ANALYSIS OF ALTERNATIVES

and

SOCIO-ECONOMIC ANALYSIS

PUBLIC

Legal name of applicant:	Becton, Dickinson U.K. Limited
Submitted by:	Becton, Dickinson U.K. Limited
Date:	June 2022
Substance:	4-(1,1,3,3-tetramethylbutyl)phenol, ethoxylated (4-tert-OPnEO); Generic class: no EC or CAS number allocated
Use title:	Use of 4-(1,1,3,3 tetramethylbutyl)phenol, ethoxylated (4-tert-OPnEO)) for the lysis of different types of cells in order to release the cell contents for subsequence analysis in diagnostics.
Use number:	1

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LIST OF ABBREVIATIONS

Abbreviation	Definition
4-tert-OP	4-(1,1,3,3-tetramethylbutyl)phenol
4-tert-OPnEO	4-(1,1,3,3-tetramethylbutyl)phenol, ethoxylated
AfA	Application for Authorisation
AMR	Antimicrobial Resistance
AoA	Analysis of Alternatives
BD	Becton Dickinson and Company
CBI	Confidential Business Information
CE	Conformité Européenne, meaning the product conforms to EU legislation on Health Safety and the Environment.
CLP	REGULATION (EC) No 1272/2008 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 16 December 2008 on classification, labelling and packaging of substances and mixtures, amending and repealing Directives 67/548/EEC and 1999/45/EC, and amending Regulation (EC) No 1907/2006.
CMC	Critical Micelle Concentration
CMT	Critical Micelle Temperature
CRO	Contract Research Organisations
CSR	Chemical Safety Report
DNEL	Derived No Effect Level
DU	Downstream User
ECHA	European Chemicals Agency
ECS	Environmental Contributing Scenario
EQS	Environmental Quality Standard
EEA	European Economic Area
EWC	European Waste Catalogue
FDA	US Food and Drug Administration
HPV	Human Papilloma Virus
HSE	Health and Safety Executive (UK Competent Authority)
IVD	In vitro diagnostic medical device
LAD	Latest Application Date
LUO	Laboratory Use Only
NGO	Non-Governmental Organisations
NHS	National Health System
NP	Nonyl Phenol
NPnEO	Nonylphenol Ethoxylates
NUS	Non-Use Scenario
OC	Operational Conditions
PCR	Polymerase Chain Reaction
PEG	Polyethylene Glycol
PNEC	Predicted No-Effect Concentration
POC	Point of Care
RMM	Risk Management Measures
RSV	Respiratory Syncytial Virus

RUO	Research Use Only
SBT	Sample Buffer Tube
SD	Sunset Date
SEA	Socio-Economic Analysis
STI	Sexually Transmitted Infections
STOT SE	Specific Target Organ Toxicity – Single Exposure
SVHC	Substance of Very High Concern
URS	Unitised Reagent Strip
UVCB	Unknown or Variable composition, Complex reaction products or Biological materials
V&V	Validation and Verification
WWTP	Waste Water Treatment Plant

DECLARATION

We, Becton, Dickinson U.K. Limited, are aware of the fact that further evidence might be requested by HSE to support the information provided in this document.

Also, we request that the information blanked out in the "public version" of the Analysis of Alternatives and Socio-economic Analysis is not disclosed. We hereby declare that, to the best of our knowledge as of today (27 June 2022), 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.

Daniel Hopkin

Director – Becton, Dickinson U.K. Limited

Winnersh, 27 June 2022

1. SUMMARY

1.1. Background

4-(1,1,3,3-tetramethylbutyl)phenol, ethoxylated (covering well-defined substances and UVCB substances, polymers and homologues) (4-tert-OPnEO, 'OPnEO') has been included in Annex XIV to Regulation (EC) No 1907/2006 ('REACH') as it has an equivalent level of concern having probable serious effects to the environment (Article 57 f).

The REACH Member State Committee supporting document for the identification of the substance as a Substance of Very High Concern (SVHC) states that OPnEO partly degrades to 4-(1,1,3,3-tetramethylbutyl)phenol, 4-tert-octylphenol (OP), either in wastewater treatment plants, or via further degradation processes in sediments (e.g. of aquatic bodies receiving the wastewater effluents) and soils (e.g. receiving sewage sludge). OPnEO was identified as a SVHC, and placed on the authorisation list on 13 June 2017, due to its endocrine disrupting properties with potential serious environmental consequences, solely on the basis of the properties of the respective alkylphenol degradation product, OP.

This Analysis of Alternative (AoA) – Socio-Economic Analysis (SEA) document supports the Application for Authorisation (AfA) of Becton, Dickinson U.K. Limited ("BD", "the applicant") to the UK authorities, for the continued use of OPnEO for the lysis of different types of cells (mammalian and bacterial) in the UK. The applicant's EU distribution centre in Belgium has applied for a REACH authorisation for this use of OPnEO in the EU.

The applicant uses OPnEO in one use in the UK:

USE 1: Use of 4-(1,1,3,3 tetramethylbutyl)phenol, ethoxylated (4-tert-OPnEO) for the lysis of different types of cells in order to release the cell contents for subsequent analysis in diagnostics.

The methodology employed in this report follows the European Chemicals Agency (ECHA) guidance for an AoA-SEA for an AfA.

BD is a global medical technology company that is *advancing the world of health* ™ by improving medical discovery, diagnostics and the delivery of care. The applicant manufactures and sells medical devices, instrument systems, and reagents. The applicant manufactures a number of diagnostics outside the UK, primarily in the USA and Canada. These diagnostics are sold into the UK via their legal entity Becton, Dickinson U.K. Limited (the applicant).

In Great Britain (England, Wales and Scotland), devices must conform to the UK Medical Devices Regulation (MDR) 2002, or the EU In Vitro Diagnostic Directive (IVD) 98/79/EC in order to be registered with the Medicines and Healthcare products Regulatory Agency (MHRA). For the purpose of this AfA, "diagnostics" mean *In Vitro* Diagnostic Medical Devices (IVD) regulated by Directive 98/79/EC and similar products (such as for Laboratory Use Only products (LUO) and Research Use Only products (RUO)).

The applicant's diagnostic systems are made up of an analytical system (the instrument) and a diagnostic test product (contains a test cassette or cartridge with reagents compatible for a specific instrument or reagents to be used with specimens). The results of each test are available in real time.

IVDs are defined in Directive 98/79/EC as "*any medical device which is a reagent, reagent product, calibrator, control material, kit, instrument, apparatus, equipment, 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:

- *concerning a physiological or pathological state, or*
- *concerning a congenital abnormality, or*
- *to determine the safety and compatibility with potential recipients, or*
- *to monitor therapeutic measures.*"

After the UK Sunset Date, the applicant estimates to place >20 types of diagnostic products on the UK market, belonging to a range of diagnostics , namely BD MAX™, BD COR™, Viper™ LT, BD Leucocount™, BD Veritor™, as well as Laboratory Use Only (LUO) and Research Use Only (RUO) products, which are part of three different groups within BD, namely molecular, point-of-care and biosciences. This equates to more than [redacted] diagnostics annually, which can be used to carry out more than [redacted] (100,000-500,000) tests each year as of 2022. The numbers of tests may increase to [redacted] (1-5) million tests annually, as the applicant expects that BD COR™ will gain market share. CBI 3

The diagnostics are shipped to hospitals, blood banks, contract research organisations (CROs), and doctor's surgeries across the UK. The diagnostics are used in the analysis of a number of endpoints. These endpoints are summarised in Table 3-5 but the main areas the applicant's diagnostics are used in are antimicrobial[1] resistance (AMR), infectious diseases and women's health and cancer. OPnEO is a key constituent of these diagnostics for the purpose of the lysis[2] of different types of cells (e.g. mammalian and bacterial) in order to release the cell contents for subsequent analysis in BD diagnostics. Distributors may be used for shipping the applicant's products to downstream users. These distributors handle the diagnostics in the same manner as the applicant, before shipping the diagnostics to the end users.

1.2. Analysis of Alternatives and Substitution Plan

Due to the variety of diagnostics the applicant puts in the market, it is expected that it will be difficult to identify one single, blanket, alternative for all of them and that the applicant will need to evaluate more than one alternative in the process of substituting OPnEO in all of their products.

The applicant formed a list of possible substitutes by collecting potential alternatives to OPnEO from documentation from the EU AfA they submitted in 2019, supplemented by additional literature review carried out since then, as well as from EU AfAs submitted by other diagnostic companies. Following the creation of this list of potential alternative detergents, the applicant carried out tests to evaluate the performance and stability of a number of alternatives that exhibited critical surfactant properties comparable to those of OPnEO.

Based on the results of the testing, the applicant decided, as a first step, to proceed with the evaluation of two potential alternatives, Alternatives 3 and 4 for some of their molecular products. Alternatives 3 and 4 are commercially available substances. Alternative 3 has been evaluated for use in a number of molecular diagnostic components.

[1] Drugs that kill infectious bacteria, viruses, parasites and fungi
[2] The disintegration of a cell by rupture of the cell wall or membrane.

Alternative 4 is also being evaluated in at least one molecular diagnostic component. Furthermore, both Alternative 3 and 4 may be considered for use in other diagnostics.

As the various diagnostics have different chemistries, the applicant would need to separately evaluate the technical feasibility of the alternatives in each diagnostic. For example, it must be noted that Alternatives 3 and 4 were not found suitable for some point-of-care diagnostics, so a different alternative may need to be identified, although the alternatives may still be trialled in point-of-care products under development.

Substitution of OPnEO in the applicant's diagnostics is restricted by the strict qualification and regulatory approval processes for *in-vitro* diagnostic devices that the applicant must follow. It may require up to 5 years to qualify and launch a single diagnostic product after a major component change, such as in this case. In addition, the more than 20 types of diagnostics sold in the UK are a sub-group of the more than 40 types of diagnostics currently placed in the EEA market. Considering the relatively small share of the UK sales in the total EEA-UK region, substitution of existing products, if feasible, will be driven by the EEA sales and associated revalidation processes, with diagnostics with high volumes of EEA sales being prioritised.

Due to all the above factors, it will not be possible for the applicant to substitute OPnEO from their diagnostics before the UK Sunset Date.

The applicant's focus has been on looking for alternative detergents, such as alternative 3 and 4, in new product development. The applicant will initiate an additional project to focus more resources on substitution.

The applicant is currently planning to use an alternative detergent in new product development and evaluate the feasibility to substitute in existing diagnostics. In some cases, this may be Alternative 3 or Alternative 4, but, as each diagnostic has different requirements, it is possible that more alternatives will need to be used. It is the goal of the applicant's R&D programme to identify such alternatives for each individual diagnostic specifically and may end up with a broad range of alternatives, as is already evident with the use of Alternative 3 and Alternative 4.

1.3. Residual Environmental Risks

The use of the applicant's diagnostic systems generates two waste streams, solid and liquid. The ratio of solid / liquid waste differs among the different diagnostic systems, but, overall, it is estimated that approximately 70% of OPnEO in the diagnostics ends up in solid waste and the remaining 30% in liquid waste.

All solid waste is incinerated in compliance with UK national biohazardous waste regulatory requirements and downstream user good practice. As such, there is no emission of OPnEO through this route. There are, however, different methods of treating liquid waste containing OPnEO. Taking a worst case scenario approach, it was assumed for the purposes of this AfA that all liquid waste will be released to the sewer and will eventually degrade to OP, regardless of the presence of any wastewater treatment.

The calculated volume of emissions of OP as a result of the use of the applicant's diagnostics in the UK are approximately [redacted] (1-10) kg per year on average. This is likely an overestimation, as it was assumed that no degradation of OP in wastewater treatment

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plants takes place and that there are no other liquid waste treatment methods in effect (e.g. incineration off site), which could reduce the emitted quantities.

1.4. Socioeconomic analysis

In the Non-Use Scenario (NUS), the applicant will stop selling their diagnostics containing OPnEO in the UK market. The monetised impacts in the NUS are estimated at approximately £[redacted] (£1-5) million per year and this only considers the applicant's lost net profits. Compared to the calculated emissions of OP, this results in approximately £[redacted] (£0.5-5) million per kg of prevented OP emissions. CBI 3

Apart from the economic impacts for the applicant, downstream users may also face costs from having to switch suppliers of diagnostic systems, and there may be shortages in diagnostics, resulting in delays in patient sample testing. These impacts, the delays in patient sample testing and the additional costs to the NHS, have not been taken into account when monetising the impacts in this AfA.

Furthermore, competitors that could take over the applicant's UK market share have also applied for and received an authorisation for the use of OPnEO, which means that the quantities of OPnEO that will be placed on the UK market and released to the environment will not necessarily be lower in a NUS.

Overall, the applicant is of the opinion that the lack of suitable alternatives for all diagnostics at the sunset date, long development timelines largely driven by the validation and regulatory approval processes, the low expected emissions of OP in the UK and the high impacts of a refused authorisation for the applicant and the UK society (healthcare system and patients) justify requesting a long review period of 12 years.

Allowing for the continued use, BD will import diagnostics into the UK to be used by DU in the diagnosis of potentially life threatening conditions for UK patients.

1.5. Review Period

The applicant is applying for a **12-year review period**. This review period is based on the following criteria:

1. There is no current alternative detergent, substance, or technique that is a technically feasible alternative to the continued use of OPnEO in all of the applicant's diagnostics. Some potential alternatives (Alternatives 3 and 4) have been found to work in in a number of new diagnostic components, but they have not been proven for existing diagnostics. As such it is not possible to have an alternative by the Sunset Date.
2. The timelines and costs associated with any potential substitution are not feasible due to the number of complex diagnostics currently placed on the UK market by the applicant. Development of a new or modified diagnostic or diagnostic system needs to follow a strict process, involving validation of the new products and production line, as well as the requirement of marketing authorisation. This is a lengthy process that needs to be carefully followed to completion. Furthermore, the UK market is not always leading substitution, as the same diagnostics are used in the EU and the rest of the world. Any substitution will have to take place across all

regions, as keeping different versions of the same diagnostic for each region is not efficient. Therefore, it is possible that substitution will be driven by the EU market.

3. There are very limited risks to the environment. In a worst case scenario, there are very small discharges of OP (via degradation of OPnEO) to the environment across the UK that are attributable to the use of the applicant's diagnostics. This discharge is low due to overall low volumes of OPnEO placed on to the market and to the risk management measures (RMM) and operational conditions employed by the end-users of the diagnostics.
4. For the applicant, the focus during the review period is the continued supply of diagnostics to UK hospitals, doctor surgeries, blood banks and contract research organisations (CRO). Not granting the AfA for the use of OPnEO in diagnostics imported and used for patient care for the UK would result in a significant impact to these end users' groups, and ultimately impact on the quality of UK patient care. As a conclusion, the benefits from the continued use of OPnEO as a processing aid in the applicant's diagnostics significantly outweigh the risk to the environment, as demonstrated in the impact assessment section of this report (Sections 4.4 and 4.5).

2. AIMS AND SCOPE

2.1. Background information

4-(1,1,3,3-tetramethylbutyl)phenol, ethoxylated (covering well-defined substances and UVCB substances, polymers and homologues) (4-tert-OPnEO, 'OPnEO') has been included in Annex XIV to Regulation (EC) No 1907/2006 ('REACH') as it has an equivalent level of concern having probable serious effects to environment (Article 57 f) [1].

As noted in the EU Member State Committee supporting document for the identification of the substance as a SVHC, OPnEO degrades to 4-(1,1,3,3-tetramethylbutyl)phenol (OP), either in wastewater treatment plants, or via further degradation processes in sediments (e.g. of aquatic bodies receiving the wastewater effluents) and soils (e.g. receiving sewage sludge).

OPnEO was identified as a SVHC and placed on the authorisation list on 13 June 2017 due to its endocrine disrupting properties with potential serious environmental consequences solely on the basis of the properties of their respective alkylphenol, i.e. OP [2].

This Analysis of Alternatives (AoA) – Socio-Economic Analysis (SEA) document supports the Application for Authorisation (AfA) submitted by Becton, Dickinson U.K. Limited ("the applicant") for the use of OPnEO for the lysis of different types of cells in order to release the cell contents for subsequence analysis in imported diagnostics.

In June 2019, Becton Dickinson submitted an Application for Authorisation under EU REACH for the use of imported diagnostics by professionals in the EU, including the UK at the time. The ECHA opinion on this AfA was published on 3 June 2021 and sent to the Commission. The European Commission has not yet issued its decision.

When UK REACH came into force in the UK on 1 January 2021, the UK retained the Authorisation provisions of EU REACH in full. This includes the substances that were already included in the Authorisation List of EU REACH. UK REACH also retains the same Late Application Dates (LADs) and Sunset Dates (SDs) for OPnEO [3].

It is now beyond the SD in the EU, so either an Authorisation or an AfA before the LAD is required for BD to keep using the substance. However, there are transitional arrangements for UK-based downstream users of an Annex XIV substance, if:

- an AfA was made under EU REACH before the EU LAD;
- the LAD is before the end of the transition period (end of 2020); and
- the SD is on or after March 2017.

If all of the above apply, then the LAD can be extended by 18 months after the end of the transition period of UK REACH, i.e. until the end of June 2022. UK downstream users of an Annex XIV substance for which a decision on an EU AfA covering their use is still pending will need to resubmit an AfA to the UK competent authority, i.e. the Health and Safety Executive (HSE).

2.2. Scope of the report

The applicant sells diagnostics containing OPnEO into the UK to hospitals, contract research organisations (CROs) and doctors' surgeries.

The geographical focus of the SEA part of the report will be the UK and the AoA and SEA will focus on the diagnostic systems using the diagnostics containing OPnEO that are placed on the UK market.

