would cease to downstream users in GB, causing the loss of GB sales associated with core laboratory IA, transfusion and clinical chemistry IVD kits.

The rationale for selecting the NUS to be explored further is explained below.

Use 1 – Customer use of IVD reagent kits

Option A - Reagent substitution prior to the sunset date

This scenario addresses the Applicant's substitution of 4-tert-OPnEO out of the reagent solutions prior to the sunset date, leaving sufficient time for GB downstream users to consume their existing inventory of IVD kits containing 4-tert-OPnEO for core laboratory, transfusion and clinical chemistry applications. Distribution to GB customers could continue as the substitution of 4-tert-OPnEO would be complete. This option is not feasible as the Applicant would not have an alternative suitable for substitution prior to the Sunset Date, due to the substitution timeline, the number of products impacted, and the country regulatory approvals required, as discussed in the AoA and elsewhere in this SEA. Furthermore, the Applicant's downstream users may need time to complete cross-over studies using both the reagents containing 4-tert-OPnEO and those containing the substituted alternative to demonstrate equivalency of results obtained before and after the product change. Therefore, Option A is not considered likely and will not be discussed further.

Option B - Cease GB Reagent Distribution:

This scenario addresses the discontinuation of distribution to GB customers under a refused authorisation. As a result, an alternative supply of IVD kits not containing 4-tert-OPnEO would be required for GB downstream users, which could cause a delay in patient result generation. Currently, GB accounts for approximately 1-10% [redacted]) of the Applicant's worldwide immunoassay, blood screening and clinical chemistry sales. GB customers would need to move to an alternative instrument system that could support a full testing panel upon the loss of 68% of the immunoassay products manufactured by the Applicant in the EU containing 4-tert-OPnEO. Switching to an alternative supplier may not be possible immediately, as switching suppliers involves publishing a tender, evaluating offers and making a decision. Any new contract would require purchasing/leasing one or more new instruments from the Applicant's competitors. Existing instruments would need to be taken out of service and new instrument installed and qualified. Considering the large number of the Applicant's instruments and reagents currently on the market in GB, it is unlikely that their competitors would be able to provide sufficient numbers of instruments to cover the demand in a short period.

2.5 Information on the length of the review period

2.5.1 Applicant's actions during the review period

Overview

The Applicant has been evaluating a potentially suitable (i.e. technically and economically feasible, and of lower risk compared to 4-tert-OPnEO) alternative for the uses of 4-tert-OPnEO in their IVD kits. The substance is used in:

- The Pre-Trigger and Trigger solutions, which are used with core immunoassay and transfusion IVD kits, are used in the sample analysis to initiate the chemiluminescence reaction that will allow the instrument to detect the presence of biological markers in the sample. Both solutions contained 4-tert-OPnEO, accounting for 192 kg released in GB throughout 2021 prior to the sunset date. Downstream users are converting to a formulation free of 4-tert-OPnEO, with the conversion complete prior to the sunset date. This use accounted for approximately 90% of the 4-tert-OPnEO used in 2018 by the Applicant and which later enters the global markets. As the substitution is complete, this use will not require an authorisation package.

- The reagents, calibrators and controls of IVD kits, supplied to GB customers, account for approximately 227 kgs of 4-tert-OPnEO over the review period. Relevant IVD kits are clinical chemistry, core laboratory immunoassay and blood screening immunoassays for GB consumption.

Substitution efforts

The Applicant intends to substitute the use of 4-tert-OPnEO from their products globally. discussed in the Substitution Plan, work is currently in progress to verify the suitability of the alternative in assays currently using 4-tert-OPnEO. Prior to and throughout the review period, the Applicant has utilised the following steps which are described in detail in the associated AoA and Substitution Plan.

1. **Identification of Alternatives Phase**: Literature review, consultation with suppliers and internal departments for shortlisting alternative surfactants that were likely to be technically feasible. A primary alternative was selected, after screening, for further evaluation.
2. **Technical Feasibility Phase**:
    a. **Preliminary feasibility**: Each product impacted by substitution is manufactured at a small scale with side-by-side batches containing either 4-tert-OPnEO or the primary alternative. Performance of the manufactured product is then evaluated using studies discussed in section 5.2 of the AoA. Where results are favourable, the product moves to the next phase for additional and more thorough evaluation. Where results are not favourable, the product requires additional characterisation to determine whether an alternative concentration or alternative substance will provide the required performance.
    b. **Design verification**: At this stage, full scale production lots of the product are manufactured with the alternative substance. Design verification testing is completed to verify that product manufactured with the alternative substance meets all product requirements and continues to perform in an equivalent manner to product manufactured with 4-tert-OPnEO.
3. **External Clinical Performance Evaluation Phase**: External studies are carried out in a clinical setting, particularly for blood transfusion and screening products.
4. **Regulatory Approval Phase**: Preparation and submission of necessary documentation to regulatory authorities, ensuring conformity of product with the relevant quality, safety and efficacy regulations. Prior to being placed on the market, the product will be required to receive approval in all countries in which the individual product is sold (> 150 countries).
5. **Implementation phase**: Replacement of documents for manufacturing each product with those drafted in the Design Verification phase. The first lots to stock utilising the alternative surfactant will be manufactured and readied for distribution. Final lot using 4-tert-OPnEO substance will be manufactured to allow time for customers to convert to the new formulation.
6. **Customer Conversion Phase**: Product is distributed to customers for use in laboratories generating patient results. In rare cases, additional time may be required for customers to perform cross-over testing studies, as required, by individual laboratory procedures. Cross-over testing studies are performed by downstream users, to demonstrate equivalency of results obtained before and after the product change. Such studies may be warranted if internal design verification and/or validation studies identify a higher-than-expected bias with the new formulation. An example would be studies performed as required, to confirm and/or establish the laboratory's quality control ranges, or normal ranges for patient results. Once a customer has begun utilising the product containing the alternative, they will no longer be able to source the product containing 4-tert-OPnEO.

The Applicant has prioritised substitution of 4-tert-OPnEO in the Pre-Trigger / Trigger solutions, as it accounted for the majority of the Applicant's use of the substance and will complete conversion within GB in 2021. At the same time, the Applicant is carrying out testing in substituting 4-tert-OPnEO in the reagents and from its use in antigen purification.

Substitution efforts cost

Substitution of 4-tert-OPnEO in the Applicant's products is the result of a significant R&D project, as described in detail in the AoA. The overall cost of substitution is approximately £10-100 million (£[redacted] million), which includes the Applicant's R&D activities (labour and materials) and the cost to submit the applications for regulatory approval. The substitution effort was initiated because of the EU REACH Regulation. As the GB sales are 1-25% [redacted] of the Applicant's EU sales, the cost of substitution used for this analysis will be proportional or £1-10 million ([redacted] million).

Similar efforts are being carried out for removal of 4-tert-OPnEO from immunoassay and clinical chemistry IVD kits produced by third party manufacturers for the Applicant. Substitution costs by the third-party manufacturers is expected to be proportional to that for assays manufactured by the Applicant.

2.5.2 Justification for the review period for Use 1 Customer use of IVD reagent kits

The Applicant is seeking a review period of **5.5 years** (through 4-Jan-2028) for the following use:

- Use 1: Professional use as a surfactant in the final use of *In-Vitro* Diagnostic Devices (IVDs) for clinical testing using ARCHITECT, Alinity and ABBOTT PRISM automated analyser systems.

The timeline required to complete substitution and phase out for the Applicant's products is shown in Figure 2-4 and coincides with Applicant's EU authorisation package.

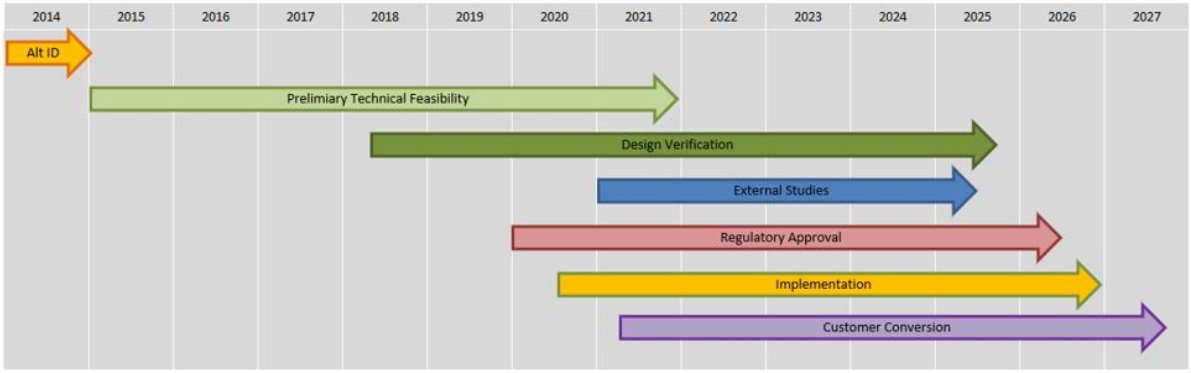


Figure 2-4: Projected timeline for the substitution of 4-tert OPnEO from Applicant's IVD reagents

With approximately 200 products undergoing substitution, the overall timeline is expected to take approximately 14 years from start of research to the end of substitution, to convert all products away from 4-tert-OPnEO. Substitution activities were initiated in 2014, upon funding approval, laboratory set up, and resourcing, with activities expected to continue through to the end of 2027.

An example timeline for a single product is provided in Figure 2-5 .

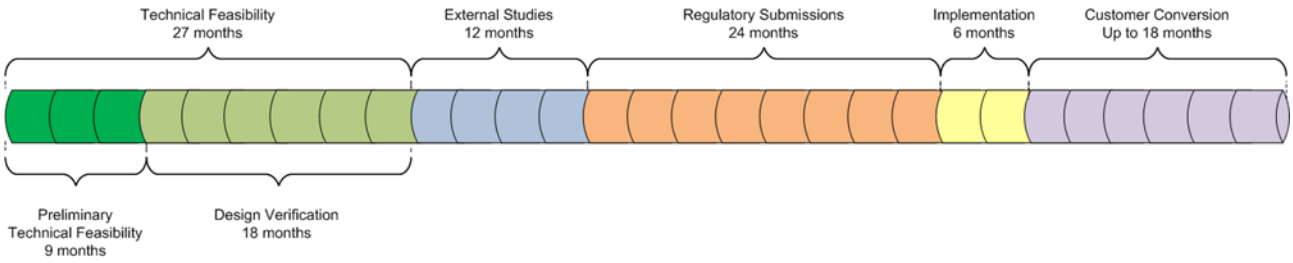


Figure 2-5: Timeline of substitution process for a single assay

There are several parameters that affect the Applicant's substitution effort for 4-tert-OPnEO in their IVD product portfolio and requires the requested review period to 5.5 years, as also discussed in Section 4.2.7 of the AoA.

The Applicant is currently within the Technical Feasibility Phase (Phase 2) of its substitution process. As each product has a specific chemistry and formulation different from any other product, each product needs to complete the entire process as outlined above before substitution is completed. The Applicant has approximately 200 products impacted by substitution, each of which needs to undergo the above process. Constraints in the physical manufacturing plant and instrument testing lab capacity make it impossible to run design verification on all products in parallel.

- **Production of Verification lots**: Production of design verification lots entails the entire multi-step IVD kit manufacturing process starting with antigen production and purification, diluent formulation, microparticle coating, conjugation, blending and bulking, filling and kit pack. The cycle time from start to finish can take several months.
- **Quality and regulatory requirements**: Quality Standards for IVD manufacture dictate that design verification lots be produced in the same production facilities by personnel trained to the same standards as those normally used to produce the IVD products undergoing verification. As a result, design verification lot production must occur in conjunction with normal production of commercial product. As such there is competition between verification and commercial production within the same plant. Therefore, the design verification activity will need to be spread out over a nine-year period beginning in 2019 and running through 2027.