It is necessary to provide a distinction of the different terms used in the report:

- **A diagnostic instrument (an analytical system)** – this is the overall body of the diagnostic system and is used to load and house the diagnostic during analysis.
- **A diagnostic** – contains test cassettes or cartridges or reagents compatible for a specific instrument. The reagents present in the diagnostic are specifically formulated for the target analyte which constitute the test. Therefore, the contents of specific reagents will vary dependent on the test being run. For example, a BD MAX™ diagnostic testing for pathogens responsible for enteric diseases will have a different reagent mix to a BD MAX™ diagnostic testing for pathogens responsible for sexually transmitted infections (STI).

2.3. Aim of the report

The aim of this AoA-SEA document is to demonstrate that:

1. Emissions to the environment are minimised. A full description of the risk management measures (RMM) employed to minimise risks to the environment are provided in the accompanying chemical safety report (CSR);
2. At the SD, there will be no suitable alternative available for the use of OPnEO for the lysis of different types of cells (mammalian and bacterial) in order to release the cell contents for subsequence analysis in imported diagnostics; and
3. The socioeconomic benefits of continued use of the substance in the use outlined above outweigh the risks to human health and the environment.

3. ANALYSIS OF ALTERNATIVES

3.1. Use applied for

BD manufactures a number of diagnostics outside the UK, primarily in the USA and Canada. These diagnostics are sold in the UK through Becton Dickinson's legal entity in the UK (Becton, Dickinson U.K. Limited henceforth "the applicant").

In Great Britain (England, Wales and Scotland), devices must conform to the UK Medical Devices Regulation (MDR) 2002, or the EU In Vitro Diagnostic Directive (IVDD) in order to be registered with the Medicines and Healthcare products Regulatory Agency (MHRA). For the purpose of this AfA, "diagnostics" mean *In Vitro* Diagnostic Medical Devices (IVD) regulated per Directive 98/79/EC and similar products (such as For Laboratory Use Only products (LUO) and Research Use Only products (RUO)).

IVDs are defined in Directive 98/79/EC [5] as "*any medical device which is a reagent, reagent product, calibrator, control material, kit, instrument, apparatus, equipment, 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:*

- *concerning a physiological or pathological state, or*
- *concerning a congenital abnormality, or*
- *to determine the safety and compatibility with potential recipients, or*
- *to monitor therapeutic measures."*

The diagnostics are stored in Becton Dickinson's distribution centre in Belgium, and from there shipped to UK customers, such as hospitals, blood banks, contract research organisations (CROs) and doctors' surgeries. Once at these locations the diagnostics are used in the analysis of the endpoints in Table 3-5. OPnEO is a key constituent of these diagnostics for the purpose of the lysis of different types of cells (mammalian and bacterial) in order to release the cell contents for subsequent analysis in the applicant's diagnostics.

The applicant has no plan to exit the diagnostic market and the relevant sections of this AfA detail the efforts made by the applicant in identifying suitable alternatives to OPnEO in their IVD products.

3.1.1. Substance details

Triton X-100 is a commercial trade name for OPnEO, which is used by the applicant in certain diagnostics. OPnEO is the generic class of substances relevant for REACH Authorisation.

The OPnEO present in the diagnostics is identified by the following two CAS numbers: 9036-19-5 and 9002-93-1. The chemical name, molecular formula and molecular weights of these two polymers is shown in the table below.

Table 3-1 Identification of OPnEO used by the applicant

Name	CAS	EC	Molecular Formula	MW
2-[4-(2,4,4-trimethylpentan-2-yl)phenoxy]ethanol	9002-93-1	618-344-0	$(C_2H_4O)_nC_{14}H_{22}O$	602 (n=9) 646 (n=10)
2-(2-[4-(1,1,3,3-Tetramethylbutyl)phenoxy]ethoxy) ethanol	9036-19-5	618-541-1	$C_8H_{17}C_6H_4(OCH_2CH_2)_nOH$	602 (n=9) 646 (n=10)

There is no harmonised classification for OPnEO and it has not been registered under EU REACH, as the substance meets the REACH definition of a polymer and is thus exempt from REACH registration. This is further indicated by the lack of inclusion of this class of ethoxylated substances in the No Longer Polymer List. Therefore, there is currently no definitive substance data set for this class of substances under REACH. There are only C&L notifications mainly for acute hazards.

OPnEO was included in the Authorisation List because of its degradation to OP in the environment. OP (EC 205-426-2; CAS 140-66-9) has a harmonised classification of aquatic toxicity (acute and chronic) according to part 3 of Annex VI of the CLP Regulation 1272/2008 (Index No: 604-075-00-6). In addition, it has endocrine disruption properties for the environment, which, at the moment, are not covered by a hazard code under CLP. The endocrine disruption properties are the main reason for the inclusion of OPnEO in the Authorisation List.

Table 3-2 shows the classifications of OP and the OPnEO substances used by the applicant in their diagnostics.

Table 3-2 Classification of 4-tert-octylphenol and OPnEO

Name	CAS	EC	C&L	Source
4-(1,1,3,3-tetramethylbutyl)phenol; 4-tertoctylphenol	140-66-9	205-426-2	• Skin Irrit. 2 - H315 Causes skin irritation • Eye Dam. 1 - H318 Causes serious eye damage • Aquatic Acute 1 - H400 Very toxic to aquatic life • Aquatic Chronic 1 - H410 Very Toxic to aquatic life with long lasting effects (M = 10)	CLP Harmonised classification (Index No: 604-075-00-6) [6]
2-[4-(2,4,4-trimethylpentan-2-yl)phenoxy]ethanol	9002-93-1	618-344-0	• Acute Tox. 4 H302 Harmful if swallowed • Skin Irrit. 2 H315 Causes skin irritation • Eye Irrit. 2 H319 Causes serious eye irritation	Notified classification (65 notifiers) [7]
2-(2-[4-(1,1,3,3-Tetramethylbutyl)phenoxy]ethoxy) ethanol	9036-19-5	618-541-1	• Acute Tox. 4 H302 Harmful if swallowed • Eye Dam. 1 H318 Causes serious eye damage • Aquatic Chronic 3 H412 Harmful to aquatic life with long lasting effects	Notified classification (1,524 notifiers) [8]

3.1.2. Analysis of the substance function and technical requirement for the product

3.1.2.1. Analysis of Substance Function

Detergents are organic compounds comprised of a hydrophobic hydrocarbon moiety and a hydrophilic charged head group. Detergents are widely used as membrane lysis agents, with cell lysis being the disintegration of a cell by rupture of the cell wall or membrane. OPnEO are common standard detergents in such applications. Due to its amphipathic character (a molecule having both hydrophobic and hydrophilic parts), OPnEO is a non-ionic detergent. The structure of OPnEO is shown in Figure 3-1.

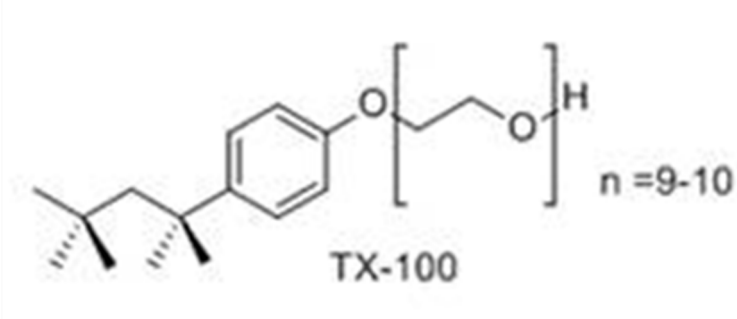

Figure 3-1 Structure of OPnEO

When dissolved in water at a given concentration and temperature, detergent molecules with an amphipathic character like OPnEO will form micelles, as shown schematically in Figure 3-2.

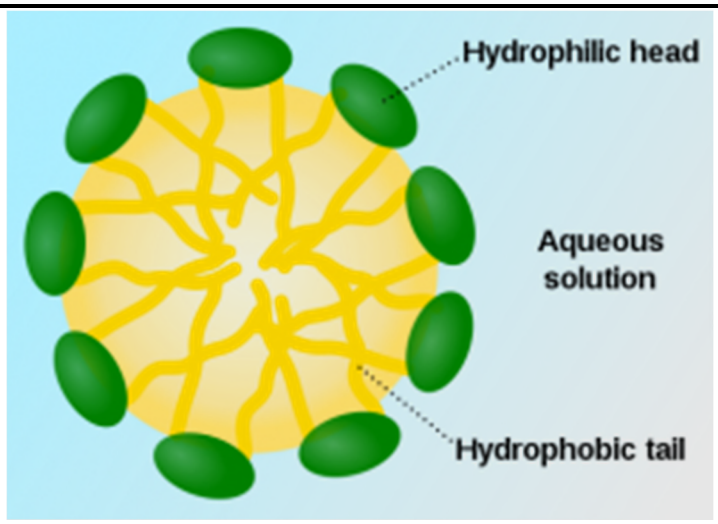

Figure 3-2 Detergent Micelle [9]

The use of OPnEO in high concentration leads to the death of cells, via cell lysis, on prolonged exposure [10]. This toxicity is ascribed to the disrupting action of the polar head group on the hydrogen bonding present in the membrane lipid bilayer, which in turn leads to the destruction of the membrane integrity. Figure 3-3 provides a graphical interpretation of cell lysis by detergents. It shows how lipids from the cell membrane react

with a detergent micelle, rupturing the cell membrane and allowing the contents of the cell to escape.

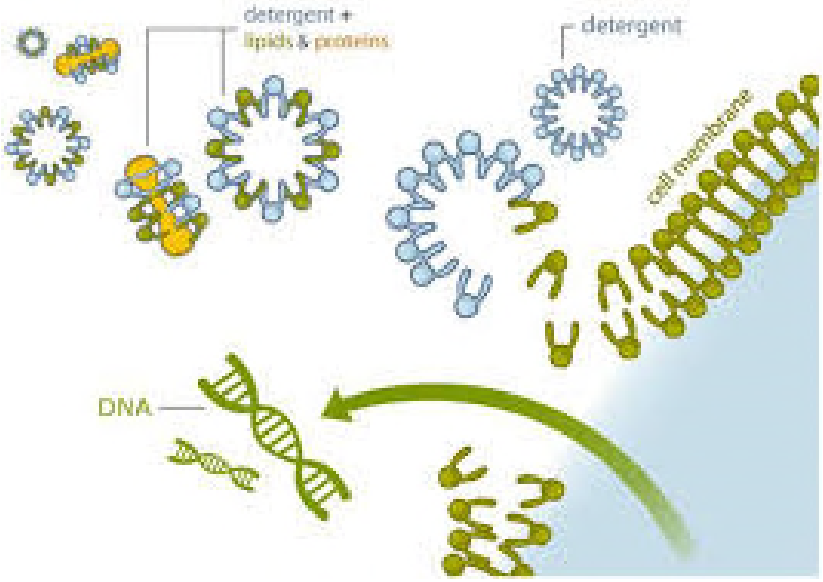

Figure 3-3 Cell Lysis by detergent

The insertion of the detergent monomer at low concentration leads to over-permeabilisation of the cell membrane at detergent concentrations above the Critical Micelle Concentration (CMC) and the Critical Micelle Temperature (CMT). The CMC is the minimal detergent concentration at which micelles are observed, and the CMT is the lowest temperature at which micelles are observed. The CMC and the CMT are important parameters for the lysis of cell membranes as, below these values, Triton X-100 would not cause the reaction shown in Figure 3-3. Koley and Bard (2010) [10] investigated the permeabilisation over membranes in HeLa[3] cells by scanning electrochemical microscopy (SEM) and concluded that any concentration of Triton X-100 at or above the CMC (0.18 to 0.24 mM) is fatal to HeLa cells.

Table 3-3 details the key properties of OPnEO that allow for the Applicant's diagnostics within the scope of this AfA to function and provide repeatable and reliable results for patients across the UK.

Table 3-3 Key Properties of OPnEO for use in the Applicant's products

Property	Reason
Water Solubility	Tests are run in aqueous media, so, if the detergent is not soluble in water, it will not be able to carry out the lysis as required and will not release the contents of the cell for analysis. This would give the potential for inaccurate results. For example when a test designed to detect a specific virus returns a negative result, i.e. no virus detected, but the cell in fact does contain the virus, but due to the detergent not being in the correct phase cell lysis has not occurred and the virus has thus not been detected.

[3] HeLa is an immortal cell line used in scientific research. It is the oldest and most commonly used human cell line and was derived from cervical cancer cells taken from Henrietta Lacks, hence the name HeLa.

Property	Reason
Non-Denaturing Property	Denaturing of proteins involves the disruption and possible destruction of both the secondary and tertiary structures of the protein. If the protein being assessed is denatured by the alternative detergent, then the test has the potential to issue a false positive, in that the structure of the protein being tested for is altered so that it is not recognisable.
High Purity available (Molecular Grade)	Any potential impurities within the substance have the potential to adversely affect the balance of the test media. Impurities are often unknown and variable and can thus have wide ranging effects that can lead to the potential for inaccurate test results as outlined above.
Amphipathic Character	OPnEO is a typical non-ionic surfactant, with an uncharged and hydrophilic head groups. All members of this family of detergents are very similar, differing only in the average number of monomers per micelle and the size distribution of the polyethylene glycol (PEG)-based head groups [11]. Its dual hydrophilic/hydrophobic properties and polyoxyethylene chain enable Triton X-100 to displace lipids and provide a lipid-like environment to solubilise proteins.
Critical Micelle Concentration (CMC)	OPnEO is derived from polyoxyethylene and contains an alkylphenyl hydrophobic group, resulting in a low CMC value. As noted above the CMC is the minimal detergent concentration at which micelles are observed. Once the micelles have been created the cell membranes undergo lysis. As such a low CMC allows a lower concentration, and thus volume, of detergent to be used. The volumes of Triton X-100 used in the applicant's diagnostics is very small. A detergent with a higher CMC value would require a greater amount of detergent in the test cartridge, thus requiring a redesign of the diagnostic.
Stability	BD diagnostics have a shelf life of 9-18 months, as such the detergent used in each diagnostic needs to be stable for that period of time. Storage temperatures can vary between 2-25°C.

Table 3-4 summarises some properties of OPnEO, which are important for its function as a cell lysis agent in the Applicant's IVD products.

Table 3-4 Properties of OPNEO

Property [11]	
Molecular Weight	625
Aggregation Number	100-155
Micelle Molecular Weight	80,000
Critical Micelle Concentration	0.24 mM = 0.0155% w/v
Critical Micelle Temperature	<0°C

3.1.2.2. Description of the function(s) of the Annex XIV substance and performance requirements of associated products

The applicant's diagnostics are placed on the UK market to provide the analysis detailed in Table 3-5.

In general, OPnEO is mainly used in the applicant's diagnostics to lyse membranes or cells, so that the cellular materials are released and detected by the instrument.

The results provided by the diagnostic system must be both reliable and repeatable. As such, the technical function of the system is the most important factor when looking at any alternative to OPnEO. If an alternative cannot provide the same result with the same confidence with regards to reliability and repeatability of the results, it must be rejected due to the sensitivity of the endpoints being assessed.

When assessing any alternatives to OPnEO used in the applicant's diagnostics, the following process criteria are crucial:

- Operated at a very small scale;
- The results produced by the systems are reliable and reproducible and have to be as they are used in clinical diagnosis;
- Based on high throughput – low volume process;
- Sensitive and specific to the endpoint they are measuring. Sample preparation for the diagnostics leads to very low unreportable rates as this process leads to a pure sample with no outside influence; and
- The diagnostics are user friendly in that they require minimum manual manipulation of the sample.

3.1.3. Description of the products resulting from the use of the Annex XIV substance

The applicant imports diagnostics into the UK from their distribution centre in Belgium through their legal entity in the UK (Becton, Dickinson U.K. Limited). The diagnostics are manufactured by BD outside the UK, primarily in the USA and Canada. OPnEO, primarily Triton X-100, is a key constituent of some of these diagnostics. The OPnEO within the diagnostic is used for the purpose of the lysis of different types of cells (mammalian and bacterial) in order to release the cell contents for subsequent analysis in the applicant's systems. Table 3-5 details the diagnostic systems placed on the UK market by the applicant.

There are three different diagnostic product groups imported in the UK that require the use of OPnEO:

1. **Molecular** diagnostics are tests that detect and measure specific cellular alterations or genetic sequences in DNA or RNA and the amino acids or proteins they express, to assess a person's health and the presence of a certain pathogen or disease. The BD MAX™, BD COR™ and BD Viper™ LT instruments are all molecular products. They are intended for use by health professionals in clinical settings, such as in hospitals.
2. **Point-of-care** products are a family of diagnostic products intended to offer rapid detection of a wide range of pathogens without the need for processing at a laboratory or of large equipment, such as molecular diagnostics. These products, which include the BD Veritor™ system, are used by doctors or in clinics, usually in the presence of the patient.
3. **Bioscience** products are mix of diagnostic and research use products. Diagnostic products are intended for use by blood banks, laboratories, and hospital

organisations for quality control of clinical leucoreduced blood products. Some products are to be used in research-only or laboratory-only applications.

Table 3-5 Diagnostic systems using OPnEO placed on the UK Market by the Applicant (not comprehensive list)

Diagnostic Instrument	Analysis	Downstream User
BD MAX™	• Extraction and purification of nucleic acids from biological samples (such as urine, swabs, cerebral spinal fluid, and stool samples); • Detection of enteric pathogens causing gastroenteritis (bacterial, parasites, viruses); • Detection of pathogens causing sexually transmitted infections • Detection of pathogens causing vaginosis /vaginitis • Detection of pathogens causing hospital acquired infections • Detection of pathogens causing respiratory infections	Hospital; Laboratory
BD COR™	• Extraction and purification of nucleic acids from biological samples (such as urine, swabs, cerebral spinal fluid, and stool samples); • Detection of enteric pathogens causing gastroenteritis (bacterial, parasites, viruses); • Detection of pathogens causing sexually transmitted infections • Detection of pathogens causing vaginosis /vaginitis • Detection of pathogens causing hospital acquired infections • Detection of pathogens causing respiratory infections • Detection of pathogen causing cervical cancer	Hospital; Laboratory
BD Leucocount™	• Enumeration of residual White Blood Cells in leucoreduced blood products	Hospital; Laboratory; Blood banks
BD Viper™ LT-BD Onclarity™	• Detection of pathogen causing cervical cancer	Hospital; Laboratory
BD Veritor™	• Detection of pathogens causing respiratory infections	Point of care office
Research Use Only (RUO)	• Analysis of target proteins	Laboratory
Laboratory Use Only (LUO)	• Detection of bacteria in non-clinical samples	Laboratory

The BD MAX™, BD COR™, and BD Viper™ LT-Onclarity™ and BD Veritor™ diagnostic systems listed in the above table work in broadly the same manner. These systems are made up of:

1. **A diagnostic instrument (an analytical system)** – this is the overall body of the diagnostic system and is used to load and house the diagnostic during analysis.
2. **A diagnostic** – contains test cassettes or cartridges with reagents compatible for a specific instrument. The reagents present in the diagnostic are specifically

formulated for the target analyte, which constitute the test. Therefore, the contents of specific reagents will vary dependent on the test being run. For example, a BD MAX™ kit testing for pathogens responsible for enteric diseases will have a different reagent mix than a BD MAX™ kit testing for pathogens responsible for sexually transmitted infections (STI).

The results of each test are available in real time, either via a results screen (i.e. BD MAX™ and BD Viper™ LT systems) or a result print out. A description of each diagnostic operation is outlined below.

The BD Leucocount™ diagnostic operates in a different manner to the above systems and it is explained separately below.

Irrespective of the type of diagnostic or system, OPnEO has the same function, namely the lysis of the sample cells as to release these cell contents for analysis.

3.1.3.1. BD MAX™

The figures below illustrate the BD MAX™ diagnostic instrument (Figure 3-4), and a breakdown of the key components (Figure 3-5) of the disposable diagnostic. The blue front of the analytical system can be opened and closed and it is into this that the diagnostic is loaded. The front is then closed and is not opened again until the analysis has been completed. The results of the analysis are displayed on the screen shown. This diagnostic system is likely to be used at hospitals and / or laboratories.

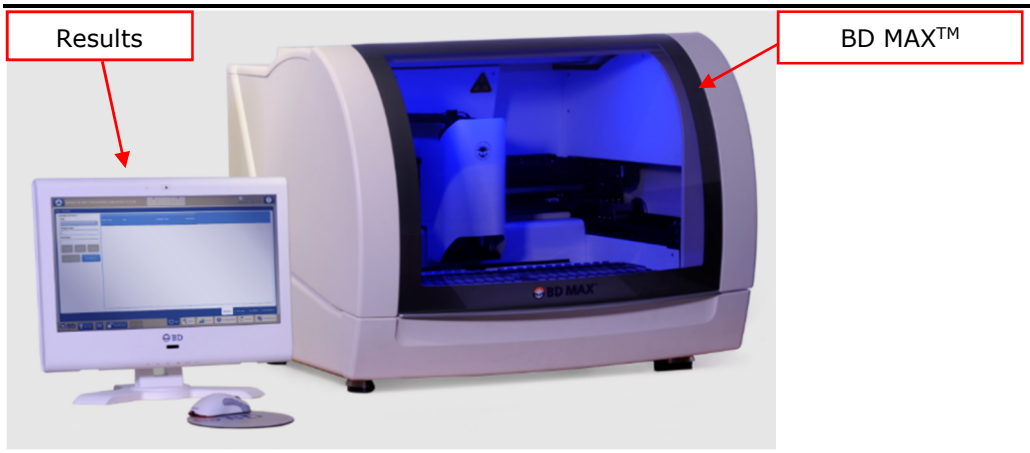

Figure 3-4 BD MAX™ Instrument

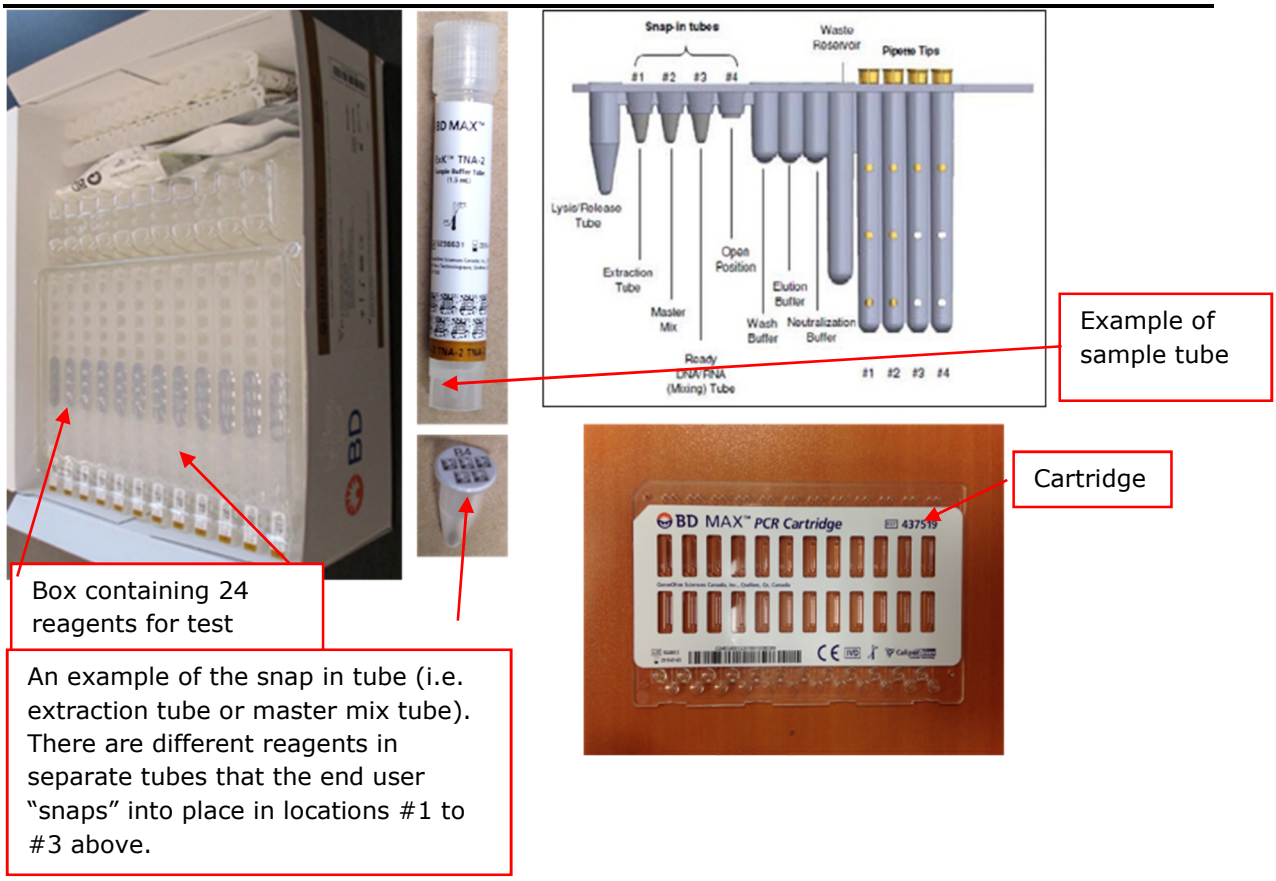

Figure 3-5 BD MAX™ Breakdown of diagnostic

Each BD MAX™ diagnostic contains 24 tests. Each diagnostic is used to detect specific pathogens. There is the option to combine the tests present in the kit to include tests for different assays, e.g. a kit could be used to detect enteric pathogens, mycobacterium tuberculosis etc. The instrument will read the barcode present on all unitised reagent strip (URS) and will determine the test to be run, ensure the correct reagents are present, and what volume to use from the patient sample.

The BD MAX™ analytical system can operate a number of different tests at the same time. The workflow for the process of all BD MAX™ tests is similar and outlined below.

- A sample specimen is collected and transported to the laboratory – the sample is then transferred to the Sample Buffer Tube (SBT). The Sample Buffer Tube is closed with a septum cap or pierceable cap.
- The unitised reagent strip (URS), including the snapped in extraction and PCR master mix tubes, along with the BD MAX™ cartridge and SBT are loaded on the BD MAX™ System and worklist is created via the software in the analytical system. The BD MAX™ system automates sample preparation, DNA extraction amplification and detection.
- OPnEO is generally found in the sample buffer tube, but can also be found in some URS buffers, the extraction tube or master mix tube depending on the test being run by the BD MAX™ system.

- All of these tubes containing reagents, including OPnEO, are filled during the manufacture of the systems in the USA or Canada. These tubes are then sealed prior to shipment.
- During normal operation, once all reagents are loaded into the analytical system, there is no human interaction and the analysis and results interpretation are run automatically. There is no manual removal of seals or packaging when loading the diagnostics.
- At the end of the process, the final reaction will be sealed by the system in the BD MAX™ cartridges to prevent evaporation and any cross contamination. The remaining SBT and URS buffer are not sealed, but are disposed as soon as the PCR cartridge is loaded for another run.
- The used sealed BD MAX™ cartridges are then suitable for disposal.

The technical documentation that is supplied with the BD MAX™ System also outlines warnings and precautions when using the kit. Whilst a number of these are related to the use of the kit and ensuring reliable and repeatable results the following are given with regards to disposal of the finished cartridges and other consumables:

- Do not use the kit if the label that seals the outer box is broken upon arrival.
- Do not use reagents if the protective pouches are open or broken upon arrival.
- Do not use reagents if the foil has been broken or damaged.
- Do not mix reagents from different pouches and/or kits and/or lots.
- Good laboratory technique is essential to the proper performance of the tests.
- To avoid contamination of the environment do not break apart the BD MAX™ Cartridges after use. The seals of the cartridges are designed to prevent contamination.
- Always handle specimens as if they are infectious and in accordance with safe laboratory procedures such as those described in the Clinical and Laboratory Standards Institute: Protection of laboratory workers from occupationally acquired infections (Document M29) and in Centres for Disease Control and Prevention, and National Institutes of Health [15].
- Wear protective clothing and disposable gloves and wash hands thoroughly after performing the test.
- Do not smoke, drink, chew or eat in areas where specimens or kit reagents are being handled.
- Dispose of unused reagents and waste in accordance with local, state, provincial and/or federal regulations.

3.1.3.2. BD Viper™ LT System - BD Onclarity™ HPV Assay

The BD Viper™ LT system operates in a similar manner to the BD MAX™ System. The main difference is that the BD Viper™ LT system has a higher throughput as it operates a greater batch size. However, the control mechanisms, such as the disposal considerations of solid waste and operation as a closed system, are the same as in BD MAX™. However, as well as solid waste, the BD Viper™ LT system also generates liquid waste. Although liquid waste may be disposed via a manner that removes the pathway for OPnEO to enter the environment, the applicant has assumed the worst case that all of the OPnEO present in liquid waste across the UK will end up in the environment.

Figure 3-6 shows the BD Viper™ LT instrument and Figure 3-7 details the BD Viper™ workflow, specifically for the BD Viper™ LT diagnostic.

Figure 3-6 BD Viper™ LT Instrument

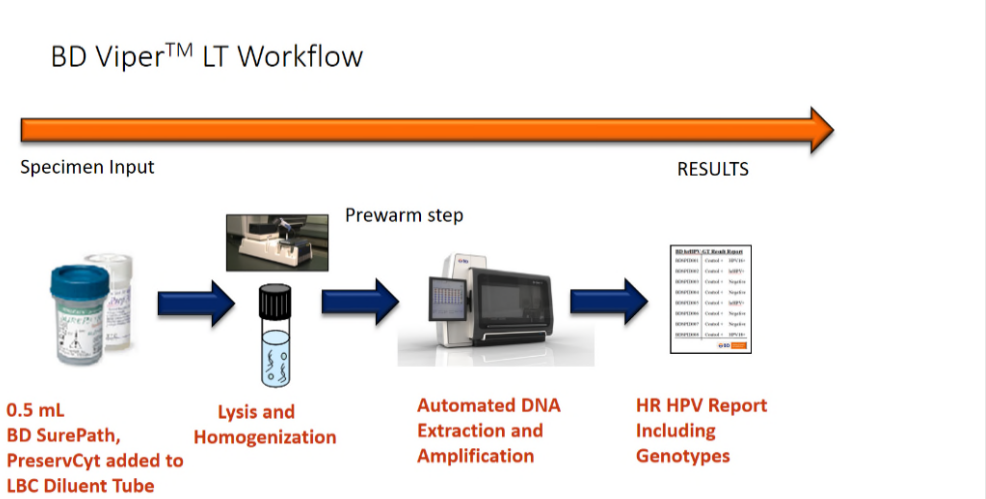

Figure 3-7 BD Viper™ LT Workflow

3.1.3.3. BD COR™

The BD COR™ System is a fully automated, modular, sample prep/PCR system that aims at addressing the Core and Reference Labs' fundamental needs to improve workflow and throughput efficiency, control costs, and provide differentiated, clinically relevant results. A flexible layout and broad test menu will allow the end user to focus on the most relevant tests for their patient population.

The BD COR™ System is comprised of three individual instruments that are configured to meet the differing needs of the Applicant's target segments. The instruments are installed in multiple configurations and do not function as standalone units. In Figure 3-8, the centre instrument (PX) is required for all installations, while the BD COR™ Instrument analysers (GX and MX) can be interchanged in various configurations to satisfy individual customer needs.

The pre-analytical module (PX) automates all processing and analysis logistics as well as receiving sample racks and storage until removed by the user. Automated sample sorting, aliquoting, vortexing, pre-warming/cooling, storage, and retrieval will minimise human errors and provide labor savings that are critical to the cost-conscious demands of today's large hospital labs. The ability to run tests like CTGCTV2[4] and Vaginal Panel from a single specimen will provide more clinically desired results in a more cost-effective manner.

The BD COR™ GX instrument is designed to perform the BD Onclarity™ HPV[5] Assay using technology found in the BD Viper™ LT system, including the BD FOX™ PCR extraction process and amplification using the same real time thermocycler. The BD COR™ GX instrument is designed to be a larger capacity BD Viper™ LT system, therefore, preserving to the technical functionality employed by the BD Viper™ LT. While the BD COR™ GX instrument is processing samples, consumables can be loaded, allowing for higher throughput and more user flexibility compared to the BD Viper™ LT system.

The BD COR™ MX instrument is designed to perform the tests that are currently processed on the BD MAX™ for labs that require a higher daily throughput of tests. The BD COR™ MX instrument uses the core technology found in the BD MAX™ system, including consumable and hardware design elements. The BD COR™ MX instrument is fundamentally designed to be a larger capacity BD MAX™ system, preserving the technical functionality employed by the BD MAX™ system. While the formulations remain the same, the BD COR™ MX instrument reagent consumables differ from those on BD MAX™ to allow for loading of reagents and consumables for processing multiple batches of samples and reloading of the consumables located in the centre drawers (blue lights) while the instrument is processing samples.

Figure 3-8 BD COR™ Instrument Configuration with the three modules PX, GX and MX

[4] STI testing for Chlamydia trachomatis (CT), Neisseria gonorrhoeae (GC) and Trichomonas vaginalis (TV)

[5] Human papilloma virus – STI that can cause cervical and other cancers

3.1.3.4. BD Leucocount™

The BD Leucocount™ kit is designed for counting residual white blood cells in leucocoreduced blood products. This counting is done via the utilisation of a flow cytometer. The components of the kit are the BD Leucocount™ reagent and BD Trucount™ tubes, as shown in Figure 3-9 and the process workflow is shown in Figure 3-10.

This product is available in the UK for use on cytometers such as BD FACSVia™ system (see Figure 3-11) and the BD FACSCalibur™ flow cytometer (see Figure 3-12).

When the workflow has been completed, the waste reagent is treated as per UK waste regulations. The same statement applies to any uncleaned or contaminated packaging, as well as equipment that has been used and may be contaminated (e.g. pipettes used for transfer of reagent). It is noted on the technical data sheets that accompany this product that any waste stream must not be disposed together with household garbage and the product cannot reach sewage system.

As with BD Viper™ LT there is a very small amount of liquid waste generated during the operation of BD Leucocount™. BD guidance has been that the liquid waste was to be treated with bleach and could then be disposed of in the same manner as BD Viper™ and BD COR™. No neutralisation step was required for this product group. However, BD is in the process of changing its guidance and the following instructions will be included in the Instructions for Use (IFU).