Therefore, for the Applicant's use of the 4-tert-OPnEO in the formulation of IVD and the subsequent end use of these reagents by its customers, the Applicant is seeking a review period of 5.5 years to allow for the complete substitution and for products containing 4-tert-OPnEO to be consumed by customers or to reach their expiry.

In addition to the regulatory submissions required, the main EU quality directive mandating approval activities will become effective during this time. The IVD Directive (98/79/EC) will be repealed and replaced with the IVD Regulation (Regulation (EU) 2017/746) in May 2022. The IVDR entered into force in 2017 and will become completely applicable in 2022 (5 years after entry into force). Leading up to the 2022 date, products being substituted will also be evaluated to determine if additional activities, i.e. performance studies, documentation, etc. are required for resubmission for adherence to the IVDR. As some of the implementing acts are pending publication, the full impact of the IVDR is not yet known. The IVD classification system is being modified and it is expected that approximately 80% of the Applicant's IVD products will need to receive notified body review, where previously, approximately 20% required the review. Not only will this be required for products undergoing substitution to remove 4-tert-OPnEO, but any product distributed in the EU may also need to be submitted. With the implementation date of the IVDR coinciding with the substitution timing, it is expected that delays for some products will be experienced based on the additional activities as well as

the potential delays as notified bodies are reviewing submission for all IVDs distributed in the EU. The EU IVDR did not take effect during the transition period and will not be transposed into law in GB. Registrations are required for IVDs being placed on the market and any changes to products will meet the requirements for law in Great Britain.

The requested 5.5-year review period (through 4-Jan-2028) takes into consideration these additional delays expected related to implementation of the IVDR and alignment to the EU REACH Authorisation package review period.

3. Analysis of impacts

3.1 Environmental impacts

3.1.1 Overview of impacts

Impacts of endocrine disrupting substances and 4-tert-OP

4-tert-OPnEO is listed in Annex XIV to the REACH Regulation because of the formation of degradation products that can have endocrine disrupting properties. It has been found that levels of 4-tert-OPnEO indicate effects in fish, amphibians and invertebrates at low concentrations, particularly regarding fertility and fecundity. The widely accepted definition for endocrine disruptors describes the effects as "exogenous substances that alter function(s) of the endocrine system and consequently cause adverse health effects in an intact organism or its progeny, or (sub)populations" [14].

As a non-threshold substance lacking a risk derivation curve, it is not possible to quantitatively describe the impact as a result of the Applicant's releases.

Description of areas potentially receiving releases of 4-tert-OPnEO

Releases from the downstream use of the Applicant's IVD reagents occur through the discharge of the IVD analyser liquid waste to the local area WWTP. Use of the IVD reagents is widely distributed in hospitals, clinical laboratories, and blood screening centres across GB. Therefore, the areas receiving releases of 4-tert-OPnEO are expected to be representative of all the WWTP receiving bodies of water across GB.

This has been further described within the CSR in Section 9.1, where the Applicant has conducted a standard local area exposure assessment along with an exposure assessment of representative local areas.

3.1.2 Environmental impacts for Use 1 Customer use of IVD reagent kits Non-Use Scenario B – Cease GB Reagent Distribution

Prevented emissions

If an authorisation is not granted for the professional use of 4-tert-OPnEO in reagents of IVD kits, use of the Applicant's IVD kits containing 4-tert-OPnEO in a concentration above 0.1% would cease. As these products constitute approximately 61% of the immunoassays distributed, the entire portfolio of core laboratory, clinical chemistry and blood transfusion immunoassay IVD kits would be discontinued in GB. Table 3-1 shows the prevented emissions from the customer use of the IVD kits over the 5.5-year review period.

Table 3-1: Prevented emissions from GB customers in NUS B - Cease GB Reagent Distribution

Year	Prevented emissions (kg)
2022	44
2023	81
2024	57
2025	21
2026	15
2027	10
2028	0
Total	227

Over the 5.5 year review period (through 4-Jan-2028), the total prevented emissions of 4-tert-OPnEO would be 227 kg from the customer emissions, as shown in Table 3-1 above.

3.1.3 Summary of environmental impacts

Risk minimisation efforts

It should be noted that, as discussed in Section 2.3.4, the Applicant has taken measures to reduce emissions to the degree that is technically and practically possible.

- Efforts are focused on substituting 4-tert-OPnEO in all existing products. Pre-Trigger and Trigger were prioritised, as they account for the highest 4-tert-OPnEO usage in customer sites, with full conversion of GB downstream users completed in 2021. Work on substituting 4-tert-OPnEO in reagents is being carried out concurrently. It is expected that emissions from the use of the reagents will decline until they reach zero at the end of the review period.
- Based on hierarchy of control principles, substitution of 4-tert-OPnEO is considered the primary risk management measure. The Applicant prioritised substitution of the product that accounted for 90% of the total 4-tert-OPnEO releases. This product (Trigger) launched in GB in 2020 and is therefore not included in the exposure assessment.
- There are no commercially available treatment technologies with proven efficacy in reducing/preventing 4-tert-OPnEO from the liquid waste stream.
- Wastewater volumes are very high. 10 – 100 (*a* million litres would have to be collected and incinerated annually in GB. For context, an e alent assessment of EU volumes determined the quantities to be equivalent to a 2.4% increase in the overall European Union hazardous waste incineration stream.
- Hospital and clinical laboratories do not have existing infrastructure or space to establish new infrastructure capable of handling this volume of wastewater.
- Even if they had the space, the disruption during facility modifications would be unacceptable. These laboratories operate 24/7 and provide critical information to support the provision of healthcare services across GB.
- In the timeframe it would take to complete facility modifications (re-routing of drainage networks and installation of large-scale external holding tanks), the Applicant will have completed most of the product reformulations to remove 4-tert-OPnEO.

Prevented risks from the substance

There may be a potential risk to the freshwater and marine aquatic (including sediment) compartments, WWTP and soil for the environments under consideration for the Applicant's downstream users. Species that may be affected include shellfish, gastropods, amphibians and fish species. Furthermore, sediment organisms may be exposed to the 4-tert-OP, either directly, downstream of the effluent, or in the longer term after its adsorption to sediment and soil. Similar holds true for pelagic organisms within affected environments such as fishes which may be exposed via remobilisation of 4-tert-OP from sediment to the water body [15]. 4-tert-OP formed by degradation of 4-tert-OPnEO may accumulate in the affected environment's sediment and short-term exposure to 4-tert-OP may result in effects to aquatic organisms.

As indicated in the Annex XV dossier for 4-tert-OPnEO, there has been a moderate amount of evidence accounting the endocrine disrupting effects on aquatic species. However, research methods are varied, results occasionally contradict one another and results show that 4-tert-OP affects marine species at various life stages (larvae, reproductive life stages and adult life).

Overall conclusions

Overall, use of 4-tert-OPnEO could potentially adversely affect populations of aquatic species in water bodies (freshwater and marine) across GB. Annual release of 4-tert-OPnEO in reagent solutions is at the worst case 93 kg/year in 2021, spread over more than 130 customers throughout GB. The Applicant is committed to substituting 4-tert-OPnEO from the IVD products. Due to the Applicant's substitution efforts, these releases have already begun decreasing and will continue rapidly decreasing until they reach zero by 2028.

3.2 Human health impacts

3.2.1 Impacts to worker's health

4-tert-OPnEO was not included in the Authorisation List for human health risks. Its impacts are limited to the environment, through its degradation to an environmental endocrine disruptor, 4-tert-OP. The human health hazard profiles of 4-tert-OPnEO and 4-tert-OP are shown in Table 3-2.

Table 3-2: Hazard classification of 4-tert-OPnEO and 4-tert-OP

	4-tert-OPnEO	**Octyl phenol (OP)**
EC No / CAS No	618-541-1 / 9036-19-5 618-344-0 / 9002-93-1	205-426-2 / 140-66-9
Endocrine disruption	ED compound for environment*By degradation to OP	Endocrine Disruptor compound for environment
Physicochemical	None	None
Human health	Skin Irritant 2 (H315) Eye Damage 1 (H318) Acute oral toxicity 4 (H302)	Skin Irritant 2 (H315) Eye Damage 1 (H318)
Environmental	Aquatic acute 1 (H400) Aquatic chronic 1 (H410) M factor = 10	Aquatic acute 1 (H400) Aquatic chronic 1 (H410) M factor = 10
Source(s)	Supplier's SDS	Harmonised classification (Index No: 604-075-00-6) [16]
Note: *Classification of 4-tert-OPnEO is based on the classification of the degradation product, 4-tert-octylphenol (4-tert-OP).		

Based on the hazard profiles, it is expected that there is little risk to human health from use of the 4-tert-OPnEO by industrial and professional workers.

The healthcare professionals using the Applicant's IVD kits use strict precautions when operating the equipment, because they are also handling potentially biohazardous materials (human blood and tissue samples). The protection factors of the RMMs used in the medical laboratories are sufficient to contain the risk from 4-tert-OPnEO. Furthermore, there is little to no manual handling of open containers of reagents by the customers' laboratory personnel. So, the change in the risks to human health from use of 4-tert-OPnEO by the Applicant and their customers in case of a refused authorisation will be very low.

Therefore, human health risks to the healthcare professionals using the IVD kits will not be considered further in the SEA.

3.2.2 Health impacts to the general population

Overview

The Applicant's IVD kits are used to diagnose and monitor many medical conditions. IVD tests provide data to physicians for earlier and more targeted treatment than more manual methods. In addition, an IVD may be used to assess the potential risk of developing a disease or disorder and to guide patient treatment. The substance is used in critical components of the IVD, which are used to examine patient samples for diseases such as HIV, hepatitis or cancer and to screen human specimens in blood banks for transfusion-transmitted diseases prior to transfusion into patients.

There are more than 500 of the Applicant's instruments used by GB customers. It was estimated that more than 200 [redacted] million immunoassay, transfusion tests clinical chemistry tests are carried out per year using the Applicant's IVD kits in GB.

In case of a refused Authorisation, the Applicant would no longer be able to supply IVD kits to customers in GB.

It is unlikely that instruments from competitors would be available in sufficient quantities to replace the Applicant's instruments at customer sites. The Applicant holds a significant share of blood donor screening, core laboratory immunoassays and clinical chemistry testing, so it is not considered likely that a sufficient number of instruments would be available immediately to replace the Applicant's base in the GB markets.

Therefore, it is expected that the Applicant's customers could face a critical shortage of tests for transfusion, core laboratory and clinical chemistry diagnostic tests.

Feasibility of substitution and response of competition

The potential IVD kit supply shortage in GB for the NUS would be dependent upon the manufacturing capacity of other IVD manufacturers, as well as the reliance on 4-tert-OPnEO for replacement assays. Based on the significant number of immunoassay, blood screening and clinical chemistry tests used by GB healthcare systems, it is likely that a supply gap would exist for a significant period. Customers would need to identify an alternative instrument system, as reagents are specific to a particular instrument system. Identifying and converting to a replacement system would be an extended process for customers. Elements included in changeover would be:

- Issuing of a request for proposal (RFP) or public tendering process potentially lasting several months; a costly and time-consuming activity by blood and plasma services

- Identification of replacement systems that meet the quality and value requirements of the customer
- Potential redesign of the laboratory and laboratory construction to accommodate new systems (floor design, power usage, water usage, heat dissipation). The cost is laboratory dependent but could be significant.
- Delivery, set-up, and establishing quality control of new systems, including IT / network interfacing. This is typically an involved and time-consuming process, depending on the complexity of the IT environment.
- Validation of new instrument systems.
- Development of updated laboratory Standard Operating Procedures (SOP)
- Training of staff responsible for operating systems

The process above is dependent upon instrument availability. Increasing instrument production requires several layers of supply chain to produce the necessary parts, and allocation of sufficient resources to increase capacity within the manufacturing facility to build the instruments. In addition, increased resources will be required to install and maintain the increased instrument base for other IVD manufacturers. Supply chains are seeing extended shipping durations during the worldwide Covid pandemic. As the Applicant holds a large share of the GB market particularly for blood screening, but also for immunoassay and clinical chemistry testing, it may be difficult to supply a sufficient number of instruments at short notice.

It should also be noted that alternative IVD kits will also be using 4-tert-OPnEO and the timing for completing substitution, if required, is not known for the Applicant's competitors. Based on information that has been collected and aggregated by the IVD manufacturers' EU association, MedTech Europe, 4-tert-OPnEO is widely used across all categories of IVD products. The Applicant's competitors using 4-tert-OPnEO in their IVD kits have applied for authorisation within the EU and may be applying for authorisation in GB. Therefore, it is unlikely that there will be sufficient supply of immunoassay, including blood screening, and clinical chemistry IVD kits at the Sunset Date.

It is thus expected that there will not be available alternative products in the short term for the Applicant's customers and that there will be a shortage in testing capacity for all types of IVD kits, i.e. core laboratory immunoassays, blood screening and clinical chemistry.

Blood and plasma screening products

Relevance for Applied for Use

The Applicant's products are used to screen a large percentage of the blood and plasma supply in GB for transfusion transmissible bloodborne diseases.

If authorisation is granted, the Applicant would continue offering IVD kits to GB as discussed in the Applied for Use section. Healthcare professionals would continue using the Applicant's IVD kits to aid in the diagnosis and monitoring of medical conditions in biological samples. In addition, blood banks would continue to screen blood, plasma and organ donations for transfusion-transmissible diseases.

Many countries require routine screening of donated blood and plasma units for transfusion-transmissible infections, particularly, HIV, hepatitis B, hepatitis C, HTLV and Syphilis. Directive 2004/33/EC, which implements EU Directive 2002/98/EC sets deferral criteria for medical conditions and infections that a donor may possess when screening the donation. Any positive results would defer the blood or plasma donation from transfusion and potentially the donor from future donation opportunities. Highly specific assays are required for blood and plasma screening to limit the number

of false-positive results which leads to the unnecessary loss of blood donations or false-negative results which may lead to a transfusion related life-threatening disease.

According to the World Health Organisation (WHO), 118.5 million blood donations were collected globally in 2018. 40% came from high-income countries, which have 16% of the world population. In high income countries, up to 75% of transfusions are given to patients older than 60 years, while in low-income countries 54% to patients younger than 5 years. Almost all (99.8%) blood donations in high income countries are screened for transfusion transmitted diseases, such as HIV, Hepatitis B, Hepatitis C and Syphilis. This percentage is 99.9% in upper-middle income countries, then drops to 82% in lower-middle income countries and 80.3% in low-income countries [17]. A refused authorisation could lead to an insufficient amount of blood and plasma screening IVD kits, causing a delay in the blood screening laboratories' capability to test blood donations, impacting the inventory of safe blood and plasma products in GB and many other countries. It could also impact the supply of plasma needed for key medical therapies. As donated blood has a short shelf life (up to 42 days for red blood cells stored in refrigerators) and supply and installation of alternative testing equipment is a lengthy process, a refused authorisation could result in a shortage of units readily available for transfusion until market gaps are filled [18].

Impacts of refused Authorisation for applied for use

The Applicant's sales of blood and plasma screening products would be significantly affected in the NUS examined in this SEA.

- Use 1 (Customer use of IVD reagent kits), distribution to GB customers would be affected.

Blood and plasma services throughout GB rely on the Applicant's products to screen a large percentage of the blood and plasma donations annually. Worldwide standards allow donated red blood cells to be kept for up to 42 days and platelets for up to five days, however actual inventories are often much shorter.

Identifying and implementing an alternative testing method typically takes much longer than 42 days. Furthermore, as it is possible that alternative IVD products may also contain 4-tert-OPnEO, considering the substance's wide use in the industry, as evidenced by a survey conducted by MedTech Europe among its members. The large share of the Applicant in the number of donated blood units tested may also make it difficult to procure sufficient supply of tests and instruments in time. As a result, it is possible that the capability of the blood screening laboratories to test all donated blood samples will be reduced, as discussed in the previous section.

The most common response of hospitals if there is a blood shortage is to prioritise operations, mainly by giving priority to emergencies. There is no legal definition of "shortage", but it has been suggested that it can be defined based on the potential consequences for patients. Serious blood shortage could mean that routine transfusions cannot be carried out and hospitals would need to reduce blood usage (mainly for elective surgeries). Critical blood shortage means that even patients requiring non-elective (i.e. emergency) surgeries may not be able to receive the required transfusion. Typical patient groups affected by a blood/blood product shortage are contained in Table 2-3.

Overall, it is possible that a refused authorisation for the uses of 4-tert-OPnEO by the Applicant can lead to significant health impacts to patients in GB, particularly to those requiring blood transfusion, blood products or organ donations.

The impacts cannot be monetised, as there are uncertainties in the numbers of patients that are affected and on the exact impacts to their health from the lack of available donated blood or blood products. According to a 2015 study for the European Commission, the total number of whole blood donations

in 2012 in the UK was approximately 2.3 million [19]. Data from 2010 show that approximately 2.1 million units of red blood cells, 303 thousand units of plasma and 287 thousand units of platelets were transfused in the UK [19 – Table 5]. [redacted]

Core laboratory immunoassays

Relevance for applied for use

In addition to being the leader in supplying diagnostic products to safeguard GB's blood and plasma donations, Core Diagnostics at Abbott also serves the core laboratory diagnostics market. The core laboratory term is used to describe facilities which provide both routine and stat testing for immunochemistry, clinical chemistry, haematology and haemostasis. These laboratories can be available 24 hours per day. The core laboratory performs patient sample testing which provides physicians with critical information which may impact patient care spanning the range of severity from routine wellness checks to acute, critical care in an emergency.

The Applicant is a global leader in providing core laboratory diagnostic products to healthcare organisations. The overall share of product that Abbott provides varies by product and geographical area but in key testing disease states, such as infectious disease (non-transfusion and transfusion related testing), cardiovascular, oncology, organ transplant, therapeutic drug monitoring and endocrinology, the Applicant plays a critical role in supplying the testing capabilities to meet the growing healthcare demand.

In many cases, patient care is dependent upon consistent performance of laboratory products and especially immunoassays. Variances in performance between multiple vendors may be overcome in the long term but not without impacting overall patient care in the short term.

Impacts of refused Authorisation for use applied for

In the event of a refused authorisation, the Applicant's IVD kits would not be available after the Sunset Date in GB. As a result, there could be a shortage in the market for tests across various applications. The Applicant's core laboratory immunoassay tests are used to screen for and monitor critical disease states including cancer, hepatitis, organ transplant, COVID-19 infection, heart attack, hyper and hypothyroidism, diabetes.

The Applicant is a leading manufacturer of assays for prostate, liver and lung cancer monitoring and treatment for oncology patients worldwide. If these are not available, the patients' monitoring regimes could be disrupted. If monitoring is transferred to an alternative instrument system, cross-over testing would be required due to variances in performance between vendor assays. It is generally accepted and preferred practice not to change the assay testing methodology due to the potential impact it would have on the patients being treated or monitored.

Essentially, most, if not all, patients whose baseline results were obtained using the original assay methodology would likely need to be re-baselined with monitoring to the new baseline. This would ensure that a change in testing methodology would not impact the monitoring and treatment of the patient.

The Applicant's assays are used to monitor the concentration of immunosuppressant drugs administered to recipients of solid organ transplants. Due to the very narrow therapeutic range for the drugs to be effective, careful monitoring of the concentration of the drug within the patient is critical. Changing the testing methodology used to monitor the drugs used may introduce additional risk to the patient because

of variances between assay performance such as sensitivity, specificity and precision. The Applicant is a leading provider of Cyclosporine testing with approximately d % market share globally.

Managing the acute care setting is most critical as emergency services are part of hospital and medical centre offerings. Cardiovascular events are a leading cause of death globally so being able to accurately and reliably detect biomarkers which help to identify risk in pre-screening and in the critical care areas in case of suspected myocardial infarctions is critical to ensure immediate treatment.

The Applicant has the highly sensitive Troponin I assay available. The assay is critical for the acute care setting and Emergency Departments for patient cardiovascular event diagnosis. Additionally, the Applicant provides a total of 6 biomarkers which are used for cardiovascular testing and are critical for managing acute care patients and monitoring.

The Applicant is among global market leaders with thyroid function testing. In some areas of the world, the Abbott Thyroid Stimulating Hormone (TSH) assay market share is d %. Monitoring of TSH is critical to ensure that the thyroid gland is functioning in its purpose of stimulating the production of T3 And T4 hormones. The Applicant's TSH assay is a market leading third generation assay and is useful in the discrimination of patients with true hyperthyroidism and some non-thyroidal illnesses. Furthermore, other thyroid tests (Free T4 estimate, Total T4, T-Uptake, and Total T3) combined with the ability to accurately measure low levels of TSH, improve the efficiency of thyroid diagnosis.

Finally, with the COVID-19 pandemic, the Applicant developed immunoassay tests for detecting the presence of both the viral antigen and the antibody. Automated tests are available on the Applicant's ARCHITECT and Alinity platform to aid in identifying individuals with an immune response to SARS-CoV-2, indicating a recent or prior infection. The persistence of the antibodies allows identification of people who have been infected in the past, recovered from the illness, and possibly developed immunity. Therefore, SARS-CoV-2 immunoassays play an important role in research and surveillance.

Clinical chemistry products

Relevance for applied for use

The Applicant is offering a diverse portfolio of clinical chemistry tests which are used for routine and emergency examinations of patients throughout GB.

The Applicant's clinical chemistry IVD assays are used to assist doctors in making well-informed medical decisions in various situations:

- Monitor the patient's condition over time. The Applicant's clinical chemistry tests are a reliable method for monitoring certain markers for a person's nutritional condition and to identify risks of developing chronic conditions, such as diabetes or heart and circulatory problems, in the future. Cholesterol, triglycerides and ions are such examples.
- Identify the presence of a chronic condition. The Applicant's clinical chemistry IVD assays are used in measuring concentrations of proteins or enzymes which are indicators of underlying conditions such as liver or kidney diseases.
- Quickly understand if there is risk of an acute condition or in emergencies, such as during surgeries. Some of the Applicant's IVD kits are indicators of a condition that could be life-threatening in the short term. For example, elevated levels of D-dimer, a clotting protein, can be an indicator of inappropriately high clotting levels, which may be indicative of deep vein thrombosis or pulmonary embolism.
- Monitor the levels of drugs administered to patients. Some drugs have a very narrow window of efficiency, outside of which they are either ineffective or toxic. The Applicant's CC assays provide vital information to doctors to adjust the dosage of the drug accordingly.

Reduced testing capacity for clinical chemistry analyses could severely reduce the capacity of doctors to make a medical decision which requires these results. Inability of some medical laboratories, hospitals and other healthcare facilities to carry out clinical chemistry tests would place a significant burden on other healthcare facilities. Also considering the possibility that competitors are also using 4-tert-OPnEO in their CC IVD kits and that they will not be able to provide sufficient number of tests and instruments in short notice, this would cause significant delays in producing results from CC tests. As some tests may be run with different assays using different instruments, the results may not be directly comparable, and doctors examining those results will be faced with uncertainties and may require additional time to reach a medical decision or they may misdiagnose the patient. A misdiagnosis is not received well by patients, as it can result in improper treatment and deterioration of the patient's condition. In the worst case, tests may not be requested at all and other forms of diagnostic tools would be used by doctors.

The CC tests have a wide range of applications. Inaccessibility to doctors could result in increased health risks to millions of patients in GB.