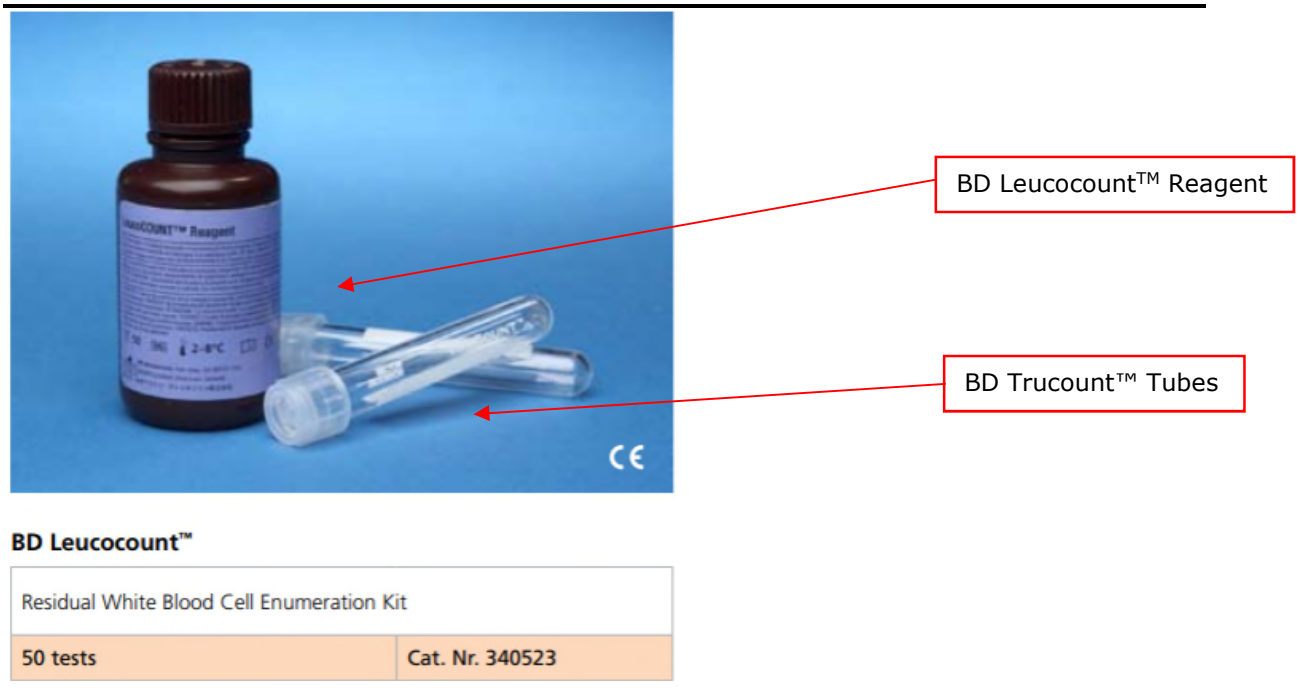

Figure 3-9 BD Leucocount™ Components

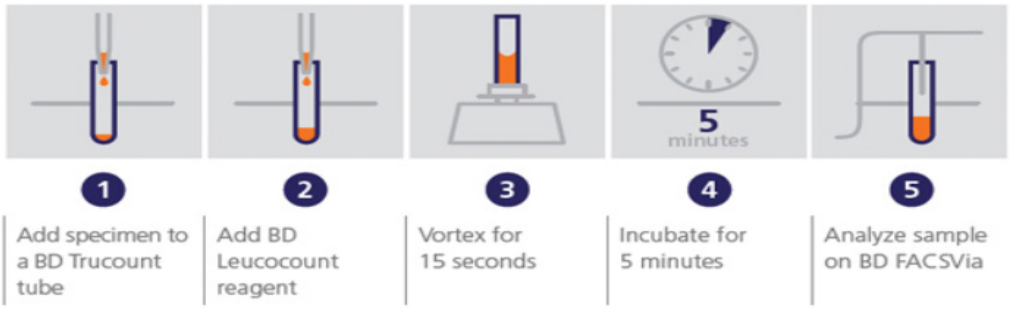

Figure 3-10 **BD Leucocount™ Workflow**

Figure 3-11 **BD FACSVia™ Flow Cytometry system**

Figure 3-12 **BD FACSCalibur™ flow cytometer**

3.1.3.5. BD Veritor™

The BD Veritor™ system is a CE-Marked line of digital immunoassay products, used in in healthcare settings that include primary-care physician offices, retail clinics, retail pharmacies, urgent-care facilities, and acute-care settings. The system is currently used to aid in the diagnosis of influenza A and B, respiratory syncytial virus (RSV), and Group

A Streptococcus. For each of these tests, the system delivers lab-quality test results at the point of care within minutes.

As with other diagnostic systems, BD Veritor™ is operated as a closed system with no exposure or emissions of OPnEO under normal conditions. During use there is a transfer of OPnEO containing solution, however there is no pipette use (like the BD Leucocount™ diagnostics). The transfer amount and speed is controlled by a cap that limits the amount of the OPnEO containing solution that is transferred onto a diagnostic strip to three drops. This transfer is carried out by a professional or trained user. The sample tube and control cap are to be disposed of as biohazardous waste.

Figure 3-13 BD Veritor™

3.1.3.6. Laboratory Use Only (LUO) and Research Use Only (RUO)

OPnEO is present in buffer solutions in the applicant's diagnostics that are used for laboratory purpose or in a R&D environment. The OPnEO present in these LUO and RUO products is used in cell lysis, i.e. the same use as OPnEO in the instruments listed above. However, the applicant's LUO and RUO products are not to be used in clinical diagnosis.

LUO and RUO make up a very small share of the OPnEO placed on the UK market by the applicant.

3.1.4. Sales of applicant's diagnostics containing OPnEO in the UK

The applicant's diagnostics imported in the UK belong to three main product groups, namely molecular, point of care and bioscience. Table 3-6 presents the sales volume and revenue for the kits sold in the UK in the 2018-2021 period.

Table 3-6 UK Sales and revenue of applicant's diagnostics for 2018-2021

Year	Total	
	Sales (diagnostics sold)	Revenue (£)
2018	[redacted]	[redacted]
2019	[redacted]	[redacted]
2020	[redacted]	[redacted]
2021	[redacted]	[redacted]

CBI 3

The applicant has seen a significant increase in their diagnostic sales in the UK since 2018, driven predominantly by their molecular products. In 2021, the applicant's revenue was

approximately £[redacted] (£1-10) million, driven mainly by molecular products. Biosciences products, namely BD Leucocount™ have also seen a small but stable increase. The applicant expects demand for their products to grow steadily in the future. The applicant considers that there will be a steady [redacted]% (1-10%) increase in overall sales, driven mainly by their molecular products. The rate of increase has been estimated for all products currently on the UK market, based on current forecasts. Growth rate varies for individual products, with some expecting an increase of as much as [redacted]% (5-15%) per year. CBI 3

The applicant's UK sales are a subset of their European operations, which also include the EEA. Based on data from 2018, the UK sales were approximately [redacted]% (<25%) of the total European (UK & EEA) sales. The applicant estimates that the share of UK sales in total European ones has not changed significantly since. CBI 3

3.1.5. Annual volume of the SVHC used

Table 3-7 shows the recent and expected volumes of kits and OPnEO imported in the UK by the applicant in the years until 2026. For years beyond 2026, the applicant does not have a forecast, so an average growth rate of [redacted]% (1-10%) across all product groups will be applied in the SEA for any calculations. It should be noted that the projections for 2022-2026 in the following table are forecasts and contain significant uncertainty, as conditions in the UK market change. CBI 3

Table 3-7 Quantities of OPnEO (in g) imported in UK in Applicant's products (2018 – 2026)

Year	Total	
	Diagnostics	OPnEO (g)
2018	[redacted]	[redacted]
2019	[redacted]	[redacted]
2020	[redacted]	[redacted]
2021	[redacted]	[redacted]
2022	[redacted]	[redacted]
2023	[redacted]	[redacted]
2024	[redacted]	[redacted]
2025	[redacted]	[redacted]
2026	[redacted]	[redacted]

CBI 3

After the sunset date the applicant expects that more than [redacted] diagnostics, containing up to [redacted] (10-100) kg of OPnEO will be shipped to UK-based downstream users each year. The downstream users comprise of hospitals, contract research organisations (CRO), blood banks and doctor's surgeries in the UK. The forecast for sales and OPnEO quantities are based on the applicant's best judgement at the time of writing, but have significant uncertainty, especially for later years. Depending on how the UK market develops and how the policies of the NHS change, the actual sales could be different. CBI 3

3.2. Efforts made to identify alternatives

The applicant is currently using OPnEO in a number of different diagnostics in the UK, split among three different groups, namely Molecular, Point of care and Biosciences. The diagnostics are designed for use on different diagnostic instruments described in Section 3.1.3.

As a result, any potential alternative must be evaluated for each specific diagnostic and diagnostic instrument. This could mean that a single alternative may not be suitable for all products, as they all deal with different biological chemistries (both for the analyte and the specimen).

Diagnostics are developed to be used on a specific instrument so the diagnostics and instrument need to be considered as a system and not as individual components, meaning that the chemistry and instrument requirements of each diagnostic need to be developed and optimised together. This is because they work together and any change in an instrument parameter can have a potentially dramatic impact on the chemistry being undertaken in the diagnostic. Also, any change to the chemistry of the diagnostic (i.e. the substitution of OPnEO for an alternative detergent) could impact significantly the instrument output. In addition, an individual diagnostic is often used across multiple sample types, such as swabs and/or urines, and the same chemistry has to be optimized to work equally across all sample types to meet product specifications. Therefore, the chemistry that may work for one sample type may not work well with another. This complexity is the main reason for the time and costs associated with developing diagnostics.

Therefore, every diagnostic will have to be evaluated separately and as such it is possible that a common, "blanket" alternative may not be possible to be identified. Rather, in the end, substitution may require identification and evaluation of several detergents, each best suited for different diagnostics. Once potentially suitable alternatives are identified, they will be assessed for every new diagnostic.

As the applicant's products belong to three different groups with different diagnostics, each managed by different teams and with different requirements and resources, a different strategy is followed for each group of products (see section 3.2.2)

It should be noted that the applicant carried out an Analysis of Alternatives as part of their EU AfA, which was submitted in 2019. The conclusion of that AfA was that there would be no suitable alternative available at the Sunset Date. No specific potential alternative was identified as feasible. This report builds on the results of the EU AfA and adds any new information that has been produced since its submission. In any case, the efforts of the applicant to identify an alternative have been ongoing and will continue until OPnEO is not used in any of the products sold in the UK market.

3.2.1. Data searches

As part of their EU AfA, the applicant undertook a literature search on the availability of alternative detergents to OPnEO in diagnostics to help triage their efforts. The outcome of this exercise was negative, in that it did not identify a suitable, available potential alternative to OPnEO in the applicant's diagnostics.

To supplement the results of the previous AfA, the applicant carried out further data searches on potential alternatives from supplier catalogues and also from long lists of previous AfAs, wherever they were claimed non-confidential, published in ECHA's website. The alternatives were then compared with the ones identified in the process of the EU AfA to create a longer list from which to identify an alternative. This list of alternative detergents can form the basis for selecting potentially suitable alternatives for diagnostics

under development. In fact, as will be discussed below, the applicant is already using some of these alternatives in the development of a number of new diagnostic components.

3.2.2. Research and development

The applicant has been assessing alternatives to OPnEO within their diagnostics. For example, the applicant has carried out a study to determine the possibility of substituting OPnEO in the BD Leucocount™ reagent with either Tween®-20 or Tween®-80. The results of this study showed minimal promise as the BD Leucocount™ reagent formulated with Tween®-20 showed serious discrepancies to the reference reagent (containing OPnEO) and the Tween®-80 reagent performed poorly as well, recovering very few test cells of interest.

The applicant has also begun work on identifying potential substitutes for OPnEO in products under development, and on evaluating the feasibility of substitution in existing products.

As is shown in this AfA, whilst there are other detergents that can permeabilise cell membranes, these substances could not be incorporated in the applicant's diagnostics prior to the Sunset Date.

The applicant has also evaluated the feasibility of different alternatives for substituting OPnEO in some of their existing products. This has involved feasibility testing of potential alternatives with selected assays, to evaluate the technical feasibility of alternatives to OPnEO. Since submission of the EU AfA in 2019, the applicant has evaluated additional substances, both on a theoretical and on a practical basis. In total, the applicant has run technical feasibility tests with 19 potential alternatives in molecular and point of care diagnostics, to evaluate the possibility of using these detergents instead of OPnEO in their products. Evaluation of Biosciences diagnostics was also carried out in 2018-2019 without success, but the applicant is planning a new substitution project.

Currently, OPnEO is not considered as a potential detergent in new diagnostics. Instead, the applicant evaluates alternative detergents first, based on a shortlist that has been developed through internal R&D. If an alternative detergent shows promising results in a diagnostic, it will be used in that kit.

However, all substitution is dependent on positive results from the R&D process as maintaining repeatable and reliable results for healthcare professionals and patients is a key goal of the applicant's business.

3.3. Identification of known alternatives

3.3.1. Long list of potential alternatives

Following the efforts made to identify alternatives, the applicant collected a list of potential alternatives to OPnEO for cell lysis. The list did not only focus on drop in alternative detergents, but also included alternative technologies, specifically lysis techniques, based on physical or chemical disruption of the cell membrane.

3.3.1.1. Physical methods of cell disruption

Based on the criteria listed in Section 3.1.2, Table 3-8 shows the potential physical or mechanical methods used for cell lysis, i.e. the opening of the cell membrane. It also

discusses the compatibility of each method on whether that technique is applicable for the use in the operation of the applicant's diagnostics.

Table 3-8 Physical Methods of Cell Disruption

Method	Description	Compatibility with BD diagnostic systems
Manual grinding	Use of a pestle and mortar. Commonly used for the disruption of plant cells frozen in nitrogen.	**Not Compatible** • Does not produce reliable and reproducible results; • Requires manual manipulation and thus a total redesign of BD diagnostic systems; • Not conducive to a high throughput - low volume process.
Liquid Homogenisation	Cells are lysed by forcing the cell suspension through a narrow space, thereby shearing the cell membranes – similar to the French press.	**Not Compatible** • Does not produce reliable and reproducible results; • Requires manual manipulation and thus a total redesign of BD diagnostic systems; • Not conducive to a high throughput - low volume process.
Sonication	Use of pulsed high frequency sound waves to agitate and lyse cells. The sound waves are generated by the vibrating probe immersed in the cell solution causing cavitation[6]. This method can be very loud and often has to be performed in an extra room.	**Not Compatible** • Does not produce reliable and reproducible results; • Requires manual manipulation and thus a total redesign of BD diagnostic systems; • Not conducive to a high throughput - low volume process.
Freezing	A cell suspension is frozen and then thawed causing cells to swell and ultimately rupture. Multiple cycles are necessary for efficient lysis, and the process can be quite lengthy. This method has been shown to be effective and has been recommended for lysis of mammalian cells in some protocols.	**Not Compatible** • Is not operated at a small scale; • Requires manual manipulation and thus a total redesign of BD diagnostic systems; • Not conducive to a high throughput - low volume process.
High Temperature	High temperatures (and pressure) created via microwave or autoclave disrupt the bonds within cell walls. The heat and pressure will also denature proteins.	**Not Compatible** • Requires manual manipulation and thus a total redesign of BD diagnostic systems; • Not conducive to a high throughput - low volume process.
Mechanical method	Usually rely on the use of rotating blades to grind and disperse large amounts of complex tissue. The "blenders" used can vary in size.	**Not Compatible** • Does not produce reliable and reproducible results; • Requires manual manipulation and thus a total redesign of BD diagnostic systems; • Not conducive to a high throughput - low volume process.

Physical methods of cell lysis are crude, especially when comparing these methods to the equipment outlined in Section 3.3.2. Furthermore, even if it was possible to refine them to a level that it would be suitable for use in the applicant's systems, it would still require

[6] tiny bubbles are formed and explode, producing a local shockwave and disrupting cell walls by pressure change

a complete redesign not only of the diagnostic, but of the analytical instruments as well. As such, physical or mechanical methods for cell lysis are not going to be considered further.

3.3.1.2. Chemical methods of cell disruption

Chemical methods of cell disruption can offer more specific means of causing cell lysis. Most chemical methods use lysis buffers, and the most common chemical family used is surfactants or detergents (see Section 3.3.1.3). Other common chemical methods used for cell disruption are shown in Table 3-9. The table also assesses whether the method is applicable for use in the applicant's systems.

Table 3-9 Chemical methods of cell disruption

Method	Description	Comparability with BD diagnostics
Enzymatic	Often seen as a first step in cell lysis. The type of enzyme used is determined by its intended use, and therefore has the potential to be very specific.	**Not Compatible** • The enzyme used is specific and, as shown in Section 3.3.2, BD systems have the potential to run multiple tests. This is not conducive to a high throughput - low volume process with multiple tests. • This would require a total redesign of BD systems.
Chatatropes	Used to disrupt hydrophobic interactions between proteins. Common chatatropes include urea, sodium iodide, and guanidine. Usually used at high molarities (as opposed to low concentrations of surfactants)	**Not Compatible** • The strong ions involved have the potential to react with existing reagents within the BD systems • This would therefore require a total redesign of BD diagnostic systems; • Does not produce reliable and reproducible results

The chemical methods of cell disruption outlined above are not technically feasible. As such, no assessment of the economic impacts, availability and risk reduction have been carried out. The reasons behind this are that the methods are not technically feasible and cannot provide the results already provided to the market, with the same confidence with regards to reliability and repeatability of results. Such alternatives have to be rejected due to the sensitivity of the endpoints being assessed. Without these repeatable and reliable results, the diagnostic system would not be able to provide the same level of detailed analysis for the sensitive endpoints outlined in Table 3-5, and would thus not be fit for purpose.

3.3.1.3. Detergent methods of cell disruption

There are a number of possible alternative detergents that can disrupt cell membranes that have been reported in the literature. In defining potential alternative detergents for examination of the efficacy of cell lysis, the applicant has taken two approaches to identify and then assess alternative detergents:

- Detergents that are known for membrane solubilisation; and
- Detergents selected upon the basis of structural similarity to OPnEO.

In addition, the original results were also compared with lists of potential alternative detergents in EU AfAs published after the submission of the applicant's EU AfA. The aim of this exercise was to ensure that no potentially suitable alternatives were missed. Table 3-10 lists the alternatives that were considered by the applicant. The table contains alternative detergents from the EU AfA, supplemented with additional alternatives that were identified since the EU AfA submission in 2019. The applicant carried out preliminary evaluation on a total of 29 alternative detergents. The alternatives in the coloured cells at the bottom of the table were identified and evaluated after the submission of the EU AfA.