For some assays used to monitor **chronic conditions**, e.g. chronic kidney or liver function, doctors and researchers need to have comparable results throughout the whole monitoring period in order to reach meaningful conclusions on the progress of a treatment or on whether the patient suffers from a chronic condition. Delayed or incorrect diagnoses in such conditions could cause additional morbidity to the patient. For example, Chronic Kidney Disease (CKD) is one of the conditions that can be monitored with the recipient assays. Patients at risk of developing CKD should be screened regularly for signs of the condition. Positive tests are normally repeated to confirm the diagnosis. CKD is normally confirmed after several consecutive test results are positive. A common metric of the disease is calculation of the Glomerular Filtration Rate (GFR). It is difficult to estimate, so a formula is used, based on results from blood or urine samples. Results from one of the recipient assays is used in the calculation of GFR. If competitor assays and instruments are using different ranges to provide a result, it could cause uncertainty to doctors that have to compare consecutive tests for a single patient. If the condition is not diagnosed early and treated, it could develop to higher stages, which progressively deteriorate kidney function.

Some **acute or life-threatening conditions** may require a quick turnaround on the test result, so the doctors can act as soon as possible to prevent serious acute health impacts to patients. For example, D-dimer concentration is a tool for diagnosing thrombosis (blood clots) and monitoring thrombolytic therapy. Elevated levels are found in clinical conditions such as deep vein thrombosis, pulmonary embolism and disseminated intravascular coagulation. A negative result can rule out thrombosis without the need for additional imaging testing. A positive result can indicate thrombosis and further imaging testing is required. Delays in receiving D-dimer test results could increase the risk to patients.

Some of the Applicant's recipient assays are used to **monitor therapeutic drugs in patients**. These drugs require monitoring of their blood concentration due to a narrow therapeutic window. This means that there is a very narrowly defined concentration at which the drug is active and effective, but not toxic. If the drug level falls below the lower limit, the drug is ineffective. If it rises above the upper limit, the patient is at risk of health issues due to toxicity from the drug. Ensuring that the patient is receiving the appropriate treatment is a challenge when using drugs with narrow therapeutic windows like some antibiotics. The laboratories are frequently called upon to test drug concentrations at times when the concentration is expected to reach a maximum to assess for risk of toxicity, and again when the drug is expected to reach a minimum concentration, usually immediately before the next dose, to ensure minimum therapeutically effective amounts are maintained. If such tests are not available in case of a refused Authorisation, the patient may receive ineffective treatment for their condition.

Overall, 100-1,000 [redacted] million sample results impacting hundreds of millions of patients could be delayed in case of a refused authorisation for the applied for use, in which CC test supply would cease in GB.

3.2.3 Overall health impacts

The Applicant is offering a wide range of IVD assays which are critical to patients' health in GB. They are the market leader in assays used to screen donated blood and plasma, as well as offering a series of diagnostic products used for various medical situations, from oncology, to drug monitoring and from endocrinology to acute cardiovascular screening.

A refused authorisation would cause a shortage of supply of the Applicant's assays and their customers would not be able to carry out tests on millions of patients. Patient categories affected are prostate, liver and lung cancer patients, recipients of solid organ transplants under immunosuppressant treatment, patients at risk of thyroidal illnesses and patients at risk of cardiovascular events. Some of the Applicant's assays, such as Troponin I for cardiovascular events and TSH for thyroid monitoring are among the best-performing in their class and removing them from the market would impact the level of medical care in GB.

The Applicant is also the market leader in blood screening, holding a very large share of the blood transfusion screening in GB. In case of a refused authorisation it is very likely that the Applicant's customers in GB could face a shortage of tests. Blood supplies in individual countries can range from a couple weeks to as little as a couple of days depending on the blood product. Therefore, any disruption to the ability to test donated blood could have an impact that would be felt within a matter of days. Additionally, due to the large number of donations tested globally on the Applicant's instruments, it is unlikely that other vendors would be able to rapidly respond to the demand currently filled by the Applicant, thereby leaving a gap in testing the blood supply in GB.

Finally, the Applicant's clinical chemistry IVD kits and instruments are used in locations across GB, offering quick and accurate results in routine and emergency tests on chemical analytes. These analytes are evaluated to monitor the patient's overall health, diagnose and monitor chronic conditions or monitor drug levels in a patient's organism. A refused authorisation would prevent a large number of healthcare facilities in GB to carry out these routine tests which have improved healthcare and treatment for millions of citizens in GB.

3.3 Economic impacts

3.3.1 Economic impacts for the Applicant

Overview

This section will assess the economic impacts that the Applicant would face in the Non-Use Scenario compared with the situation in the Applied for Use Scenario. The analysis will be based on economic impacts from the inability to distribute IVD kits in GB.

Applicant's and competitors' response to refused authorisations

In event of a refused authorisation, the Applicant would stop supplying some or all of their IVD kits to the GB market. Considering the Applicant's high share in the GB IVD market, there would be a significant gap in the market for a period, which may not be filled immediately. IVD downstream users would need to identify alternative instrument systems and reagents to perform testing.

The availability of alternative IVD instruments and assays would be based on the manufacturing capacity, availability of stock and status of 4-tert-OPnEO use in the alternative IVD kits. The Applicant's EU sector association, MedTech Europe, carried out a survey among its members and found that 4-tert-OPnEO is used across all IVD product categories, however, the products impacted by the substance were not identified [20]. Therefore, it is possible that no alternative product exists without 4-tert-OPnEO and if any exist, they may not be sufficient to cover the Applicant's market share.

Even if the reagents were available, the largest bottleneck is expected to be the supply of the replacement instruments. The Applicant maintains more than 500 ARCHITECT, Alinity and ABBOTT PRISM instruments in GB. If the Applicant could no longer provide reagents for these instrument systems, it is unlikely that an alternative supplier would maintain sufficient stock of instruments, as they are of high value. Based on the high cost of instruments, an inventory to replace the magnitude of instruments would need to be built, which would require activities in several levels upstream in the supply chain. This requires time and, considering the large number of instruments that would be required, would be very difficult to be achieved at a short notice.

Therefore, the Applicant's customers may not be able to source an alternative instrument quickly, limiting their capacity to carrying out IVD testing for a significant period.

Early contract termination clauses

The Applicant has ongoing contracts with customers that go beyond the Sunset Date. In case of a refused authorisation, these contracts would be terminated prematurely. Depending on the nature of the contract, there could be fees for early termination or that the Applicant ensure testing capability for customer testing labs.

In current practice, when products are not available to customers, the specimen may be sent to a third party for testing. Additional costs are incurred to send out a sample for testing which are often higher than the costs to test within the customer laboratory, with many variables impacting the total cost, including:

- Duration of the absence of product and the need for third party testing.
- Market differences in third party test pricing versus the Applicant's test
- Some critical care assays, such as High Sensitivity Troponin, used in acute care scenarios, cannot be sent out for testing due to the urgent need for results
- In some cases, customers may also request reimbursement from the Applicant for the remaining value of existing immunoassay and clinical chemistry instruments, in the situation where they switch to an alternative supplier.

Non-Use Scenario B (Cease GB Reagent Distribution) for Customer use of IVD reagent kits

Description of impacts

If there is a refused authorisation for the applied for use (customer use of 4-tert-OPnEO in reagents of IVD kits in GB), the Applicant would no longer be able to distribute these products within GB, so the sales and profits from those products would be lost.

The GB market for core laboratory immunoassays, clinical chemistry and blood transfusion products accounted for approximately 1-10% ([redacted]) of the Applicant's worldwide sales in 2018 and would no longer be available to the Applicant. As customer contracts can last up to 5.5 years, an alternate source of IVDs would be required to continue customer testing activities. For the Applicant, it would be difficult to re-enter the GB market upon completion of substitution, as many customers may have

converted to alternative instrument platforms with the associated reagents and may have extended contracts with the new IVD supplier.

As a result, the Applicant would be manufacturing IVD kits to serve the customers outside GB only.

Loss of revenue and profits for the Applicant

The economic impact for the Applicant in this Non-Use Scenario would be the loss of the GB revenue and profits. This cost is estimated to be £10-100 million (£*d* million) in net profits over the 5.5 -year review period (discounted to 2021 prices using a 4% discount factor). Table 3-3 shows the annual loss of revenue and profits over the review period in the event of a refused authorisation.

Table 3-3: Losses of revenue and net profits from GB sales of the Applicant's sales of IVD kits in NUS B

Year	GB			
	Revenue	Profits	Revenue (2021 prices)	Profits (2021 prices)
2022	*d*			
2023				
2024				
2025				
2026				
2027				
Total to 2027				

Notes:

These values were calculated from the 2018 values from the Applicant's sales, assuming a 4% annual increase in consumption, driven by increased demand.

3.3.2 Economic impacts to upstream stakeholders

During the Applied for Use scenario, operations of the Applicant would continue with no expectation of supply chain disruption.

Economic impacts to upstream stakeholders in Non-Use Scenario B (Cease GB Reagent distribution) for Professional use of IVD reagent kits containing 4-tert-OPnEO

In this NUS, raw material suppliers would be minimally impacted, as GB is 1-10% (*d*) of the Applicant's worldwide sales.

3.3.3 Economic impacts to customers

Description of impacts to healthcare practitioners and blood banks

The Applicant's clients are hospitals, testing laboratories, medical centres, physician offices and blood banks performing clinical and diagnostic monitoring on patients and screening of blood and blood products for infectious diseases or other conditions. Diagnosis is carried out using the IVD kits on samples from the patient on the diagnostic platforms marketed by the Applicant. If the authorisation is refused, supply of IVD kits available to the Applicant's GB customers would cease. The customers would then need to identify an alternative source for IVD kits.

The ability to run IVD tests to assist healthcare professionals reach a diagnosis on a patient is vital in modern-day clinics and hospitals. Automated IVDs have allowed for faster and more precise testing of patient samples, therefore, the Applicant's customers would need to identify an alternative testing platform quickly.

Blood and plasma services across the world depend on the Applicant to supply systems and assays to screen blood and blood products for infectious diseases, such as HIV and Hepatitis, to ensure the blood supply and patients requiring transfusions receive them free of transfusion-transmissible diseases. The Applicant's products are used by blood and plasma services that are in government, non-profit, and private industries. The primary purpose of the product is to help national health systems ensure an adequate supply of safe, life-saving blood, plasma, and organs free of pathogenic agents.

Blood and plasma services throughout the world rely on the Applicant's products to directly screen a large percentage of the blood and plasma donations each year in GB. Interruption of supply of the Applicant's reagents, would impact the ability of customers to test donated blood samples.

The Applicant's large presence in blood and plasma screening is based on purpose-built systems and high-quality assays. The Applicant is the leader in infectious disease assays and detection, with science that has been depended upon for more than 40 years. Using less specific assays may result in a higher number of false-positive results, and consequently lead to an unnecessary loss of blood donations. This is a socioeconomic disadvantage, as well as an ethical concern for the needless discarding of a charitable contribution of a blood or plasma donor.

As discussed in Section 3.2.2, changeover to a replacement system is a lengthy process for customers. Issuing of a public tender could potentially last several months to identify a replacement system that meets the quality and value requirement of the customer.

A potential laboratory redesign or construction to accommodate the new system (floor design, power usage, water usage, heat dissipation) would be required, which could range from tens of thousands to hundreds of thousands of Pounds Sterling for each site depending on their needs. Delivery, set-up and establishing quality control of the new systems including IT/network interfacing would be required. The new systems and assays would need to be validated once installed, which typically takes several weeks. The laboratory would need to develop updated Standard Operating Procedures specific to the new instrument. The staff responsible for the operating systems would need to be trained on the new platform. Lastly, it should be noted that results from different manufacturer's tests cannot be used interchangeably. The laboratory would need to undertake extensive comparison (cross-over) studies to establish equivalency of results between the two instruments or to define new reference ranges. Any changes would have to be notified to physicians who would be using the results.