Table 3-10 List of identified potential alternative detergents

Trade Name	Substance Name	CAS Number	EC Number
Triton X-100	N/A	9002-93-1	-
Igepal CA-720	2-(2-[4-(1,1,3,3-Tetramethylbutyl)phenoxy]ethoxy)ethanol	9036-19-5	618-541-1
CHAPS	3-[(3-Cholamidopropyl)dimethylammonio]-1-propanesulfonate hydrate	75621-03-3	616-246-2
DDM	2-[6-dodecoxy-4,5-dihydroxy-2-(hydroxymethyl)oxan-3-yl]oxy-6-(hydroxymethyl)oxane-3,4,5-triol	69227-93-6	614-943-6
OG	Octyl β-D-glucopyranoside	29836-26-8	249-887-8
Tergitol TMN-6	Polyethylene glycol trimethylnonyl ether	60828-78-6	612-043-8
Tergitol-15-S-40	Polyethylene glycol trimethylnonyl ether	84133-50-6	617-534-0
Brij 58	Polyethylene glycol hexadecyl ether	9004-95-9	500-014-1
Brij L23	dodecyl tricosaoxyethylene glycol ether	9002-92-0	500-002-6
Poly(ethylene glycol) octyl ether	Octan-1-ol, ethoxylated	27252-75-1	500-058-1
Span 60	Sorbitan stearate, Sorbitane monostearate	1338-41-6	215-664-9
OTG	Octyl β-D-1-thioglucopyranoside	85618-21-9	617-729-0
SDS	Sodium dodecyl sulphate	151-21-3	205-788-1
Tween-20	Sorbitan monolaurate, ethoxylated	9005-64-5	500-018-3
Tween-80	Sorbitan monooleate, ethoxylated	9005-65-6	500-019-9
Lauryldimethylamine N-oxide	Dodecyldimethylamine oxide	1643-20-5	216-700-6
Digitonin	N/A	11024-24-1	234-255-6
deoxy-BigCHAP	N,N-Bis[3-(D-gluconamido)propyl]deoxycholamide	86303-23-3	635-520-2
APO-10	Dimethyldecylphosphine oxide	2190-95-6	623-754-8
Triton CG 110	alkyl polyglucoside, D-Glucopyranose, decyl octyl glycoside	68515-73-1	500-220-1
Polyoxyethylene (10) tridecyl ether	2-[2-(2-{2-[2-(11-methyl-dodecyloxy)-ethoxy]-ethoxy}-ethoxy)-ethoxy]-ethanol	78330-21-9	616-609-5
Ecosurf EH-9	2-((1-((2-ethylhexyl)poly-oxy)poly-propan-2-yl)oxy)ethanol	64366-70-7	613-582-1
Zephiran	Benzalkonium chloride, alkyldimethylbenzylammonium chloride	63449-41-2	264-151-6
	Alcohol C13-iso, ethoxylated	9043-30-5	
Genapol X 100	Fatty alcohol ethoxylate	9043-30-5	
Dodecyl maltoside	n-Dodecyl-β-D-maltoside	69227-93-6	
Triton X-100 Reduced	Polyoxyethylene (10) isooctylcyclohexyl ether	92046-34-9	682-156-5
Tergitol TMN-10	Branched secondary alcohol ethoxylate	60828-78-6	
Tergitol 15-S-20	Polyethylene glycol trimethylnonyl ether	84133-50-6 & 25322-68-3	617-534-0 & 500-038-2
Tergitol 15-S-15	Polyethylene glycol trimethylnonyl ether	84133-50-6 & 25322-68-3	617-534-0 & 500-038-2
CHEMAL LA-9	Polyoxyethylene (9) lauryl alcohol	3055-99-0	221-284-4
Tergitol 15-S-9	Alcohols, C12-14-secondary, ethoxylated, & Polyethylene Glycol	84133-50-6 & 25322-68-3	617-534-0 & 500-038-2

3.3.2. Screening of alternative detergents

In order to assess and identify suitable candidates to be taken forward for assessment, the detergents were evaluated against the criteria in Table 3-11, with the results shown in Table 3-12.

Table 3-11 Alternative Detergent Screening Parameters

Parameter	Reason
Hazard Profile	Risk for the environment - If the substance is of equivalent or greater concern to human health (i.e. CMR) or the environment (i.e. PBT or vPvB) than OPnEO then it will be discounted. Any substance that is present on Annex III was also discounted. The first criterion in Annex III is based on a prediction that a substance will have the type of hazards that could lead to it being a SVHC.
Water solubility	Reliable and repeatable results - for the reasons outlined in Table 3-3.
Non-denaturing properties of the detergent	Reliable and repeatable results - for the reasons outlined in Table 3-3.
High Purity available (Molecular Grade)	Reliable and repeatable results - for the reasons outlined in Table 3-3. BD purchase chemicals from approved suppliers and distributors. These distributors are predominately based outside of the UK as this is where the systems are manufactured.

An initial screening of detergents was carried out using toxicological profile and commercial criteria as factors for removal of consideration. Substance names, EC numbers, presence on SVHC list of Annex III lists have been obtained from either registration dossiers, CLP notifications or the relevant lists, all available on the ECHA website. If the substance passed for further screening the process criteria in the above table were then used as part of the assessment.

Table 3-12 First screening of potential alternative detergents

Trade Name	Substance Name	CAS Number	EC Number	SVHC	Annex III presence	Water Solubility	Enzyme Denaturing	Purity - Molecular grade Available	Further Assessment Required
Triton X-100	N/A	9002-93-1	-	Yes	N/A	Soluble	No	Yes	No - SVHC
Igepal CA-720	2-(2-[4-(1,1,3,3-Tetramethylbutyl)phenoxy]ethoxy)ethanol	9036-19-5	618-541-1	Yes - OPnEO	N/A	N/A	N/A	N/A	No - SVHC
CHAPS	3-[(3-Cholamidopropyl)dimethylammonio]-1-propanesulfonate hydrate	75621-03-3	616-246-2	No	Yes	N/A	N/A	N/A	No – Annex III Substance
DDM	2-[6-dodecoxy-4,5-dihydroxy-2-(hydroxymethyl)oxan-3-yl]oxy-6-(hydroxymethyl)oxane-3,4,5-triol	69227-93-6	614-943-6	No	Yes	N/A	N/A	N/A	No – Annex III Substance
OG	Octyl β-D-glucopyranoside	29836-26-8	249-887-8	No	Yes	N/A	N/A	N/A	No – Annex III Substance
Tergitol TMN-6	Polyethylene glycol trimethylnonyl ether	60828-78-6	612-043-8	No	Yes	N/A	N/A	N/A	No – Annex III Substance
Tergitol-15-S-40	Polyethylene glycol trimethylnonyl ether	84133-50-6	617-534-0	No	No – but assumed likely to be included based on similar substance to above	N/A	N/A	N/A	No – based on Annex III entry above
Brij 58	Polyethylene glycol hexadecyl ether	9004-95-9	500-014-1	No	Yes	N/A	N/A	N/A	No – Annex III Substance
Brij L23	dodecyl tricosaoxyethylene glycol ether	9002-92-0	500-002-6	No	No – but assumed likely to be included based on similar substance to above	N/A	N/A	N/A	No – based on Annex III entry above
Poly(ethylene glycol) octyl ether	Octan-1-ol, ethoxylated	27252-75-1	500-058-1	No	Yes	N/A	N/A	N/A	No – Annex III Substance

Trade Name	Substance Name	CAS Number	EC Number	SVHC	Annex III presence	Water Solubility	Enzyme Denaturing	Purity - Molecular grade Available	Further Assessment Required
Span 60	Sorbitan stearate, Sorbitane monostearate	1338-41-6	215-664-9	No	No	Low solubility 0.012 mg/L - REACH registration dossier	N/A	N/A	No - Solubility
OTG	Octyl β-D-1-thioglucopyranoside	85618-21-9	617-729-0	No	No	Low Solubility 20 mg/L	N/A	N/A	No - Solubility
SDS	Sodium dodecyl sulphate	151-21-3	205-788-1	No	No	Yes	Yes	N/A	No – Enzyme Denaturing
Tween-20	Sorbitan monolaurate, ethoxylated	9005-64-5	500-018-3	No	No	Soluble	No	Yes	No – historical results (see Section 3.2.1)
Tween-80	Sorbitan monooleate, ethoxylated	9005-65-6	500-019-9	No	No	Soluble	No	Yes	No – historical results (see Section 3.2.1)
Lauryldimethylamine N-oxide	Dodecyldimethylamine oxide	1643-20-5	216-700-6	No	No	Soluble	No	No	No - Purity
Digitonin	N/A	11024-24-1	234-255-6	No	No	Soluble	No	No	No - Purity
deoxy-BigCHAP	N,N-Bis[3-(D-gluconamido)propyl]deoxycholamide	86303-23-3	635-520-2	No	No	Soluble	No	No	No - Purity
APO-10	Dimethyldecylphosphine oxide	2190-95-6	623-754-8	No	No	Soluble	No	No	No - Purity
Triton CG 110	alkyl polyglucoside, D-Glucopyranose, decyl octyl glycoside	68515-73-1	500-220-1	No	No	Soluble	No	No	No - Purity
Polyoxyethylene (10) tridecyl ether	2-[2-(2-{2-[2-(11-methyl-dodecyloxy)-ethoxy]-ethoxy}-ethoxy)-ethoxy]-ethanol	78330-21-9	616-609-5	No	No	Soluble	No	TBC	Yes
Ecosurf EH-9	2-((1-((2-ethylhexyl)poly-oxy)poly-propan-2-yl)oxy)ethanol	64366-70-7	613-582-1	No	No	Soluble	No	Yes	Yes

Trade Name	Substance Name	CAS Number	EC Number	SVHC	Annex III presence	Water Solubility	Enzyme Denaturing	Purity - Molecular grade Available	Further Assessment Required
Zephiran	Benzalkonium chloride, alkyldimethylbenzylammonium chloride	63449-41-2	264-151-6	No	Yes (acute toxicity)	Soluble		N/A	Yes
Alcohol C13-iso, ethoxylated	Alcohol C13-iso, ethoxylated	9043-30-5		No	No			Yes	Yes
Genapol X 100	Fatty alcohol ethoxylate	9043-30-5		No	No			Yes	Yes
n-Dodecyl beta-D-maltoside		69227-93-6		No	Yes (aq.tox, repr. Tox)			Yes	Yes
Triton X-100 Reduced	Polyoxyethylene (10) isooctylcyclohexyl ether	92046-34-9	682-156-5	No	No			Yes	Yes
Tergitol 15-S-20	Polyethylene Glycol Trimethylnonyl Ether	84133-50-6 & 25322-68-3	617-534-0 & 500-038-2	No	No			Yes	Yes
Tergitol 15-S-15	Polyethylene Glycol Trimethylnonyl Ether	84133-50-6 & 25322-68-3	617-534-0 & 500-038-2	No	No			Yes	Yes
CHEMAL LA-9	Polyoxyethylene (9) lauryl alcohol	3055-99-0	221-284-4	No	Yes			Yes	No – Annex III Substance
Tergitol 15-S-9	Alcohols, C12-14-secondary, ethoxylated, & Polyethylene Glycol	84133-50-6 & 25322-68-3	617-534-0 & 500-038-2	No	No			Yes	Yes

Along with the first screening, the applicant also assessed the performance of some of the potential alternatives in their diagnostics. These alternatives were selected based on their physicochemical characteristics (e.g. HLB, CMC) and their structural similarity to OPnEO.

The performance testing involved analytical sensitivity studies and very limited clinical testing with a small number of retrospective samples. The tests evaluated specimen stability and accelerated stability of the sample buffer. All experiments were executed as feasibility tests to down-select detergents. They were carried out separately for molecular / biosciences and point-of-care products in some cases. Here, it should be noted again that even if a potential alternative has positive results in one product or one group of products and specimen types, it may not be suitable for the rest.

Table 3-13 summarises the results of the preliminary performance testing.

Table 3-13 Preliminary performance test results of some potential alternative detergents

Trade Name	Substance Name	CAS Number	EC Number	Result
DDM	2-[6-dodecoxy-4,5-dihydroxy-2-(hydroxymethyl)oxan-3-yl]oxy-6-(hydroxymethyl)oxane-3,4,5-triol	69227-93-6	614-943-6	[redacted]
Tween-20	Sorbitan monolaurate, ethoxylated	9005-64-5	500-018-3	[redacted]
Tween-80	Sorbitan monooleate, ethoxylated	9005-65-6	500-019-9	[redacted]
Polyoxyethylene (10) tridecyl ether	2-[2-(2-{2-[2-(11-methyl-dodecyloxy)-ethoxy]-ethoxy}-ethoxy)-ethoxy]-ethanol	78330-21-9	616-609-5	[redacted]
Ecosurf EH-9	2-((1-((2-ethylhexyl)poly-oxy)poly-propan-2-yl)oxy)ethanol	64366-70-7	613-582-1	
Zephiran	Benzalkonium chloride, alkyldimethylbenzylammonium chloride	63449-41-2	264-151-6	[redacted]
CTAB	Alcohol C13-iso, ethoxylated	9043-30-5		[redacted]
Genapol X 100	Fatty alcohol ethoxylate	9043-30-5		[redacted]
n-Dodecyl beta-D-maltoside		69227-93-6		[redacted]
Triton X-100 Reduced	Polyoxyethylene (10) isooctylcyclohexyl ether	92046-34-9	682-156-5	[redacted]
Tergitol 15-S-20	Polyethylene Glycol Trimethylnonyl Ether	84133-50-6 & 25322-68-3	617-534-0 & 500-038-2	[redacted]
Tergitol 15-S-15	Polyethylene Glycol Trimethylnonyl Ether	84133-50-6 & 25322-68-3	617-534-0 & 500-038-2	[redacted]
CHEMAL LA-9	Polyoxyethylene (9) lauryl alcohol	3055-99-0	221-284-4	[redacted]
Tergitol 15-S-9	Alcohols, C12-14-secondary, ethoxylated, & Polyehylene Glycol	84133-50-6 & 25322-68-3	617-534-0 & 500-038-2	[redacted]
Tergitol TMN6	Polyethylene glycol trimethylnonyl ether	60828-78-6	612-043-8	[redacted]
Tergitol TMN10	Polyethylene glycol trimethylnonyl ether	60828-78-6	612-043-8	[redacted]
Benzalkonium Chloride	Alkyldimethylbenzylammonium chloride	8001-54-5	616-786-9	[redacted]
TMN6 and Tween-20				[redacted]
TMN6 and 15-S-15				[redacted]

CBI 1

3.3.3. Shortlisted alternatives

Based on the results of the screening process and the preliminary performance testing carried out in-house, the applicant shortlisted two potential alternatives for closer consideration in the applicant's diagnostics. These alternatives were selected mainly based on their performance in analytical sensitivity and stability tests. As mentioned earlier, it cannot be guaranteed that these alternatives will be suitable for all of the applicant's products. They will need to be tested separately with each diagnostic considered for substitution before they are deemed feasible or not for some or all of the diagnostics.

The alternative detergents that were shortlisted and evaluated as part of the EU AfA will also be presented in the following sections, for continuity purposes.

It must be noted that it is possible that some of the alternatives that were not shortlisted may find limited application for some of the applicant's diagnostics. As there is limited information on their suitability, however, they will not be evaluated separately.

Table 3-14 lists the shortlisted alternatives.

Table 3-14 Shortlisted alternatives

#	Substance Name	CAS / EC Number	Discussion on alternative
1.	Ecosurf EH-9	64366-70-7 / 613-582-1	Shortlisted in EU AfA. Unlikely to work on all products, but considered together with Alternative No.2
2.	Polyoxyethylene (10) tridecyl ether	78330-21-9 / 616-609-5	Shortlisted in EU AfA. Unlikely to work on all products, but considered together with Alternative No.1
3.	[redacted]	[redacted]	Shortlisted based on similar performance to OPnEO in some diagnostics.
4.	[redacted]	[redacted]	Shortlisted based on acceptable performance to OPnEO in some diagnostics

CBI 1

3.4. Assessment of shortlisted alternatives

3.4.1. Alternative 1&2 – Alternatives identified in EU AfA

3.4.1.1. Description of Alternative Detergents

Table 3-15 shows the identity of the two alternatives that were shortlisted in the EU AfA by the applicant.

Table 3-15 Substance identification of Alternatives 1 and 2

Property	Alternative 1	Alternative 2
Trade name	Ecosurf EH-9	
Name	2-((1-((2-ethylhexyl)poly-oxy)poly-propan-2-yl)oxy)ethanol	Polyoxyethylene (10) tridecyl ether
CAS / EC Number	64366-70-7	78330-21-9

3.4.1.2. Availability of Alternative 1&2 Detergents

The alternatives that passed the screening process in the EU AfA are available in molecular grade. However, the detergents have not been approved by the applicant's internal procurement procedures at this time. The applicant does not see this as a reason to not substitute and any validation of suppliers as part of a procurement procedure is seen as a cost of doing business and not included in this assessment.

In conclusion, these are commercially available alternatives, which can be used by the applicant if they are found to be technically feasible.

3.4.1.3. Technical Feasibility of Alternative 1&2 Detergents

The applicant cannot confirm that Alternatives 1 & 2 are suitable for OPnEO substitution in their diagnostics. For this to be confirmed, continued R&D work would be required to show there would be no significant impacts to the diagnostic system output. Currently all that can be confirmed is that these detergents passed the first screening phase, which consisted mainly of hazard and high-level technical feasibility assessments. If the alternative detergents do not produce the repeatable and reliable results, then they will have to be rejected. The applicant will need to carry out more testing with individual diagnostics before they can conclude on the technical feasibility of the Alternative 1 & 2 detergents for these products.

In feasibility testing (trials) carried out for POC products with Alternative 2, the result was that the performance was [redacted]. As a conclusion for POC products, Alternative 1&2 detergents are not considered technically feasible and are not considered further.

CBI 1

3.4.1.4. Economic feasibility of Alternative 1&2 detergents

Diagnostics produced by the applicant are highly regulated within the EEA and the UK. In the EEA, every marketed IVD must carry a CE mark as set forth in the IVD Directive (Directive 98/79/EC), and upon implementation the IVD Regulation (EU) 2017/746. For the existing diagnostic systems that the applicant puts on the market, the smallest change to any aspects of the product formulation, such as the removal of the small quantity of OPnEO and replacing it with one of the alternative reagents will require a revalidation of the medical device.

Once an alternative has been identified, there is R&D development to determine performance levels of the product using the alternative, including both internal analytical Verification & Validation studies and clinical simulation studies. If results meet product performance, requirements around sensitivity and specificity then lab trials, designed by the applicant, and usually operated by an independent CRO, will be run to confirm the assumptions made in the initial assessment are correct. If they pass the lab trials, the product development moves onto the next phase. If the lab trials are not a success, then it would have to go back for another phase of development and product optimisation.

As detailed in Table 4-1 the cost of a significant change in the diagnostic, such as the switching of the detergent, is estimated at £5-8 million, including the cost for regulatory review and CE mark certification. Therefore, the cost in the UK to revalidate the more than 20 diagnostics containing OPnEO placed onto the UK market by the applicant is estimated to be £50-240 million over the time that would be needed for full substitution in all products. It should be noted that the cost provided here includes the costs for market

authorisation, which are included in the launch costs in Table 4-1. However, such a cost is theoretical at the moment, as it is unlikely that these two substances will be considered technically feasible for the applicant's products.

In terms of operational costs, it is expected that either alternative detergent will be a "drop in" alternative, in that it will replace OPnEO in the formulation. The prices of the two alternative detergents compared to Triton X-100 are shown in Table 3-16.

Table 3-16 Price comparison between OPnEO and alternatives

#	Substance Name	CAS or EC Number	Price (Sigma-Aldrich website)
1.	Triton X-100	CAS 9036-19-5	€ 67.10 for 100 ml
2.	Ecosurf EH-9	CAS 64366-70-7	€ 44.90 for 100 ml
3.	Polyoxyethylene (10) tridecyl ether	CAS 78330-21-9	€ 38.40 for 100 g

As can be seen, the prices of the alternative detergents are comparable to that of Triton X-100. Nevertheless, the overall contribution of the detergent in the price of the diagnostic product is very small, so any change of detergent will not significantly affect it or the applicant's profitability. The main cost element, therefore, would be the R&D and global revalidation cost including the necessary CE Marking, as described above.

3.4.1.5. Reduction of overall risk due to transition to Alternative 1&2 Detergents

Based on the classifications of the alternatives that passed the screening process, their use would result in a reduction of overall risk to environment.

3.4.1.6. Suitability of Alternative 1 & 2 Detergents for the applicant and in general

Alternative 1 & 2 detergents (Ecosurf EH-9 and Polyoxyethylene (10) tridecyl ether) were shortlisted for further evaluation in the EU AfA submitted by the applicant in 2019. They were selected based on their hazard profile and some high-level technical criteria (solubility, protein / enzyme denaturation) identified through literature review. The alternatives are both available and less hazardous to the environment than OPnEO.

While potentially suitable, their technical feasibility is not yet proven in applicant's diagnostics. It would require performance testing on the applicant's diagnostic systems. If this evaluation is successful, the applicant would have to carry out a very resource- and time-intensive R&D process, to substitute OPnEO from their current and future products.

In conclusion, Alternative 1 & 2 detergents may potentially be suitable for substitution of OPnEO in some of the applicant's diagnostics, but their technical feasibility needs to be proven first, in a series of performance and stability tests with the diagnostic products in question. However, at the moment the applicant is focussing on more promising alternatives (Alternatives 3 & 4) that have recently been identified. The Point of Care team in particular does not consider them feasible, based on feasibility testing results with similarly structured detergents.

3.4.2. Alternative 3 & 4: [redacted] & [redacted]

CBI 1

3.4.2.1. General description of Alternative 3 & 4

Alternatives 3 and 4 are non-ionic detergents, marketed for the solubilisation of membrane-bound proteins, i.e. cell lysis. Table 3-17 shows the substance IDs for both alternatives.

Table 3-17 Substance identification of Alternative 3 & 4

Property	Alternative 3	Alternative 4
Trade name	[redacted]	[redacted]
Name	[redacted]	[redacted]
CAS / EC Number	[redacted]	[redacted]
Chemical formula	[redacted]	[redacted]
Chemical structure	[redacted]	[redacted]

CBI 1

3.4.2.2. Availability of Alternatives 3 & 4

Alternative 3 is commercially available from the manufacturer at sufficient purity. While the available quantities of Alternative 3 in the market are not known with any certainty, it is expected that this would not be a problem, as the applicant is using relative low volumes of OPnEO. Furthermore, if demand were to increase, it is expected that the supplier of Alternative 3 will increase output to meet it.

Alternative 3 is not registered under EU or UK REACH, and it can fall under the polymer exemption. However, its components have to be registered by the manufacturer or importer, if their volumes exceed 1 tonne per year. The expected imported quantities are lower than that threshold, so a registration is not considered necessary at the moment.

The above also apply to Alternative 4. While not registered under EU or UK REACH, the expected quantities of the components are below 1 tonne per year. The alternative is also commercially available in the UK.

In conclusion, it is expected that Alternative 3 and 4 will be available in sufficient quantities.

3.4.2.3. Safety considerations related to using Alternatives 3 & 4

According to the notified classifications for the substance, Alternative 3 may have the following hazards: [redacted], while some notifiers have also notified an [redacted] hazard [12].

CBI 1

Alternative 4 classification notification according to CLP predominantly lists [redacted], while there is a small number of notifiers mentioning [redacted] (oral and dermal).

Compared to OPnEO, both alternatives pose fewer risks to the environment, despite the notified chronic aquatic toxicity for Alternative 3. The [redacted], so Alternatives 3 and 4 are unlikely to be associated with endocrine activity for the environment. CBI 1

At the moment, therefore, based on currently available data, the risks to the environment from the use of Alternatives 3 or 4 are lower.

3.4.2.4. Technical feasibility of Alternatives 3 & 4

The applicant has run preliminary performance tests with Alternative 3 and 4 in a number of (mostly molecular) diagnostics. These tests involved analytical sensitivity studies and very limited clinical testing with a small number of retrospective samples for Alternative 3. The tests evaluated specimen stability and accelerated stability of the sample buffer in the sample buffer tube.

Alternatives 3 and 4 showed very good results for a number of new molecular diagnostic components, with regards to both performance and stability. In particular, Alternative 3 has been tested in, and selected for use in a number of ([redacted]) new diagnostic components so far. There are still other diagnostic components that require to be evaluated. CBI 1

Alternative 4 has also shown promising results in at least one new molecular diagnostic component, with Validation and Verification (V&V) expected to start in the near future.

As each product and specimen are different, Alternative 3 and/or Alternative 4 will need to be evaluated in each new product, before either is considered suitable for use.

However, if Alternative 3 or 4 are to be considered technically feasible for all products that currently use OPnEO, the applicant will need to carry out an extensive (and resource-intensive) R&D and regulatory approval campaign, as discussed in Section 4.1.3 below. Considering that the time needed for substitution in even a single diagnostic can be as long as [redacted] (1-5) years, it is not possible to substitute OPnEO in existing diagnostics before the Sunset Date. It should also be noted that similar evaluation of the alternative for some point-of-care diagnostics ([redacted]) did not produce equivalent results to OPnEO, so they are not considered technically feasible and other alternatives will need to be identified for these products. CBI 1

3.4.2.5. Economic feasibility of Alternatives 3 & 4

Alternative 3 is more expensive than OPnEO at the moment. Alternative 4 is actually cheaper than OPnEO at the Sigma-Aldrich website. However, as the overall contribution of the detergent to the price of the diagnostic product is small, any change of detergent will not significantly affect it or the applicant's profitability.

While the impact in the material costs and the diagnostic systems' price from switching to Alternative 3 or 4 is expected to be minimal, the R&D costs related to substitution are expected to be very high.

Even if one considers that the R&D costs are relevant to the EEA sales as well, of which UK sales were less than [redacted]% in 2018, it is still a significant cost. It should be noted, however, that such an R&D project will not necessarily increase the R&D budget for diagnostics. Instead, it is quite likely that the additional R&D resources required will be diverted from other projects, reducing the applicant's ability to develop new and innovative diagnostics.

CBI 3

3.4.2.6. Suitability of Alternatives 3 & 4 for the applicant and in general

Alternatives 3 and 4 appear to be technically feasible for a number of new molecular diagnostic components. This is supported by performance and stability tests that have been carried out in the diagnostics.

However, it should be noted that:

- The applicant must carry out more tests, especially stability ones, before they can conclude on Alternative 4's technical feasibility for their diagnostics under evaluation. Even so, as each diagnostic and specimen combination is different, these tests will have to be repeated every time a new product is developed.
- The alternatives do not appear to be technically feasible for use in some of the applicant's point-of-care diagnostics. In that case, the applicant may need to identify other potentially suitable alternatives and go through the feasibility trials again. This may also be the case for some molecular products, for which Alternative 3 or 4 may not show promising results.

Therefore, it is possible that Alternatives 3 and 4 will not be feasible for all the applicant's products currently using OPnEO.

In conclusion, Alternatives 3 and 4 are promising alternatives, which can be technically feasible for use in a number of the applicant's diagnostic systems sold in the UK. However, this will require additional testing and close watch of any regulatory processes in the EU and the UK, which could affect the substance's availability.

They also indicate that the final substitution portfolio of the applicant is very likely to contain more than one (and possibly more than two) alternative detergents, due to the possible interactions of the detergent with the different specimens and chemistries used in the various diagnostics.

3.4.3. Conclusion on shortlisted alternatives

At the moment of writing, there are no technically feasible alternatives to OPnEO for use in all of the applicant's diagnostics, which will be available for use by the applicant by the Sunset Date.

In the EU AfA submitted in 2019, the applicant identified two potential alternative detergents (Alternative 1 and 2), stating, however, that "the feasibility of these substances has not been confirmed at the time of submission. If the alternative detergents prove to not produce the repeatable and reliable results, then they would have to be rejected."

The same would apply to Alternatives 3 and 4, which have been identified since the submission of the EU AfA. Alternatives 3 and 4 are non-ionic detergents and were selected as potentially suitable substitutes for OPnEO in the applicant's products, based on their physicochemical properties and their performance in preliminary tests in components of

some molecular diagnostics (they have already been selected for use in a number of new diagnostic components). However, the applicant needs to carry out additional testing to verify its technical feasibility in existing diagnostics before OPnEO can be substituted out.

At the moment, Alternative 3 is more expensive than OPnEO, while Alternative 4 is cheaper. This is not expected to impact the applicant's decision in adopting it, if proven suitable, as the overall impact in material costs will be very small.

It should be noted that the applicant tested Alternative 3 and 4 in some point-of-care diagnostics, but their performance was not satisfactory. This suggests that a combination of alternative detergents will be needed to substitute OPnEO in all of the applicant's UK products.

Regarding existing products, the applicant would expect that substituting OPnEO in even one of the existing diagnostics could take as long as [redacted] (1-5) years and have a cost of £5-8 million. Considering that the applicant places several different diagnostics in the UK market, the substitution cost could rise to £50-240 million. In addition, the additional R&D budget will likely be very difficult to be secured, which means that it will have to be transferred from other R&D activities, thus delaying the development of novel, innovative diagnostic products by the applicant.

CBI 1

In conclusion, there are no technical or economically feasible alternatives to OPnEO for use in the BD diagnostic systems listed in this AfA. Furthermore, considering the different product – specimen combinations in the applicant's molecular products, the applicant may need to evaluate the alternatives' performance in each product separately, before a decision is made. While Alternative 3 or 4 may end up being suitable for some of the applicant's molecular products, it is unlikely they will be a "blanket" alternative, suitable for all, so a wider portfolio of alternatives may be needed.

4. SOCIO-ECONOMIC ANALYSIS

4.1. Continued use scenario

4.1.1. Summary of substitution activities

The applicant has carried out literature review on a large list of potential alternative detergents, to identify those that would be most likely to be suitable for use in their diagnostics.

Potential alternatives were collected from suppliers' documentation, as well as from EU AfAs submitted by other diagnostic companies. The applicant had also submitted an EU AfA for the same use in 2019, in which they carried out screening of potential alternatives for their physico-chemical properties and their hazard profile.

Following that exercise, the applicant also carried out preliminary performance and stability testing on a smaller number of potential alternatives, which were selected because their critical properties as surfactants were comparable to those of OPnEO.

Any alternatives that produced acceptable results in this preliminary testing are currently considered for further evaluation, for use predominantly in new diagnostics of the applicant.

It should be noted that the applicant's products fall within different product groups, namely molecular, point-of-care and biosciences. While the function of the detergent in each of these product groups is the same, the products themselves are different, especially point-of-care. Therefore, the applicant needs to evaluate the technical feasibility of the alternative in each product group.

As of now, the applicant's R&D efforts have been focused on not using OPnEO when developing new diagnostic components. . Successfully identified alternatives are prioritised for use in new diagnostics, instead of OPnEO. The applicant will also evaluate the possibility of substituting OPnEO in their existing products once suitable alternatives are identified and is currently planning to start a project focused on existing diagnostics, which will assess the costs and timelines, along with the feasibility of substitution in those products.

4.1.2. Conclusion on suitability of available alternatives in general

The applicant has identified some potentially suitable alternative detergents, Alternatives 3 and 4, based on their results in performance and stability tests in sample buffers for a number of new diagnostic components. Alternative 3 has received regulatory approval in the EU for use in a number of diagnostic components. Alternative 4 is also evaluated in at least one molecular diagnostic component.

Nevertheless, the applicant must also ensure that there are no other constraints (e.g. performance, lack of stability, incompatibility with the other buffer components, intellectual property or potential for chemical regulation restrictions), before they proceed with using it in their diagnostic systems. The R&D process of the applicant is described in Section 4.1.3. Furthermore, both Alternative 3 and 4 may be considered for use in other diagnostics.

However, it was seen that Alternative 3 and 4 did not perform adequately in some point-of-care products, it is expected that the applicant may need to identify more suitable

alternatives to use in their diagnostics. Therefore, the applicant needs to examine each diagnostic separately, to consider alternative detergents instead of OPnEO.

The applicant is also aware of other EU AfAs that have concluded on potentially suitable alternatives for IVD applications. The applicant understands that this means that these could be considered suitable alternatives generally available (SAGA).

However, it must be understood that, while diagnostic systems from different manufacturers may have the same or similar principle of function, the characteristics of each company's diagnostic systems are different. Therefore, an alternative that is considered suitable by a competitor IVD manufacturer, may not perform acceptably in the applicant's diagnostics. This can happen, e.g., due to interactions of the detergent with the other components in the buffer solution or due to the fact that the diagnostics are used for different endpoints and the sample chemistry is different.

Therefore, it is important that the applicant carefully evaluates every potentially suitable alternative in all their diagnostic products, before concluding if it is technically feasible to substitute OPnEO in each one.

4.1.3. Substitution plan

4.1.3.1. Factors affecting substitution

Considering that the applicant has a number of potentially suitable alternatives for at least some of their products, but that technical feasibility has not yet been verified, a substitution plan will be described, under the assumption that the potentially suitable alternatives that have been identified prove to be technically feasible. As mentioned above, to substitute OPnEO in all of the applicant's products, it is very likely that more than one detergent will be needed, due to the variety and complexity of the applicant's diagnostic systems. This substitution plan is developed under this assumption.

Factors that are currently affecting substitution of OPnEO in the applicant's diagnostic systems can be summarised in the following:

- Large number of diagnostics to consider and complexity of products
- Applicant's R&D and the global regulatory approval process with regards to changes in the diagnostic products, as any changes will impact all regions that the diagnostic products are marketed in.

R&D process and regulatory approval

Substituting a key raw material, such as OPnEO, within a diagnostic is not a straightforward process. Even assuming that a suitable alternative (or alternatives) is identified, the work stream around placing a new diagnostic system on the market is expected to take approximately [redacted] years (1-5 years) per diagnostic to complete, primarily because of the validation tests and the regulatory approvals required.

CBI 1

The process involved in developing (or changing some part of) a diagnostic includes a number of sequential phases that have to be carried out carefully, to ensure that the sensitive product will perform as required. The main phases are as follows:

- Concept
- Definition

- Development
- Qualification
- Launch

Each of these phases must be completed before the next one begins, and any failure in any of them may push the development of the diagnostic back to the beginning, with a new alternative. It is thus imperative that the applicant carries out their R&D efforts with due diligence.

This is also important for the regulatory approval process (part of the Qualification phase). The competent authorities that will examine the applicant's request for a new diagnostic system or for a change in an existing one will need to see that all procedures were carried out properly and that the results produced are reliable and reproducible.

Applicant's diverse diagnostic systems portfolio

The applicant has received regulatory approval for diagnostic products that use OPnEO for sale in the UK. These products belong to three main product groups, namely molecular, point-of-care and biosciences. Furthermore, the individual diagnostics are complex products, consisting of a large number of components and each diagnostic is developed for use on a specific analytical instrument.

The complexity of the diagnostics and the reagents in which the detergent is used mean that there are many factors that could impact the compatibility of a potential alternative. OPnEO is widely used in diagnostic products because, apart from its excellent performance in cell lysis, it is also compatible with the chemical components of the various reagents / buffers it is used in.

This does not appear to be the case with the potential alternatives. Preliminary tests showed that even the most likely ones, Alternative 3 and Alternative 4, may not have acceptable performance with all of the applicant's diagnostics, particularly point-of-care ones. In the end, the applicant needs to extend the evaluation to every single diagnostic that is currently using OPnEO, because each diagnostic uses a different chemistry and on a different biological specimen, so compatibility with each will need to be verified. As a result, it is possible that a single alternative may not be suitable for all the applicant's products.

The substitution process will thus have to be carried out for all of the diagnostics containing OPnEO that the applicant currently places on the UK market. Due to the demanding nature, timeframe and cost of the work, and given the large scope of the project to replace OPnEO, since all testing would have to meet original test requirements on each specific instrument, the applicant may not be able to carry out all of the R&D and Clinical work in parallel.