Economic implications for downstream users

Instrument substitution cost

If the Applicant could no longer supply customers with IVD kits and testing instrument platforms, the customers may be required to convert to a replacement system that is not dependent upon 4-tert-OPnEO. Due to the number of organisations that rely on the Applicant's products, and how integrated those products are into the operations of the customers, it is unlikely that an alternative supplier could rapidly respond to the demand currently filled by the Applicant.

Alternative instrument systems would need to be available to cover the Applicant's instrument base for immunoassay, including blood screening, and clinical chemistry testing, along with the reagents associated with the instrument. As discussed earlier, it is not expected that there would be sufficient instruments in warehouses that would be immediately available to cover all demand to replace blood

screening, other immunoassay and clinical chemistry testing. In addition, sufficient resources to install the instruments may not be readily available in the short time.

The customer would incur additional costs of purchasing new instruments ranging from £0.2-2 (£[redacted] million, and a one-off cost of converting to new reagents, calibrators and controls of £1,000-10,000 (approximately [redacted]. The reagents will be used to perform cross-testing between the old and the new instruments, before commercial use starts. The time to convert from one system to another could take 3 - 6 months, provided instrument availability. This is non-productive time, which would have been used for running tests on patient samples in the Applied for Use Scenario.

In any case, these costs would be brought forward by as much as 6 years, considering that the Applicant's contracts with their customers may be up to 7 years long. Accurately calculating these costs is not possible without having to speculate on the competitors' capacity and pricing policies. In any case, an indicative calculation can be carried out, under the following assumptions:

- The Applicant's customers would need to purchase/lease new equipment and IVD kits at the same prices as they would under the contract with the Applicant. As a very conservative approach, the average internal purchasing cost of an instrument system by the Applicant is used, which was approximately £0.1-1 million (£[redacted] million).
- The cost of new reagents, calibrators and controls to run cross-testing between the old and the new platform when converting to an alternative instrument system. The low value of £1,000-10,000 (approximately [redacted] will be used.
- Costs for obtaining new instruments that would be paid at the end of the contract (or the start of new ones) would be brought forward. The discount factor used for this would be the default 4% used elsewhere in this document.
- The remaining years of a contract at the Sunset Date would be assumed 3 on average, assuming a typical contract is 7 years and the Applicant continues to pursue new contracts through the Sunset Date.
- It is possible that some of the Applicant's customers would have switched to a different supplier at the end of their contract regardless of the decision on authorisation. These will not be considered as additional costs. The Applicant estimates that this is on average 10%.
- There will be additional costs to remove the existing instrument from customer sites. The instruments are bulky, and they will have to be disconnected from the utilities, possibly dismantled and transported to a suitable vendor for recycling.

Use 1 - (Customer use of IVD reagent kits Non-Use Scenario B – Cease GB Reagent Distribution

In NUS B, all the analysers in GB will have to be replaced. If it is assumed that 90% of the customers would decide to purchase a new analyser, approximately 100-1,000 ([redacted] new instruments would be purchased.

The cost of switching away from the Applicant's instruments may be £10-100 ([redacted] million over the entire review period, in 2021 prices, assuming substitution 5.5 years after the Sunset Date.

3.3.4 Summary of economic impacts

Table 3-4 summarises the economic impacts for this NUS.

Table 3-4: Summary of economic impacts for NUS (in £ million in 2021 prices)

Use applied for	Use 1
Review period	5.5 years (thru 4-Jan-2028)
Lost GB profits	10-100 ([redacted])
Costs to GB downstream users	10-100 [redacted]

3.4 Social impacts

3.4.1 Direct job losses

In 2018, the Applicant employed more than 10,000 ([redacted]) people globally. Of these, more than 150 ([redacted] were based in GB. These numbers include both Applicant and contractor employees.

It is expected that sales of IVD kits would increase during the review period with an approved authorisation, which could lead to an increase in the number of employees over time.

Social costs of unemployment

Unemployment caused by a refused authorisation for any of the uses applied for may have impacts to GB society. These impacts can be quantified using the methodology described in Appendix II, which is based on the note by Dubourg that is published on ECHA's website [21].

The SEA focuses on four main social cost elements:

1. The value of wages / output that were lost while the person remained unemployed
2. The value of leisure time during the period of unemployment, minus the cost of searching for a new job
3. The 'scarring effect', i.e. the impact of being unemployed on future earnings and employment possibilities
4. The costs associated with hiring and training employees for new positions

The Applicant has employees in GB, who could be affected by a refused authorisation. Personnel numbers and average Applicant salaries were used to calculate the social impacts of unemployment.

The total number of employees includes workers employed directly by the Applicant and contractor workers. Only salaries paid directly by the Applicant will be considered in the calculations of the social cost of unemployment. This will most likely underestimate the total impacts.

A report on the tax burden of UK workers was used to determine average employer contributions (e.g. employer tax and social insurance for the employees), average income tax and social security rates for GB [22]. The average salary for the Applicant's GB employees are shown in Table II-1 of Appendix II. The Net Present Value (NPV) of the lost output was calculated for the years 2021 through 2023, using 2021 as the base year and 4% as the discount factor for the scenario evaluated below and is shown in Table II-4 of Appendix II.

The average duration of unemployment was calculated from publicly available information from Eurostat. Therefore, 2017 unemployment data were used. The duration of unemployment for GB is shown in Table II-3 of Appendix II.

Assumptions were made on the magnitude of the scarring effect to future wages of unemployed individuals. A 10% value for 6 years after re-employment is assumed, as a conservative approach, considering the strong presence of the MedTech sector in GB and the competitive salaries offered by the Applicant. The scarring cost per the Applicant's employee in GB is shown in Table II-5 of Appendix II.

When examining the reservation wage (the lowest wage at which an individual is willing to work) as a proxy of leisure time, it was assumed to be 80% of the net wage after the scarring effect was applied. This value was applied across the Applicant's GB employees and is shown in Table II-6 of Appendix II.

Social impacts for Non-Use Scenario B (Cease GB Reagent distribution) for Customer use of IVD reagent kits

In this NUS, the Applicant would stop manufacturing IVD kits for GB customers, so the Applicant's manufacturing plants would only produce sufficient quantities to cover the demand for the rest of the world.

All GB sales would be lost, because there would be no IVD sales in that market, so more than 140 [redacted] commercial jobs would be lost.

Total number of direct job losses would be more than 150 [redacted] in GB.

Table 3-5 summarises the social costs of unemployment for the NUS B (Cease GB Reagent distribution).

Table 3-5: Summary of social costs for NUS (£ million)

Lost output	Scarring Effects	Hiring Costs	Leisure Time	Total
[redacted]	1-10 [redacted]	1-10 [redacted]	1-10 [redacted]	2-20 [redacted]

Overall, the total GB social cost of unemployment for this Non-Use Scenario would be approximately £10-100 (£[redacted] million.

3.4.2 Indirect and induced job losses

It has been estimated in a report published by the European Federation of Pharmaceutical Industries and Associations (EFPIA) that each job in the pharmaceutical sector can support a multiplier of 4.65 additional jobs in the EU, as a result of materials consumption and support of economies via the salary of the workers [23].

Therefore, in this use (Customer use of IVD reagent kits) the indirect and induced job losses would be 100-1000 [redacted].

3.5 Wider economic impacts

3.5.1 Impacts on competition within GB

The market in Great Britain for IVD tests is concentrated in a small number of large companies. At the same time, there is a larger number of many smaller niche companies, which specialise in particular assays and do not have the expertise or the capacity to offer the range of products offered by the Applicant and other large IVD manufacturers. The Applicant and other IVD manufacturers offer a wide range of products, covering the testing needs of laboratories.

If the AfA is refused, the Applicant's GB share would likely be split among existing companies, which have established production infrastructure. This, however, would not be possible immediately, as explained earlier in this SEA. The Applicant's customers operate over 130 instruments in Great Britain, and it is unlikely that competitors' instruments would be available to fill the gap left by the Applicant exiting the market on short notice.

Ultimately, the number of companies in the GB IVD market would decrease and the level of competition in GB would decrease. This could have a negative impact for users of IVD devices, in the form of decreased product options and, potentially, higher prices.

4. Combined assessment of impacts

4.1 Comparison of impacts

The cost-benefit analysis in this SEA consists of a semi-quantitative discussion on the impacts from a refused authorisation for the applied for use. The main impacts that could be quantified, i.e. the prevented emissions of 4-tert-OPnEO, the lost net profits, social impacts from the Applicant's operations are compared and used to carry out a cost effectiveness analysis comparing the authorisation with the R&D project by the Applicant.

Other quantifiable or monetised impacts, which have higher uncertainty were examined separately and were used to support the main argument. Finally, as it was not possible to quantify or monetise the impacts from the release of 4-tert-OPnEO to the environment, a qualitative discussion is given.

4.1.1 Economic impacts to Applicant vs emissions of 4-tert-OPnEO

Table 4-1 compares the cost per kg of 4-tert-OPnEO for the NUS examined in the SEA. The costs include the lost net profits for the Applicant and their supplier impacts in the NUS and the social cost of unemployment in GB.

Table 4-1: Net profits lost per kg of 4-tert-OPnEO emissions prevented in the NUS

Impact over review period	Use 1
Review period	5.5 years
GB prevented emissions (kg)	227
GB economic impacts (£ million)	10-100 [d]
GB social costs of unemployment (£ million)	1-10 [i]
Impacts per kg 4-tert-OPnEO in GB (£/kg)	116,719

The monetised economic impacts per kg of prevented 4-tert-OPnEO emissions in Great Britain are approximately £116,000/kg.

For comparison, the Applicant's R&D project to substitute 4-tert-OPnEO from reagents has an overall cost of £10-100 (£[f] million, including research and regulatory costs as discussed previously. If the Applicant took no action to substitute 4-tert-OPnEO from reagents, the total quantities of 4-tert-OPnEO over the 5.5-year period would be 1-10 t ([c] t), assuming a 1-10% increase in demand ([h] [h]). As discussed in section 2.5.1, the substitution effort was initiated due to the EU REACH Regulation. As the GB sales are 1-25% ([d] of the Applicant's EU sales, the cost of substitution used for this analysis will be proportional based on sales or £1-10 million (£[f] million). The cost per kg of prevented emissions of 4-tert-OPnEO from the reagents in the Applicant's IVD kits from their own R&D and substitution efforts would be approximately £6,556 per kg using the GB proportion of the Applicant's R&D project. This is significantly lower than that calculated £116,719 per kg for the GB emissions and economics from the Applicant's lost net profits and social costs from the Non-Use Scenario. After the end of the review period, the Applicant's R&D project would have the same effect as a refused authorisation, as there would be no use of 4-tert-OPnEO by the Applicant's customers.

Therefore, the Applicant's substitution project is a more cost-effective option to reduce emissions of 4-tert-OPnEO to the environment. For use 1 (Customer use of IVD reagent kits) the ratio differs by a factor of **19**.

The cost per kg ratio is calculated for emissions of 4-tert-OPnEO. However, it is 4-tert-OP that has endocrine disrupting properties. If the ratio in Table 4-1 were calculated for the 4-tert-OP quantities, the value would be divided by a factor of 0.33, which is used to convert kg of 4-tert-OPnEO to kg of 4-tert-OP. The comparison with the cost efficiency of the Applicant's substitution project is not going to be affected, as the ratio would also have to be divided by 0.33.

The costs per prevented emissions shown above are aggregated over the requested review period for the NUS. If the lost economic impacts per kg are examined on an annual basis, it would be observed that it is increasing year by year, as the usage and emissions of 4-tert-OPnEO decrease, while the lost profits increase. Annual environmental emissions in GB would decrease as 4-tert-OPnEO is substituted from reagents in the Applicant's IVD kits. This shows that the authorisation, as a measure to reduce emissions of 4-tert-OPnEO would bring diminishing returns and would be most effective in the first few years after the Sunset Date. Compared to the Applicant's efforts, a refused authorisation is a less effective risk management option for the use applied for.