The UK market is not a driver for R&D investment for substitution

The applicant currently only applies for the use of OPnEO in the UK, but the same products are also sold in the EEA and the rest of the world. In fact, the diagnostics in scope of this AfA are only a subset of the more than 40 different products sold in the EEA and the US, mentioned in the EU AfA. Considering that these products are the same for the different regions, R&D activities for substitution of OPnEO will have to be performed at a global level. It is not possible to make changes to a diagnostic only for the UK or for the EEA, as

this would add supply line and manufacturing complexity in order to support more variations of the same diagnostics. Regulatory / marketing approvals can be applied for separately for the UK, the EEA and the US, but this is the final step in the process. Nevertheless, it is a significant cost and must be carefully considered by the applicant.

It should also be noted that the cost of the substitution process for a single product is very high, as will be shown in Table 4-1 in the following chapter. For some of the smaller volume diagnostics that the applicant sells in the UK, such a cost may not be justified, so instead of substituting, the applicant may end up removing those products for the market.

CBI 3

The UK accounted for roughly [redacted]% (less than 25%) in 2018 of the total EEA-UK sales. The larger EEA market is thus expected to be the one driving any substitution of OPnEO in existing diagnostics. In addition, it is possible that the sales percentage of each product is not the same in the UK and the EEA, meaning that, prioritisation of the substitution would be based on the overall, not just the UK, sales volume.

If the US market, which at the moment is the largest market for the applicant's diagnostic systems, is taken into consideration as well, the situation becomes more complicated, as the final decision becomes global instead of regional. In practice, any change intended for the EEA or UK market will have to be implemented for the US as well, and registration with the FDA will also be required.

In summary, the UK market is not the leading market for the applicant's diagnostics in the region and it is not a driver for directing how R&D investment should be allocated and which diagnostics should be prioritised for substitution. It is therefore likely that, even if suitable alternatives are selected for substitution in existing products, they may not immediately be used in diagnostics sold to the UK.

4.1.3.2. List of actions and timetable with milestones

Diagnostics are developed to be used on a specific instrument so the diagnostic and instrument need to be considered as a system and not as individual components.

It should be noted that the chemistry and instrument requirements of each diagnostic and system need to be developed and optimised together. This is because they work together and any change in an instrument parameter can have a potentially significant impact on the performance of the system. Also, any change to the chemistry of the diagnostic (i.e. the substitution of OPnEO for an alternative detergent) could impact significantly on the instrument output. In addition, an individual diagnostic is often used across multiple sample types, such as swabs and/or urines, and the same chemistry has to be optimised to work equally across all sample types to meet product specifications. Therefore, the chemistry that may work for one sample type may not work well with another. This complexity is the main reason for the time and costs associated with developing diagnostic systems.

Therefore, when assessing any possible alternative to OPnEO, the work is not just associated with finding a detergent that functions in the same manner. The assessment has to start at the initial concept phase and then repeat all the critical design studies required in the development of a diagnostic system. Once the new diagnostic is ready, clinical studies and/or testing with clinical samples would have to be completed to demonstrate product requirements are being met.

If it is proved both technically and economically feasible for any of the diagnostics listed previously in this document to change from OPnEO (see Section 3.4) this would be classified as a raw material change and thus be classified as a change to form, fit for function of the product. This type of change would therefore require Regulatory authority approval. In addition, if the change was determined to result in the requirement of a new product number then an evaluation to the existing country product registration would be required.

Product Development for diagnostics can be broken down into five phases, as shown in Figure 4-1.

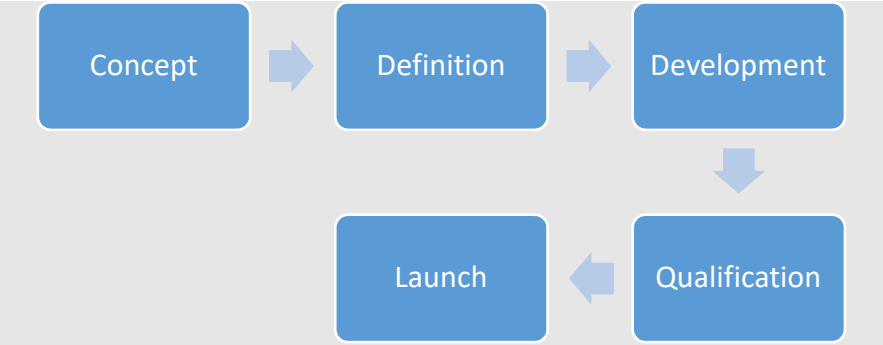

Figure 4-1 Diagnostic Product Development

During each phase of development, there are specific milestones that need to be achieved before the process can move on to the next phase. The five phases, and their respective milestones are expanded on below and the costs and timelines are detailed in Table 4-1.

Concept

In the concept phase the system, manufacturing and consumer requirements are set out. At this phase it is important to understand the needs of the customer and it is here that the applicant will resource the cross functional project team.

It should be noted for the substitution of OPnEO in the applicant's existing diagnostics the concept phase **is not required**, as the requirements are already known. It is still needed for new products that will only focus in using alternatives to OPnEO, but, even in that situation, selection of the detergent takes place after the concept of the diagnostic has been defined.

Definition

In this phase, the following requirements are investigated and resourced:

- Product
- Supply chain and packaging
- Regulatory – requirement for a CE marking etc.
- Quality
- R&D
- Manufacturing
- Medical (i.e. clinical trial design)

As with the Concept phase, when assessing a substitution of OPnEO in the applicant's diagnostics, this phase **is not required** as the requirements are already known. This phase does not include carrying out the tasks outlined above, only the scoping and resourcing.

Development

During this phase, product documentation, design and specifications are finalised, new suppliers and /or materials are qualified and a validation and verification plan is developed. These plans and designs will include a completed instrument workflow and risk assessments. All critical parameters and raw materials (in the tests and the instruments) have been identified by the end of development and the test and system chemistry have been optimised. The supply chain and shipping requirements are also finalised.

Once the above have been completed, the clinical and regulatory requirements and strategies are confirmed. It is during this phase that ownership of the project begins to be transferred from R&D to Manufacturing.

Qualification

It is during this phase that an assessment of the product stability begins. Stability testing alone can take between [redacted] months, depending on the product. Full shelf life stability testing is essential, as it verifies that the product will perform as designed throughout its shelf life. Such testing must be carried out in real time, because an accelerated stability test would destroy the enzymes used in the assay.

CBI 1

Also during this phase, a number of the processes and procedures outlined above are completed, including:

- Manufacturing process,
- Product validation,
- Clinical studies design validation and verification,
- Risk assessment and analysis,
- Design reviews,
- Quality Assurance plans, and
- Product labelling and packaging requirements.

The final act of the qualification phase is to develop and submit documents for product registration in the country / region the product is being marketed. The classification of the diagnostic system will determine the complexity and the length of time it will take for this submission to be approved. Diagnostic systems produced by the Applicant are highly regulated within the UK. In the UK, every marketed IVD must carry a CE/UKCE mark. Any change to the reagent content for a diagnostic would be classified as a raw material change and thus be classified as a change to form, fit or function of the product. This type of change would therefore require Regulatory agency review within the UK (and the other regions where the diagnostics are placed in the market) and require a revalidation of the medical device.

A change in a product will not only affect a single region or country. As the same diagnostic systems are sold worldwide, the applicant will have to revalidate their products worldwide. As a result, the applicant will need to receive regulatory approval from the relevant

regulatory authorities in all their markets, most importantly from the FDA in the US. This may in general not affect the applicant's sales in the UK, but it is possible that, in some cases, larger markets will have priority for regulatory approvals.

Launch

In this phase, the final labelling and packaging is in place, the product stability requirements are completed, and all necessary regulatory clearances and registrations are approved. The product is then manufactured for sale and placed on the market.

The launch phase also includes any requirements for post market surveillance planning.

Applicant's R&D

As of now, the applicant has focused their R&D efforts in not using OPnEO when developing new diagnostic components. The process described above applies for all these products and product components, but the cost and duration may be different, depending on the product. Table 4-1 shows an indicative cost of developing a new diagnostics. The actual cost for a new product can depend on a number of factors, including, but not limited to, the complexity of the product, the clinical trial design and the prevalence of the disease.

For all new product development activities, the R&D team will select some chemicals to target specific actions required in the assay: lysis of the micro-organisms liquefaction of the clinical samples, stabilisation of DNA/RNA or any other actions required to ensure the product performance. Functional testing will be performed to screen and select the compounds which allow to meet specification with the right level of performance. The chemicals will then be evaluated in term of concentration, band guards and within the manufacturing tolerance specific to each process. When the products will be ready for, verification and validation studies will be performed as well as clinical trials. The established performance will support regulatory submissions world-wide.

Table 4-1 Cost of Diagnostic system Development

Year	Stage		Labour Effort		Expenses* (£)	Clinical Trials** (£)	Total
			FTE	Cost (£)			
1	Development		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2	Qualification		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Launch	Pre-Launch	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3		Launch	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	TOTAL		[redacted] **(10-100)**	[redacted]	[redacted]	[redacted]	[redacted] **(£5-8 M)**

CBI 1

* Non-labour expenses (materials, equip, instrumentation, samples, etc.) are generally 70-80% of Labour expense.
** Clinical trial costs generally range between £[redacted] million.

When it comes to replacing OPnEO in existing products, a similar development process will be followed with the goal to ensure equivalent or non-inferior performance to the existing product to limit the impact to the regulatory submissions. A cross-functional team will be in charge of evaluating candidates, potentially specific to each product, and assess each

chemicals efficacy versus performance goals. The existing product with the chosen replacement will undergo some level of validation to show that it is not inferior to the existing formulation. The validation data collected will support any new regulatory submission required to support the change. The applicant is developing a plan to work on this substitution and will assess cost estimates for such activities. It will be within the same cost estimates than the one presented in table 4.1, but again can vary based on the complexity of the product, the need or not for clinical validation and the effort for such a study if required.

As mentioned above, the applicant is currently focused on introducing alternatives to OPnEO in new diagnostic components. Substitution in existing products is more difficult, due to the allocation of additional R&D resources (labour, laboratory time, clinical trials, etc.). Nevertheless, the applicant is developing a plan to work on this substitution and will assess cost estimates for such activities in molecular products, but specific details are not yet finalised, due to the magnitude and complexity of such an endeavour.

The following is a theoretical exercise on how long substitution of OPnEO in existing products could take, assuming that a suitable alternative has been identified for all of the applicant's diagnostics.

In general, concept and definition takes [redacted] months, development phase between [redacted] months and qualification phase is also between [redacted] months based on the clinical trial duration. The regulatory submission, its review and approval will take between [redacted] months depending on the country and the regulatory bodies. In total, development of a new diagnostic can take between [redacted] (1-5) years. CBI 1

In the EU AfA, it had been estimated that, based on the available resources and conditions at the time, it could take post 2054 before the OPnEO used in all applicant's diagnostics on the EU market at the time would be substituted.

It should be noted that this was a provisional timeline and an estimated worst case assuming all diagnostics containing OPnEO would still be in use throughout the proposed timeline. However, as new products come onto the market customers would be converted and sales volumes from older products containing OPnEO are expected to decrease as new products replace them.

After the submission of the EU AfA, the applicant has reassessed their approach to reduce use of OPnEO in their diagnostics as much as technically and economically feasible. To that end, the applicant has decided to assess the possibility of substituting OPnEO in diagnostics already on the EU and, by extension, the UK market. A substitution project is currently under planning and is expected to commence within 2022. However, due to the magnitude and complexity of such an endeavour, it is not yet possible to have any indication on the timeline or the costs of substitution in existing diagnostics.

Substitution in the existing products will depend on a number of factors:

- Considering the large number of individual diagnostics that may require to use an alternative detergent, the applicant does not have the capacity to run the substitution for all products in parallel. Therefore, the R&D feasibility and clinical validation work would need to run sequentially, with 2-3 projects running in parallel, each set taking on average [redacted] (1-5) years. CBI 1

- As discussed in Section 4.1.3.1, such a substitution effort will need to include the diagnostics supplied to the EEA-UK markets. It was assumed that, even though substitution activities need to be scheduled based on global priorities, these products will be prioritised for substitution. In practice, it is possible that other products will be prioritised for substitution, also considering that the EU AfA covers more diagnostics.
- The applicant is currently focusing their substitution efforts in new product development, some of which may replace test-kits using OPnEO. This could reduce the overall need for R&D work on existing products, which could eventually shorten the time required for substitution. However, they are also planning to initiate a substitution project for diagnostics covered by the EU AfA.
- The whole endeavour could carry a very high R&D cost, in the range of £5-8 million per diagnostic product, and as high as £50-240 million or higher overall. This R&D investment would be diverted from other projects, hampering the applicant's ability to develop novel, innovative diagnostics and harming their overall competitiveness in the market. It is thus possible that the allocated resources for substitution in existing products will be less than assumed and could thus further delay the effort. However, the exact costs for substitution will be determined once the substitution project actually kicks off.

Furthermore, as outlined in the accompanying CSR, the applicant has concluded that:

1) BD diagnostic systems are designed in a way that allows for the collection of liquid waste generated during operation that contain OPnEO.

2) Current guidance offered by BD leads to the removal of the solid waste generated from diagnostics. This accounts for 70% (estimated) of OPnEO placed on the UK market by the applicant.

3) It is a reasonable assessment that solid waste generated by BD diagnostic systems within the UK is disposed of via incineration, thus removing this pathway of OPnEO to the environment.

4) Although liquid waste may be disposed of via a manner that removes the pathway for OPnEO to enter the environment BD have assumed the worst case and that all of the OPnEO per year present in liquid waste in the UK will end up in the environment. However, as outlined in the CSR, not all OPnEO released will be present as OP. As there is too much uncertainty about the fate of the liquid waste (i.e. final treatment via biological WWTP or not) it was assumed that all OPnEO will eventually degrade to OP.

Furthermore, it should be noted that the applicant is committed to providing guidance to DUs as to how to better treat liquid waste generated by the use of BD diagnostics. It is anticipated this new guidance will remove the remaining 30% of OPnEO, resulting from liquid waste, placed on the UK market. Due to conditions currently in place for the treatment of solid waste at DU facilities it is not expected that there will be significant increased costs incurred with adhering to the new guidance.

The applicant is committed to the above measures and would like to clarify that the overall use of OPnEO within the applicant's diagnostics across the UK is very small ([redacted] kg per year). The above measures, when operational, will provide DUs with the capability to

CBI 2

remove OPnEO discharge that can be attributed to the use of the applicant's diagnostics to all environment compartments. If customers follow the guidance, the discharge should come as close to zero as possible. However, due to the large number of DUs the applicant supplies to the UK, the applicant would not be confident committing to a zero discharge policy. The applicant feels it is not possible to micro manage such a large number of customers. However, continued positive and proactive dialogue with DUs could get discharge rates of OPnEO that are attributed to the applicant to a very low number.

4.1.3.3. Monitoring of the implementation of the substitution plan

When working on developing or changing their diagnostics, the applicant applies all internal project management and monitoring procedures. The project is allocated a budget and a timeline for the individual tasks that need to be carried out. The same procedures will apply if a broader, higher level substitution project is initiated for existing products.

Such projects are monitored by the applicant's corporate Project Management Organisation. The project timeline and budget, once agreed upon and approved, will be reviewed and revised as part of the annual budgeting process of the applicant. Additionally, whenever there is a significant change in project scope, the budget and timeline will be re-evaluated. Changes in scope, timeline and/or budget and confirmation of project plans are addressed in periodic reviews and presentations from the project owner / project manager.

Such projects typically have a defined governance structure of a dedicated cross-functional core team, a core team leader (CTL) and an executive sponsor. In order to ensure adherence to budget and timelines, there is a Product Development Team (PDT) providing executive oversight and guidance.

In team meetings, project risks that could impact the project scope, hence also the timeline and budget, risk mitigations and contingency plans, are discussed and documented in meeting minutes. The progress of the project will be monitored using commercial software, such as Microsoft Project. The tool will provide details on the tasks that need to be carried out in each phase of the project and connects those tasks with the team responsible for them. It will also be used to keep track of the timing of the milestones for each phase and to ensure that the project is on track. This information can inform the project management about the status of the project and provide warning of any issues that may arise, which could delay timely project completion.

Table 4-2 overleaf presents the risk management process for the development of a new diagnostic or a major change to an existing one. As mentioned in section 4.1.3.2, the two processes are similar as far as the required tasks are concerned. These procedures apply to all of the applicant's R&D efforts.

Table 4-2 Monitoring plan summary and risk mitigation

Phase	Actions	Milestones	Resources	Monitoring options	Risks and mitigation
Concept	Recognise requirements for product Resource cross-functional team	Understand product requirements and specifications	Product strategy R&D team	Phase completion (Not relevant for existing products)	Not relevant
Definition	Scoping of product requirements Scoping of necessary resources Clinical trial design	Product specifications and project plan defined	R&D team Manufacturing Quality	Phase completion (Not relevant for existing products)	Not relevant
Development	Finalise product documentation, design and specifications New suppliers and /or materials are qualified Validation and verification plan is developed	Product and design specs finalised Suppliers and materials qualified Finalise V&V plan	Program Mgmt R&D Team Mfg Eng Team Product Strategy Quality Manufacturing	Phase completion Gate Review	Failure in qualifying suppliers -> may cause delays in sourcing of materials and manufacturing of validation lots in following phase. Mitigation: Have list of multiple suppliers that can provide necessary materials
Qualification	Manufacture validation lots Run validation tests, including stability and clinical trials Develop qualification documentation Apply for regulatory approval	Validation lots ready Validation tests successful Process validated Regulatory approval received	R&D Team, Mfg Eng Team Product Strategy Production Plant Quality Compliance Manufacturing	Phase completion Gate Review	Unacceptable performance during testing -> need to redesign the product or even select a different alternative Mitigation: Have several potential alternatives evaluated

4.1.3.4. Conclusions

The applicant is working towards identifying technically and economically feasible alternative detergents that they will then aim to use in their diagnostics sold in the UK, to replace OPnEO. The applicant has made progress with alternative detergents (Alternatives 3 and 4) for use in a number of new diagnostic components. However, there is uncertainty on whether Alternatives 3 and 4 will be suitable for all of the applicant's diagnostics using OPnEO in the UK, because of the variety and complexity of the affected diagnostics. For that reason, only a provisional substitution plan is presented in this AfA.