4.1.2 Discussion of qualitative impacts

A refused authorisation is expected to have an impact to the global public health, especially where blood screening is performed. The Applicant's products screen a large percentage of the UK blood donations. In case of a refused authorisation, the blood banks testing donated blood and blood components would need to identify a replacement supplier quickly, due to the short expiration dating of donated blood components (i.e. 42 days). Overall, a refused authorisation could create a significant gap for screening the GB blood supply, especially in cases where donated blood and blood components are needed in an emergency (e.g. surgeries) or for chronic conditions (e.g. anaemia, low blood cell count, etc.).

Risks to human health are also expected from the removal of the Applicant's immunoassay IVD kits from the market in GB. IA IVD kits have the highest volume of units sold from the Applicant's products. If the immunoassay products are no longer available, interruption of the supply would impact the ability for laboratories to maintain the testing schedules until alternative systems are identified. Because of the integral nature of these instrument systems in core laboratory testing, changeover to replacement systems is a lengthy process for customers. In addition, it is unlikely that replacement instruments would be available to replace the Applicant's more than 500 analyser instruments currently operated by customers in GB. It is not common practice to maintain large stocks of instruments in the warehouse and building new instruments requires time and resources, as well as manufacturing space, which may not be immediately available. As a result of a shortage of immunoassay and clinical chemistry testing capacity, patients suffering from conditions requiring screening or monitoring, including chronic conditions or cancer may see delays in testing.

Overall, risks to human health of patients, that need the results generated by the Applicant's immunoassay and clinical chemistry tests, would increase in event of a refused Authorisation.

Overall, a granted authorisation for the uses applied for would allow the Applicant to continue providing their customers with high quality IVD kits that can be used to improve quality in the healthcare provided to a large number of patients across GB for the short review period requested.

On the other hand, the ecosystems in the areas that would receive the treated wastewater, containing 4-tert-OPnEO from the GB customers' sites could potentially experience some impacts from the degradation of the substance to 4-tert-OP. As this is an endocrine disruptor, it is possible that the

populations of species in those ecosystems would be affected. Certain species could see their populations change, which could present an opportunity for invasive species to proliferate. Such impacts could affect the stability of the ecosystems and the quality of the receiving waters. However, the Applicant's 4-tert-OPnEO emissions are relatively low, minimising any potential effects of the degradation products of 4-tert-OPnEO from the Applicant's downstream users.

4.1.3 Combined impacts

Table 4-2 summarise the impacts to stakeholders that are affected by this application for authorisation.

Table 4-2: Combined impacts for Non-Use Scenario B (Cease GB reagent distribution) – 5.5-year review period

Impact category	Stakeholder	Use Non-Use Scenario	
		Differences between AfU and NUS	**Monetised impacts (where possible)**
Environmental	Local environment	Prevented GB emissions: 227 kg	GB: £116,719 per kg 4-tert-OPnEO
Economic	Applicant	All GB sales and profits lost	5.5-year lost profits: - GB: £10-100 (£ *d* million
	Downstream customers	Increased costs to obtain new instruments for testing, training personnel and updating documentation (GB)	£0.1–1 (£ *d* million per instrume GB: £10-100 (£ *d* million
Human health	Patients	*d* of donated blood samples ially not tested in GB. Higher number of false positives in blood sample testing Reduced capacity for testing of patients with IA/CC tests. Potentially increased risk for deterioration of conditions or for ineffective or wrong treatment administered for up to 3-4 years.	Not possible to monetise
Social	Applicant's employees	100% of positions in support positions for GB eliminated – possibly find similar job in different region.	GB jobs: >150 *g* GB social cost: £10-100 (*d* million
	Local societies	Indirect and induced jobs lost	Indirect and induced jobs lost in GB: >700 (*i*
Wider Economic	Competition	GB market will be in the hands of fewer companies	Not possible
	Competitiveness	Decreased competition in the GB	Not possible

4.2 Distributional impacts

The various stakeholders that are relevant to this AfA would be affected differently in case of a refused authorisation. Table 4-3 presents the distributional impacts of a refused authorisation. The figure shows which stakeholders would benefit and which would not from a refused authorisation, along with a presentation of the severity of the impacts to each stakeholder. The severity of impacts for each stakeholder are presented qualitatively, with one symbol (either a plus or a minus) for low, two for medium and three for high impacts.

Table 4-3: Distributional impacts

Stakeholders	Benefit of continued use	Cost of continued use
EU suppliers	+ +	n/a
Non-EU suppliers	+	n/a
EU manufacturing sites (Applicant)	+ + +	n/a
Non-EU manufacturers (Applicant – instruments)	+ ++	n/a
Non-EU manufacturers (TPMs)	+ +	n/a
Non-EU manufacturers (competition)	n/a	-
Users of IVD kits (hospitals, clinics)	+ + +	n/a
Users of IVD kits (blood banks)	+ + +	n/a
Global Society	+ + +	n/a
Applicant's employees	+ +	n/a
Environment	n/a	- - -

GB society would be severely impacted by a refused authorisation. Interruption of supply of the Applicant's reagents, would impact the ability of GB to supply safe blood and plasma products, impacting blood and plasma needed for emergencies as well as regular blood recipients. Additionally, it would impact the supply of plasma needed for key medical therapies. The blood banks would need to identify and secure alternative resources for testing. These may not be immediately available, as the Applicant's products screen the GB blood donations and the availability of alternative instrument systems and reagents may not be readily available due to inventory or dependence of alternative testing on 4-tert-OPnEO.

Other patients may also experience impacts from the delay of testing and uncertainty in diagnosis. Due to the considerable number of instruments in GB customer sites, the availability to provide alternative systems and reagents on short notice. Therefore, a reduction in the capacity of immunoassay and clinical chemistry testing is expected, leading to possible delays in testing and producing results.

If the customer use of reagents is not authorised, the impacts would be significant. Support positions for the GB market, including commercial, would no longer be required and positions would be eliminated.

Alternative IVD suppliers could benefit in the event of refused authorisations, as IVD laboratories would need to identify an alternative testing system if the Applicant's systems are not distributed in GB.

The environment in GB could also benefit from a refused authorisation, as 4-tert-OPnEO emissions from the IVDs would no longer be emitted.

4.3 Uncertainty analysis

4.3.1 Assumptions – uncertainties

Throughout the socio-economic analysis, assumptions were required due to the length of the review period (5.5 years beyond the Sunset Date) and the fact that the impacts would reach far into the future.

The demand forecast for the Applicant's IVD kits was evaluated over the short term, however the review period far exceeds the timing for an accurate forecast. A growth rate of 1-10% ([redacted]) was used. If the future growth rate exceeds the assumption, Applicant impacts would increase and vice versa.

A profit margin of 1-10% ([redacted]%) was assumed based on information from the Applicant's finance department and would provide a conservative estimate of the Applicant's business. Profit would be expected to fluctuate over the review period and could be higher or lower. If the profit is higher in future years, the impact on the Applicant would exceed what has been assumed from the calculations and vice versa.

When calculating the impact to raw material suppliers, the same profit margin as the Applicant was used. As the Applicant has multiple suppliers providing raw materials, a common value for the profit margin was used to estimate the impact to suppliers, based on the Applicant's net profit margin.

The substitution schedule for removal of 4-tert-OPnEO from the Applicant's assays has been developed based on the assumption that the validation/verification activities are completed with minimal to no additional optimisation required for assays. The process is lengthy as described previously in this SEA and in the AoA and would be influenced by the verification outcome for each specific assay and the timing of regulatory approvals from the multiple impacted countries. Preliminary feasibility studies have been completed on many of the approximately 200 assays dependent upon 4-tert-OPnEO, to provide information on optimisation needed to complete the substitution on some products. Technical feasibility will not be established until completion of the design verification phase. As individual products complete substitution activities and receive regulatory approvals from the impacted countries, those products would be converted to the substituted products.

The calculations within the SEA assume a rapid rate of substitution in terms of 4-tert-OPnEO volume decreases over the review period. Substitution is expected to be completed over 5.5 years for the reagents. There are additional uncertainties for the regulatory approvals in the EU as the IVDD is being replaced by the IVDR which includes a reclassification for IVDs with updated requirements.

The IVD Directive (98/79/EC) will be repealed and replaced with the IVD Regulation (Regulation (EU) 2017/746) in May 2022. The IVDR entered into force in 2017 and will become completely applicable in 2022 (5 years after entry into force). Leading up to the 2022 date, products being substituted will also be evaluated to determine if additional activities, i.e. performance studies, documentation, etc. are required for resubmission for adherence to the IVDR. As some of the implementing acts are pending publication, the full impact of the IVDR is not yet known. The IVD classification system is being modified and it is expected that approximately 80% of the Applicant's IVD products will need to receive notified body review, where previously, approximately 20% required the review. Not only will this be required for products undergoing substitution to remove 4-tert-OPnEO, but any product distributed in the EU may also need to be submitted. With the implementation date of the IVDR coinciding with the substitution timing, it is expected that delays for some products will be experienced based on the additional activities as well as the potential delays as notified bodies are reviewing submissions for all IVDs distributed in the EU. Based on these uncertainties, the rate of substitution could vary from the

planned schedule, with the volumes being substituted quicker if verification activities, regulatory approvals and IVDR impacts occur as planned or sooner.

To calculate the emitted quantities of 4-tert-OP to the environment, it was assumed that all 4-tert-OPnEO would be converted to 4-tert-OP in the municipal STPs. This does not consider the possibility of full or partial degradation (minimisation) of a part of 4-tert-OPnEO in the STP, which would reduce the quantities of 4-tert-OP released to the environment. This assumption was made to present a worst-case scenario of 4-tert-OP releases to the environment.

The assumptions mentioned above address those uncertainties that can be qualitatively presented. The following are those that have been addressed quantitatively:

- Semi-quantitative:
  - If an authorisation is refused, it is assumed that the changeover to a replacement system would take many months to occur. This could cause a gap in the availability of IVD testing to customers. In the worst case, this could cause a disruption in the ability to screen blood for transfusion that would be felt within a matter of days for those facilities utilizing the Applicant's products for screening blood and plasma donations, due to the short shelf life of blood. Interruption of the Applicant's assays could impact the ability of many hospitals to supply safe blood and plasma products, impacting blood and plasma needed for emergencies. In addition, an economic burden to testing laboratories to purchase new equipment, requalify staff and documentation could occur. For immunoassay and clinical chemistry assays, an interruption of supply would cause a delay in IVD testing causing a subsequent delay in the diagnosis and monitoring of hundreds of diseases in GB. The assumption is dependent upon the timing and volume of alternative replacement systems to assume the Applicant's IVD GB volumes.
  - Similar to the impacts to blood supply, immunoassay test capability of several clinics, hospitals and analytical laboratories in GB would be compromised for a significant period. This would depend on the Applicant's competitors' capacity to supply replacement IVD instruments and kits. It is not known whether sufficient instruments would be available on short notice to replace the Applicant's instruments at the customer sites. If instruments are available, then the gap in the GB market would be covered more quickly and the impacts to patients would be lower.

4.3.2 Sensitivity analysis

IVD kit demand trends – changes in Applicant's sales

An annual 1-10% ([redacted] increase in sales revenue and profits from IVD kits and instrument platforms was assumed. The Applicant's business is expected to move from the legacy instrument distributed currently (ARCHITECT and ABBOTT PRISM) and move to the newest launched systems Alinity which provide features that align with the needs of today's laboratories; provide innovative solutions to current and future challenges; designed to be interconnected and work together seamlessly while using less space in today's laboratories.

Growth projections are assumed over a long period, therefore there is a higher uncertainty involved when assessing impacts in the mid- to long-term. Different conditions than those assumed could lead to different sales in the mid- to long-term. This source of uncertainty was examined for different rates of increase through the review periods. The impacts were examined for extreme cases of [redacted] and [redacted] growth throughout the review period.

Table 4-4: Comparison of impacts per kg of 4-tert-OPnEO emissions prevented for different growth rates

Impact over review period	Use 1
Review period	5.5 years
Low [redacted] growth GB (£/kg)	107,513
High [redacted]) growth GB (£/kg)	130,783
Base case GB (£/kg)	116,719
Substitution Cost (£/kg)	6,566

With respect to the GB impacts, even at a low growth rate, the cost per kg of prevented 4-tert-OPnEO emissions is very high when compared to the cost of the Applicant's ongoing substitution project.

Net profit margin

An average profit margin, based on the Applicant's operations, was used in the assessment. If this were to change in the future, e.g. due to different economic conditions, changes in the Applicant's strategies or improved efficiency in manufacturing, the profit margin could vary. The Applicant's actual profit margin is pooled with those of divisions within the company and is not published publicly, therefore the net profit margin used may not be fully representative of the Applicant's products affected by a refused Authorisation.

Table 4-5 compares the cost per kg of prevented emissions for the use applied for. The costs also include the social costs of unemployment in GB.

Table 4-5: Comparison of impacts per kg of 4-tert-OPnEO emissions prevented for different net profit margins

Impact over review period	Use 1
Review period	5.5 years
Low [redacted] profit GB (£/kg)	[redacted]
High [redacted]) profit GB (£/kg)	
Base case GB (£/kg)	116,719
Substitution Cost (£/kg)	6,566

The impact from the profit margin is more severe than that from the growth rate. This is explained by the fact that, while the growth rate affects both emissions and sales, the profit margin only affects the economic costs. However, the GB ratios are still significant, in the range of £65,000-168,000 per kg in the low/high profit margin scenario, which is still much higher than the costs per kg expected to be achieved by the Applicant's substitution project.

Duration of impacts – assessment over a shorter period

In the SEA, the impacts have been calculated over the entire review period for the Use and Non-Use Scenario. This could be considered an overestimation, as it may be possible that the Applicant's market share could be consumed by other IVD manufacturers. Therefore, the overall impact from lost value in GB would be lower. This would not affect the social cost of unemployment caused by the Applicant having to shut down operations or lay off employees.

This may not be possible immediately for a number of reasons, discussed earlier in the report. The Applicant's customers are operating over 500 instruments for IA, CC and transfusion tests in GB. It is unlikely that other IVD manufacturers would maintain sufficient instruments in stock to replace the Applicant's wide instrument base and whether they would be able to immediately scale up their production for either instruments or reagents.

The costs per kg of prevented emissions were recalculated, based on the assumption that the Applicant's share would be taken over 2.5 years. This would affect the economic impacts from the lost sales but would not affect the prevented emissions.

Table 4-6 compares the cost per kg of prevented emissions for the use applied for. The costs for the GB region also include the social costs of unemployment in GB.

Table 4-6: Comparison of impacts per kg of 4-tert-OPnEO emissions prevented for impacts lasting only 2.5 years

Impact over review period	Use 1
Review period	5.5 years
GB impact over 2.5 years (£/kg)	80,438
Base case GB (£/kg)	116,719
Substitution Cost (£/kg)	6,566

While the economic impacts are less severe, it should be noted that the potential health impacts would still be significant, particularly for blood supply, as described in Section 3.2.2. In comparison to the efficiency of the Applicant's own substitution project, the costs from a refused authorisation are still several orders of magnitude higher.

The results presented in Table 4-6, do not consider the costs of replacing the customers' existing instrument system with a new one, however. If the Applicant's customers were forced to replace their now obsolete instruments with competitors' instruments, they would be incurring an additional cost that they had not initially planned for. This cost would place a significant burden on the national health systems and on the budgets of the healthcare facilities. The cost to replace the instruments is referenced in Table 3-4. If it was added to the overall costs, Table 4-6 would be modified as per Table 4-7 below. The total cost would then be much higher than the base case in this situation.

Table 4-7: Comparison of impacts per kg of 4-tert-OPnEO emissions prevented for impacts lasting only 2.5 years (including new instrument costs)

Impact over review period	Use 1
Review period	5.5 years
GB impact over 2.5 years (£/kg)	334,434
Base case GB (£/kg)	116,719
Substitution Cost (£/kg)	6,566

Social cost of unemployment – different unemployment duration

In calculating the social costs for the non-use scenario, certain assumptions were taken into consideration which if modified, would impact the overall cost. Most of the assumptions tend to underestimate the overall cost. For example, no increase in salaries from 2018 to 2021 has been applied, even though an annual increase is expected. Furthermore, only the salaries of the workers directly employed by the Applicant were considered. No increase in the number of employees was applied, despite the expected growth in the Applicant's operations.

An uncertainty that could overestimate the social costs of unemployment assumed is the average duration of unemployment for each country, however, this could cause overestimation of the social costs. The methodology described by DuFour in the ECHA document on unemployment costs is followed, using 2017 data from Eurostat.

The Applicant's employees would likely be informed in advance of being made redundant. Typically, a notice of one to three months is given. As a conservative approach, it can be assumed that the larger period (three months) would be used by the employee for job hunting and could be deducted from the total unemployment duration. The social costs of unemployment were recalculated based on this assumption, to calculate a more conservative value. An even more conservative reduction of 6 months was also considered. The results are shown in Table 4-8.

Table 4-8: Comparison of social costs of unemployment in base case and with reduced employment duration

Impact over review period	Use 1
Review period	5.5 years
Base case (£/kg)	*i*
3-month reduction (£ million)	
6-month reduction (£ million)	

The impact of the unemployment period to the overall impacts and the Pounds Sterling per kg of prevented emissions is shown in Table 4-9 for the non-use scenario.

Table 4-9: Comparison of impacts per kg of 4-tert-OPnEO emissions prevented with reduced unemployment

Impact over review period	Use 1
Review period	5.5 years
3-month reduction GB (£/kg)	76,646
6-month reduction (£/kg)	73,251
Base case GB (£/kg)	116,719
Substitution Cost (£/kg)	6,566

The impact of the social cost of varying unemployment durations on the overall costs per kg of prevented 4-tert-OPnEO emissions is relatively low.

4.3.3 Discussion on overall uncertainty in SEA

The results of the SEA are considered robust. As the sensitivity analysis showed, even at a conservative scenario, the ratio of monetised costs per kg of prevented emissions of 4-tert-OPnEO is very high in GB, and a refused authorisation is much less efficient than the Applicant's own R&D substitution project.

It should also be considered that, all calculations of the cost per kg ratio, only costs related to profits of the Applicant, and the social costs of unemployment were considered. The high costs associated with switching customers to an alternative instrument has not been included in the calculations. If these were included, the overall economic costs would be higher. Most importantly, the ratios do not consider the significant health cost for patients relying on test results from the Applicant's IVD kits. A refused authorisation would lead to delayed test results potentially leading to increased health risks for millions of patients in GB that need to have their samples tested with the Applicant's immunoassay and clinical chemistry kits. A refused authorisation could significantly impact the availability of tests for donated blood in GB, where 100% of the blood donations are tested using the Applicant's assays. These impacts are significant but cannot be monetised.

The assumptions made in the SEA were based on a conservative approach. Even so, the overall benefits of a granted authorisation for the economy and the society far outweigh the impacts to the environment, as shown in the calculations made for the sensitivity analysis. Even if the worst possible scenarios were combined, the cost per kg ratio would still be high and much higher than the respective ratio of the Applicant's R&D project.

5. Conclusions

The analysis completed in this SEA shows that a refused Authorisation for the use applied for is not a cost-effective option for reducing emissions of 4-tert-OPnEO to the environment, particularly if compared to the Applicant's ongoing substitution project over the length of the review period.

If the Applicant's IVD kits are removed from the GB market, as discussed in the non-use scenario, the potential for disruptions in the operations of clinics, hospitals and other medical facilities using the IVD kits is high. Capacity of these facilities to run tests to detect infections or other conditions (e.g. cancer, diabetes) in patients, as well as analyses of important chemicals in patient samples may be at risk. This could increase risks to patients' health, in case a delayed or erroneous diagnosis is made.

The risks are significantly higher for blood screening services and blood banks, as the Applicant's transfusion products screen a large percentage of the blood and plasma donations each year for transfusion-transmitted diseases such as HIV, HCV, HBV, HTLV, Syphilis, Chagas and CMV in GB. Interruption of supply of the Applicant's reagents, would impact the ability of GB to supply safe blood and plasma products, impacting blood and plasma needed for emergencies as well as regular blood recipients. Additionally, it would impact the supply of plasma needed for key medical therapies. The risk to patients in GB could be put at risk in the event of a refused authorisation.

In the event of a refused authorisation, over 150 positions would be eliminated within GB, as evaluated within this SEA, causing impact to the regions where these employees reside.

This SEA calculated the cost of authorisation for the use, which includes lost profits for the Applicant and their suppliers and the social cost of unemployment, per kg of prevented 4-tert-OPnEO emissions. The ratio is greater than £116,000 per kg for the GB impacts. This cost is significantly higher than the reduction in emissions expected to be achieved during the same period by the Applicant's R&D project to substitute 4-tert-OPnEO out of the reagent. The expected cost per kg of prevented emissions from the Applicant's ongoing substitution project over the review period is approximately £6,566, per kg 4-tert-OPnEO for reagents. Overall, it is considered that a refused authorisation for the use examined in this SEA, would have a disproportionate impact to the Applicant, their customers and, most importantly, the lives of patients who are in need of blood and blood components (e.g. emergency in operations) and those who are being tested for serious diseases and conditions (e.g. thyroid or cancer) with the immunoassay IVD kits of the Applicant. The predicted environmental concentrations are low and dispersed across GB, therefore it is expected that environmental impacts would not be significant. As the Applicant is actively substituting 4-tert-OPnEO, from the reagent solutions of their IVD kits thereby decreasing emissions to the environment.

The Applicant is actively working to substitute 4-tert-OPnEO and other SVHCs from their products distributed in GB and globally. With the significant number of impacted products (over 200), a review period of 5.5 years (through 4-Jan-2027 to coincide with the review period of the Applicant's EU review period) is required to complete substitution activities for the manufacturing of IVD kits, and the use of the IVDs in professional laboratories, while concurrently meeting the regulatory requirements of the EU IVDR. Identifying and implementing an alternative in the Applicant's IVD kits requires significant testing to verify that the substituted assays perform within specifications, and receipt of regulatory approval from UK, EU and non-EU countries.

As shown here, the benefits offered to the GB society by the use applied for are much more significant than the impacts to the environment. It is not technically and economically possible to reduce further emissions from the downstream uses.

Therefore, based on the analysis completed in this SEA, the benefits of granting the Applicant authorisation for the requested use outweighs the risk to the environment over the requested review periods of 5.5 years. It is concluded that a refused Authorisation is not a cost-efficient option for reducing emissions of 4-tert-OPnEO, especially compared to the Applicant's existing risk management measures and the on-going substitution project.

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Annex 2 – Methodology of calculation of unemployment costs

Overview

Calculation of the social costs associated with unemployment in case of a refused authorisation is based on the methodology developed by Dubourg [21]. According to its adaptation of the paper from Haveman and Weimer, there are seven major impacts arising from job loss [24]:

1. The value of wages / output that were lost while the person was unemployed
2. The cost of searching for a new job, along with hiring and firing employees
3. The 'scarring effect', i.e. the impact of being unemployed on future earnings and employment possibilities
4. The value of leisure time during the period of unemployment
5. The costs of health and other well-being effects of being unemployed on the unemployed person
6. The costs of health and other well-being effects of being unemployed on others
7. External costs of unemployment (e.g. health treatment costs paid by taxpayers)

The paper further describes calculation methods for elements 1-4 above, as available literature suggests the relationship between mental/physical health and unemployment is not well understood.

This appendix to the SEA describes the methodology followed in the calculation of the social costs of unemployment and calculates cost elements 1-4 above for a single impacted employee. These costs are then applied to the non-use scenario of the applied for use being addressed within the SEA. As addressed within the SEA and AoA, the Applicant's commercial offices are present in GB.

Methodology

The value of wages /output lost during unemployment

If an employee becomes unemployed, the valuable output produced by this individual would be lost to society. This lost output can be calculated by multiplying a measure of labour output with the expected duration of the individual's unemployment. It is suggested by Dubourg to use pre-tax worker compensation as the labour output measure. This includes taxes paid by the worker (e.g. income tax) and employer contributions (e.g. social insurance).

The loss of the wage/output contribution does not include the redundancy payment that the individual would receive from the Applicant. While this would reduce the individual's loss during the unemployment period, it would at the same time increase the Applicant's loss. Therefore, redundancy payments are a zero-sum social cost element and not considered in the calculation of the total social costs.

Labour costs

The average salary of employees within GB will be used to calculate the gross salary, which includes income tax paid by the employee. Gross salaries are based on the average salary for the Applicant's employees in GB. The total salary only referred to employees that were directly employed by the Applicant. The gross salaries do not include the employer's social contributions.

To calculate the total wage contribution by the Applicant, the SEA uses values for the average social contribution as a percentage of the gross salary paid to the employee in the UK [22]. The rate was calculated as the quotient of the employer social security to the employee's gross salary. The result was used to increase the Applicant's employee gross salary.

Table II-1 shows the average wage paid to the Applicant's employees and the total output, including employer's social contributions.

Table II-1: Average annual salaries for the Applicant's employees

Country	Average annual salary for Applicant's employees (£)	Employer social contributions rate*	Gross annual salary including employer contributions (£)
Great Britain	*i*	11%	*i*

Notes
*: Calculated from data in: Rogers, J. & Philippe, C. (2018). The Tax Burden of Typical Workers in the EU 28-2018. Paris-Brussels: Institut Economique Molinari. Available online at: http://www.institutmolinari.org/IMG/pdf/tax-burden-eu-2018.pdf
A 0.72 £/$ exchange rate was used to convert the average salaries from $ to £

The average gross salary for GB will be used to calculate the lost output per year of unemployment for the Applicant's employees that would lose their job in the Non-Use Scenario for the use applied-for.

Unemployment duration

The second input required for the calculation of social output loss is the duration of unemployment for the employees that would lose their job in case of a refused authorisation.

The Applicant employs over 150 employees in GB, where commercial offices are located.

The average unemployment duration for the Applicant's GB employees was calculated using unemployment duration data collected from Eurostat [25]. The dataset contained information on the number of unemployed who were in that situation for various durations, ranging from less than 1 month to over 2 years. Data were available as quarterly figures, so a full year average was calculated for 2017. Afterwards, the share of each duration range was determined. The average duration of unemployment for the Applicant's GB employees was calculated as the sum of the products of the percentage of unemployed for a certain duration and the mid-point of the respective range. Table II-2 shows an illustrative example of calculating the average duration of unemployment in Great Britain.

Table II-2: Calculation of duration of unemployment in GB

Duration (months)	Assumed duration (months)	# of unemployed ('000)	% of unemployed	Cumulative months
Less than 1 month	0.5	238.1	16.4	0.08
From 1 to 2 months	1.5	348.1	24.0	0.36
From 3 to 5 months	4.0	233.7	16.1	0.65
From 6 to 11 months	8.5	229.9	15.9	1.35
From 12 to 17 months	14.5	118.4	8.2	1.18
From 18 to 23 months	20.5	53.8	3.7	0.76
From 24 to 47 months	35.5	97.2	6.7	2.38
48 months or over	48	105.4	7.3	3.49
Total		**1,424.5**		**10.26**

Source: Eurostat (2018)

Table II-3 summarizes the unemployment duration of the Applicant's GB employees. The number of employees includes those employed directly by the Applicant and contract employees.

Table II-3: Average unemployment durations for GB

Country	Number of Applicant's employees	Average unemployment duration (months)	Average unemployment duration (years)
Great Britain	*g*	10.26	0.85

The Applicant's employees have a wide range of ages, education levels and working experience in their respective fields. Many are highly skilled professionals, which could be highly desirable by other companies, meaning they could have lower unemployment durations. Others, having more general skills may face higher competition in the labour market, thereby potentially causing extended unemployment durations.

The Applicant's employees may receive sufficient notice for their redundancy, e.g. 3 months or longer. This would give them time to search for a new job, effectively reducing the duration of their unemployment. If this is assumed for employees in GB, the calculated average unemployment durations shown in Table II-3 could be reduced by 3 months, also allowing for a more conservative calculation. However, considering the number of the Applicant's employees, the average unemployment duration is considered to be applicable to those that would be made redundant in case of a refused authorisation.

Calculation of loss of output

The lost output in case of a refused authorisation is calculated as the product of the pre-tax gross salary, including employer's social contribution, and the average duration of unemployment for the Applicant's employees that would lose their jobs in GB. Table II-4 shows the cost per employee in GB.

Table II-4: Average loss of output per employee in GB

Country	Average unemployment duration (years)	Average real gross annual salary for Applicant's employees including employer contributions (£)	Average loss of output per employee (£)
Great Britain	0.85	*i*	

The lost output would be spread over less than one year in GB, therefore, 2022 is used as base, being the first year after the sunset date (beginning in July) and therefore the first year of potential unemployment. Output loss incurred in subsequent years is discounted to 2022 prices, using a 4% discount factor.

Scarring costs

'Scarring' effects describe the impact of unemployment to the unemployed individual's subsequent jobs. These can manifest as a prolonged period of unemployment or reduced wages, as a result of economic pressure for the individual, de-skilling due to inactivity, opportunity costs of not getting work experience or not finding a position that matches the individual's skillset as well as the previous position.

There have been several studies in the EU to calculate the scarring effects on wages after a period of unemployment. The studies, as presented in Dubourg's paper, were conducted in different time periods, countries and different populations of workers. The penalties in wages vary significantly among the studies, ranging from as low as 4.4% to 34.6% or even higher.

The studies also show that the scarring effect declines over time. Haveman and Weimer assume that the scarring in wages will persist for six years after re-employment, provided that the individual remains fully employed during that time.

The Applicant's employees have on average higher earnings than the average worker within the UK [22].

Overall, it is expected that the Applicant's employees that could lose their jobs could face scarring effects in their next wage. The scarring effects could persist for the 6 years following re-employment of the individual. The magnitude of the scarring effects is assumed to be 10% of the gross wage, including employer contributions. The scarring cost is assumed constant throughout the 6-year period. This value represents the loss to society from the individual's unemployment, not just the loss to the individual. The value selected for this evaluation is near the low end of wage scarring reported in literature, to present a more conservative approach to the calculation of the social costs of unemployment.

One could argue that unemployed individuals would choose a job that offers economic remuneration that is at the level offered by the Applicant. Considering that the Applicant's employees are earning relatively high wages compared with the average worker in the UK, waiting for such an opportunity could prolong the unemployment period, increasing the impact from loss of output.

As wage scarring could persist for up to six years from the time the individual starts in a new position, the Net Present Value (NPV) is calculated, with 2022 as the base year and using a default 4% discount factor. As the sunset date is in July, the first-year scarring cost covers 6 months, and final 6 months would be in year 7. The NPV for a single employee was calculated for the Applicant's GB employees and the results are shown in Table II-5.

Table II-5: Calculation of scarring costs for a single employee in GB (in £)

Country	Scarring cost	Y1	Y2	Y3	Y4	Y5	Y6	Y7	Y8	NPV
Great Britain	*i*									
A 4% discount factor is used. Y1 is 2022										

In the NUS, the total social cost from wage scarring was calculated as the product of the number of employees that would lose their job in GB and the NPV per employee calculated in Table II-5.

Reservation wages and value of leisure time

The notion of 'reservation wage' is important in labour market theory. It is defined as the lowest wage at which an individual is willing to work. Empirically, the reservation wage has been positively correlated with the duration of unemployment, i.e. higher reservation wage leads to longer unemployment, as the individual would look longer for a higher paying job. Reservation wage and duration of unemployment are further interconnected because the size of the reservation wage may also be affected by the length of the unemployment spell [26].

Reservation wage can be considered as a metric for the value of an individual's leisure time. This value should be deducted from any costs of unemployment in this exercise. The value of leisure time has not been studied extensively, so the reservation wage is used as a proxy. A review of available literature conducted by Dubourg suggests that a fair reservation wage would be approximately 80% of the

expected future wage. The expected future wage should only include the post-tax (take-home) earnings of the individual and should also consider potential wage scarring due to the unemployment spell.

Therefore, assuming a 10% reduction of the last wage due to scarring, the value of a year of the individual's leisure time would be equal to 80% of 90%, i.e. 72% of their last net wage before unemployment. This assumption provides an average value for the Applicant's employees. It is possible that different demographic groups among the employees would have different reservation wages, e.g. those with lower salaries would be having a higher reservation wage, percentwise, due to the higher share of living expenses in their current wage. Nevertheless, the average value will be used for all employees to simplify the calculations.

To calculate the net wage, the share of employee contributions, in the form of income tax and social insurance contribution, were calculated from the data collected by Rogers & Philippe [22]. The average employee tax rate was calculated by measuring the average income tax and social contribution against the average employee income in GB.

Table II-6 shows the steps to calculate the value of a single employee's leisure time in GB for the duration of their unemployment.

Table II-6: Value of leisure time per employee in the UK

Country	Average unemployment duration (years)	Average employee tax and social contribution (%)	Average employee net wage (£/y)	Reservation wage (£/y)	Value of leisure time per employee (£)
Great Britain	0.85	23	*i*		

The total value of leisure time for the Applicant's workers that would lose their job in the NUS can be calculated by multiplying the value of leisure time per employee, as shown in Table II-6, with the number of employees that would lose their job. The sum will be deducted from the overall costs of unemployment.

Job search and hiring costs

The loss of jobs at the Applicant's sites would cause additional costs to be incurred that would not have been incurred in the applied for use scenario. These are human resource costs associated with administrative procedures on the Applicant's side for the redundancies, as well as interviewing and training costs for the new employer. Furthermore, the unemployed individual would also spend time looking for a new job, which would incur additional costs.

Haveman and Weimer [24], as referenced in Dubourg [21], estimated that, in the US, unemployed individuals spent on average 4 hours per week looking for a new job, which is approximately 10% of a typical 40-hour work week. A more recent study in EU countries reported job hunting between zero and four hours a week, depending on age and country of the individual. Based on these figures, the job-hunting time for GB unemployed individuals can be assumed as 2 hours per week or approximately 5% of a 40-hour work week. The cost of these hours should be deducted from the value of leisure time of the individual, because job hunting would be taking away from the unemployed individual's free time.

Hiring a new employee incurs costs to the new employer. This is normal procedure for all new hirings. However, unemployment for the Applicant's employees caused by a refused authorisation is unexpected and causes an additional hiring cycle, thus incurring additional costs. The new employer would have to allocate man-hours for reviewing the applications and interviewing the candidate. After

hiring, there would be a period of training, during which the new employee would be performing at lower productivity.

According to Dubourg, the costs for hiring a new employee can be equal to 10-17 weeks of salary, i.e. 19%-32% of the first year of the employee's wages, though literature is scarce on the subject. These values may depend on the position and the industry sector. This cost will apply on the gross salary, with employer's contributions. Applying the low end of that range on the average gross wage with employer contributions gives the results in Table II-7.

Table II-7: Average hiring costs for individual employees in GB

Country	Average real gross annual salary for Applicant's employees including employer contributions (£)	Average hiring costs per employee (£)
Great Britain	*i*	

Total unemployment costs

Table II-8 shows the unemployment cost for each of the individual components discussed above for an individual employee in GB.

Table II-8: Total social costs of unemployment for individual employees in GB

Country	Lost output	Scarring cost	Value of leisure time per employee	Hiring costs	Total unemployment cost per employee
Great Britain	*i*				