Once an alternative has been identified, there is R&D development to determine performance levels of the product using the alternative, including both internal analytical Verification & Validation studies and clinical simulation studies. If results meet product performance, requirements around sensitivity and specificity then lab trials, designed by the applicant, and usually operated by an independent CRO, will be run to confirm the assumptions made in the initial assessment are correct. If they pass the lab trials, the product development moves onto the next phase. If the lab trials are not a success, then it would have to go back for another phase of development and product optimisation.

Considering that the time needed to qualify and launch a diagnostic after a major component change, such as substitution of OPnEO by an alternative, can be as long as [redacted] (1-5) years, the time required for a complete substitution could be until 2054. Furthermore, such an effort could require an additional R&D investment of £50-240 million or even more. CBI 1

The above plan is based on the estimates from the EU AfA. The plan cannot be determined solely by the UK market but will also need to consider the implications of other markets. Therefore, a substitution of OPnEO in existing products, while theoretically possible, depends on several factors, not all of which are in control of the applicant in the UK.

Nevertheless, the applicant is committed to reducing releases of OPnEO associated with the use of their diagnostic products in the UK. So far, the focus has been on new product development and the applicant will increase focus on existing products through an additional project that will be initiated in 2022. In addition, the applicant is also working on minimising the release of waste containing OPnEO to the environment, as discussed in the CSR.

4.1.4. R&D plan

At the moment of writing, there is no technically and economically feasible alternative available. As such, a substitution plan was prepared. The applicant has a robust R&D plan in place, which aims at identifying the best suited detergent for use in their new products.

As of now the applicant's substitution focus has been primarily on new product development. However, the applicant continues to examine substitution on existing products and has evaluated a number of alternatives as substitutes of OPnEO in existing diagnostics (Table 3-13). Based on the data to date the majority of the tests have been unsuccessful in providing equivalent/acceptable performance. The applicant will increase focus on existing products through an additional substitution project that will be initiated in 2022.

4.2. Risks associated with continued use

For the "non-use" scenario there would be no further import of the applicant's diagnostics s containing OPnEO into the UK and therefore there would be no possibility of any OPnEO emission to the environment.

There is no environmental release from the storage of diagnostics. As outlined in the CSR, diagnostics are shipped to the applicant's DUs. The diagnostics placed on the market generate solid and liquid waste, with each waste stream being handled in a different manner. Table 4-3 provides the estimated breakdown of maximum solid waste vs. liquid waste produced from the diagnostics expected to be placed on the UK market after the Sunset Date.

Table 4-3 Estimated amount of OPnEO and Solid vs Liquid waste (per year)

Waste Type	Amount (kg per year)	%
Solid	[redacted] (7-70) kg OPnEO	70%*
Liquid	[redacted] (3-30) kg OPnEO	30%*
Total	[redacted] (10-100) Kg OPnEO	

CBI 2

*waste percentages are estimated using projected sales figures of all BD diagnostic systems.

The applicant states in their technical documentation that users should "always handle specimens as if they are infectious and in accordance with safe laboratory procedures".

By stating that the specimens are infectious, the solid waste generated is thus classified in the UK as biohazardous waste. The definition of biohazardous waste includes:

- Human blood and its components, in liquid or semi-liquid form, dried or not
- Human bodily fluids in liquid or semi-liquid form, dried or not
- Human pathological waste: all human tissues, organs, and body parts

The European Waste Catalogue (EWC) codes are used for the classification of all wastes and hazardous wastes and are designed to form a consistent waste classification system across the EEA. As noted above the diagnostic waste is biohazardous as the specimen should be treated as infectious. Using the EWC codes this waste is classified as follows:

- Code 18 - Wastes from human or animal health care and/or related research (except kitchen and restaurant wastes not arising from immediate health care)
- Category: 18 01 - wastes from natal care, diagnosis, treatment or prevention of disease in humans
- Sub-category: 18 01 03* - wastes whose collection and disposal is subject to special requirements in order to prevent infection. Under the EWC Codes any waste marked with an asterisk (*) is considered as a hazardous waste and would thus be disposed as directed by individual country legislation.

Under the waste legislation in place, holders of hazardous waste shall ensure that waste undergoes safe disposal and that they should take necessary measures to ensure that waste management is carried out without endangering human health or harming the environment [13].

4.2.1. Impacts on humans

As noted in the accompanying CSR, risks to human health do not need to be assessed in this AfA as OPnEO was listed on Annex XIV on the basis of their endocrine disrupting properties for the environment.

4.2.2. Environmental impacts

When assessing any OPnEO that may be released into the environment, the biodegradation behaviour needs to be considered. OPnEO, and alkylphenol ethoxylates in general, degrade in a complex manner within the environment [14]. The step degradation process is shown in Figure 4-2 with a more detailed version provided in the Member State Committee support document for identification of 4-(1,1,3,3-Tetramethylbutyl)Phenol, Ethoxylated as a SVHC [16]. Based on the molecular structures, the molecular weight of OPnEO (646 g/mol) is 3.14 times greater than that of OP (206 g/mol based of the formula $C_{14}H_{22}O$). Therefore, the total mass of emissions of OP to the environment will be 3.14 times lower than the OPnEO emitted.

However, if OPnEO containing liquid waste from the applicant's diagnostic is released, it is expected that this will be via a municipal sewer system and not directly into a water source. As such, the fate of OPnEO within biological waste water treatment plants (WWTP) needs to be assessed, as this is by the far the most common treatment method of sewer water within the UK. The figure below shows a stepped degradation progression that ends in the alkyl phenol, however the reality is that in a WWTP not all of the alkylphenol ethoxylate is degraded to the alkyl phenol. For example, the carboxylic acids shown below are more resistant to biodegradation than the alkylphenol ethoxylates. Ahel (1994) noted that nonylphenol ethyoxylate (NPnEO) degraded to several metabolites, with nonylphenol accounting for a total of 25% of the original NPnEO (corrected for molecular weight). In addition, 90% of this 25% was adsorbed onto digested sludge due to the lipophilic nature of nonylphenol (NP), therefore resulting in just 2.5% of the original NPnEO being released as NP in the effluent of sewage treatment plants.

OPnEO is structurally very similar to NPnEO, with just one methyl group difference. It is therefore highly likely that similar levels of OP, to those of NP, would be observed in effluent. Additionally, the molecular weight correction factors are very similar. Therefore, it can be concluded that approximately 2.5% of OPnEO would be released as OP in the effluent.

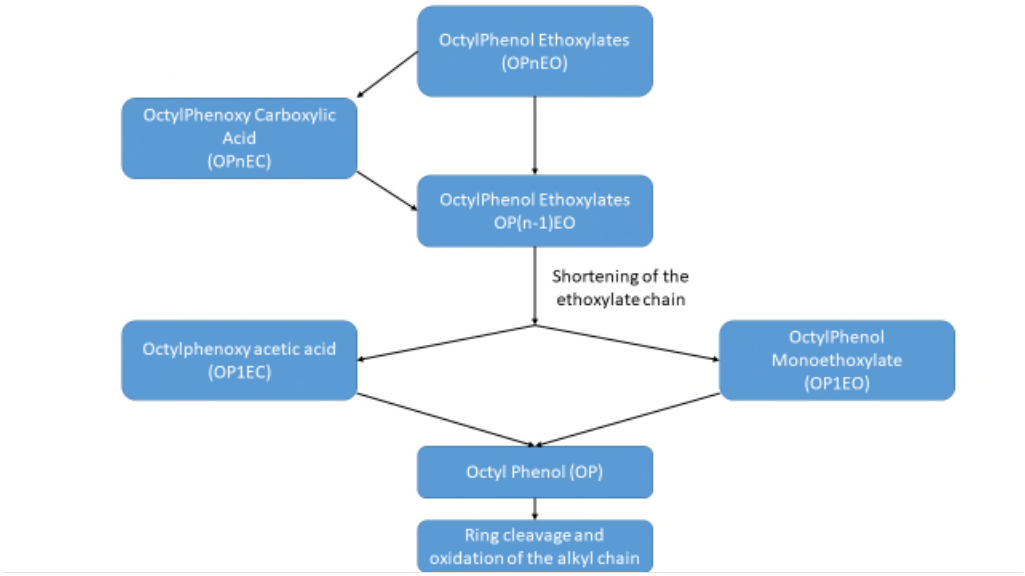

Figure 4-2 Biodegradation pathway for alkylphenol ethoxylates

- There are no emissions of OPnEO to the environment during the storage and use of the diagnostics.
- The diagnostics containing OPnEO do not require any cleaning and maintenance so there are no associated emissions to the environment.
- Once used, the solid waste produced by the diagnostics is classified as biohazardous waste. Based on the current national legislation of the UK regarding the disposal of hazardous waste, the applicant has concluded that it is a reasonable assessment that solid waste generated from the use of the applicant's diagnostics is disposed of via incineration within the UK. This disposal route removes this emission pathway for OPnEO.
- Although liquid waste may be disposed of via a manner that removes the pathway for OPnEO to enter the environment the applicant has assumed the worst case and that, at most, [redacted] (3-30) kg of OPnEO present in liquid waste across the UK will end up in the environment. However, not all OPnEO released will be present as OP. As there is too much uncertainty about the fate of the liquid waste (i.e. final treatment via biological WWTP or not) this AfA will calculate the amount of OP released into the environment via the mass reduction method outlined, giving a calculated total annual OP release across the whole of the UK of [redacted] (1-10) kg OP per year. The applicant is in the process of evaluating their guidance on liquid waste. New guidance will direct downstream users to collect and dispose of liquid waste that may contain OPnEO via adequate treatment methods that limits the possibility of OPnEO entering the environment. The updated guidance for liquid waste will be available to the UK customers of Bioscience and Molecular products by early 2023.

CBI 2

As detailed in the accompanying CSR, there are a number of risk management measures (RMM) and operational controls to limit the release of OPnEO, namely the classification of the solid waste stream as biohazardous waste and the practices in place within the UK for handling of this waste type, namely incineration. Due to these conditions an estimated 70% of all OPnEO present in the applicant's diagnostics is removed via incineration, with no emissions to the environment. The remaining estimate of [redacted] (3-30) kg per year of

CBI 2

OPnEO is emitted via liquid waste. This waste is spread across the UK. As mentioned above, the applicant is reviewing their guidance to customers on how to dispose of liquid waste that may contain OPnEO and it is expected that it will become available by early 2023.

As per the applicant's updated waste handling instructions, which are agreed to be included in the IFU for products containing OPnEO, the users should also:

"*Collect and dispose of all used and unused reagents and any other contaminated disposable materials following procedures for biohazardous or potentially biohazardous waste. It is the responsibility of each laboratory to handle solid and liquid waste according to their nature and degree of hazardousness and to adequately treat and dispose of them (or have them treated and disposed of) in accordance with any applicable regulations. Do not discharge liquid waste down the drain where prohibited.*"

4.2.3. Summary of environmental impacts

The environmental risks associated with the "applied for use" are higher than those for the "non-use" scenario. However, as shown above (and in greater detail in the CSR) the RMM and OC in place, particularly the heavily regulated disposal of biohazardous waste, limits any potential releases of OPnEO to the environment to [redacted] (3-30) kg/year in a worst case situation.

CBI 2

The ECHA document "SEA-related considerations in applications for authorisation for endocrine disrupting substances for the environment, specifically OPnEO and NPnEO" (30 Nov 2017) confirmed that the environmental risk or impacts from OPnEO is not possible to quantify as there are no thresholds or dose-response relationships defined [17].

In this situation the ECHA document suggests that monetised benefits of continued use and the quantified release estimates form the basis of a semi-quantitative approach to justifying that the benefits of continued use outweigh risks.

Table 4-4 shows the expected releases of OP to the environment as a result of the use of the applicant's diagnostic systems by professional users in the UK.

Table 4-4 Summary of remaining releases to the environment

	Per year
Total releases/emissions (in kg per year)	[redacted] (3-30) kg OPnEO [redacted] (1-10) kg OP

CBI 2

4.3. Non-use scenario

4.3.1. Discussion of potential Non-Use Scenarios

In case of a refused authorisation, use of OPnEO in the applicant's diagnostics in concentrations at or above 0.1% w/w will not be permitted. As a result, use of these diagnostics by the applicant's customers in the UK will have to cease.

As concluded in Section 3.4.3, the applicant will not be able to substitute OPnEO in their diagnostics with a technically and economically feasible alternative by the end of the transitional period for the substance. As a result, the applicant will be forced to withdraw

the specific diagnostics from the UK market, until they can substitute OPnEO or until a new product, without OPnEO, becomes available.

The affected diagnostics can only work in a specific system, e.g. the BD MAX™ or BD COR™ systems and there are no replacement diagnostics (without OPnEO) in the same system. It is possible that other instrument platforms may offer an alternative test without OPnEO, but this would require the customer to also purchase additional instruments, which may not meet their operational needs. Therefore, the applicant will not be able to offer alternative diagnostics to replace those affected by a refused authorisation. As a result, the UK market for these diagnostics will be lost to the applicant.

The applicant's customers include hospitals, blood banks, clinics and testing laboratories (CROs). The applicant's diagnostic systems are essential for the operations of these customers, so the downstream users will need to find alternatives immediately, so that they can continue offering their services. This is particularly important for blood banks, which need to carry out testing on donated blood to ensure sufficient blood supply, but also for hospitals, which need to quickly diagnose and to monitor patients' conditions.

As such, the applicant's customers are expected to set up a new procurement deal, most likely with the applicant's competitors. Such deals typically require for the customer to initiate the call for tenders, select suppliers, receive the new equipment needed to run the replacement tests and validate the new tests. This can be a long process, especially with regards to the new diagnostics' validation and could result in a shortage of test capacity for the endpoints currently covered by the applicant's diagnostics.

In theory, the applicant can develop new diagnostics, without OPnEO, and re-enter the UK market. However, this option is not easy. Developing alternative diagnostics is a lengthy and resource intensive process, as discussed in section 4.1.3.1. Furthermore, the applicant will need to develop replacement diagnostics for all the products affected by the refused authorisation. Therefore, the applicant will not be able to recapture the market share they currently hold immediately, especially after the potential reputation impact they will face in case they withdraw their products at short notice. Users of diagnostic systems want reliability from their suppliers and prefer to have long contracts, to ensure security of supply. Once the applicant's customers move to a competitor, it will be very difficult for the applicant to regain their trust. As a result, it is expected that the market for the particular tests will be lost to the applicant.

4.3.2. Conclusion on the most likely non-use scenario

Based on the discussion in section 4.3.1, the most likely NUS would be for the applicant to cease sales of their diagnostic systems containing OPnEO in the UK and leaving the relevant market for the particular products. It is unlikely that the applicant will be able to re-enter the market and recapture their market share, as the process for developing, validating and commercialising replacement diagnostics for all those affected by a refused authorisation will be long and with uncertain results.

This will result in the applicant losing all revenue and profits from the diagnostic systems sold in the UK. The applicant will also suffer a reputational impact with their customers, which may potentially affect any future prospective deals.

The applicant's customers will need to move to a competitor's diagnostic system. However, this process will not be possible to be completed at a short notice, so it is expected that,

until the new diagnostic systems are in place and validated, there may be restricted capacity to run tests on patient samples or donated blood units. These are critical operations for the UK health system and could result in a disruption to the diagnosing and monitoring patients in the UK, as well as a potential shortage for donated blood components for transfusion.

It should also be noted, however, that, when a new supplier of IVD systems is selected, the contract includes a new diagnostic instrument along with the diagnostics. Diagnostic instruments can be very bulky, as seen for example in Figure 3-4 and Figure 3-8 for the applicant's BD MAX™ and BD COR™ systems, respectively. In many cases, floor space is limited, which precludes the use of multiple analytical instruments. Furthermore, use of several different analytical instruments could add complexity to the daily operations, and prevent a more streamlined process. Finally, it is common practice to run certain diagnostic tests in arrays on a single patient's sample. Therefore, it is possible that the applicant's customers will choose a different supplier for the entirety of the test portfolio currently offered by the applicant and not just for those tests that contain OPnEO above 0.1%. However, it is not possible to predict how each customer will respond.

The socioeconomic impacts of a refused authorisation will be examined in more detail in the following section 4.4.

4.4. Societal costs associated with non-use

4.4.1. Economic impacts on applicant

The removal of the applicant's diagnostics from the UK market will have a detrimental effect on the applicant's revenue. Table 4-5 shows the applicant's sales of diagnostics in the UK in 2021, along with their forecast for the duration of the review period.

Table 4-5 UK revenue of applicant's diagnostics during the review period (in £)

Year	Revenue	Profit	Revenue (2022 prices)	Profit (2022 prices)
2022	[redacted]	[redacted]	[redacted]	[redacted]
2023	[redacted]	[redacted]	[redacted]	[redacted]
2024	[redacted]	[redacted]	[redacted]	[redacted]
2025	[redacted]	[redacted]	[redacted]	[redacted]
2026	[redacted]	[redacted]	[redacted]	[redacted]
2027	[redacted]	[redacted]	[redacted]	[redacted]
2028	[redacted]	[redacted]	[redacted]	[redacted]
2029	[redacted]	[redacted]	[redacted]	[redacted]
2030	[redacted]	[redacted]	[redacted]	[redacted]
2031	[redacted]	[redacted]	[redacted]	[redacted]
2032	[redacted]	[redacted]	[redacted]	[redacted]
2033	[redacted]	[redacted]	[redacted]	[redacted]

Over a 12-year review period, the applicant will lose approximately £[redacted] (£75-150) million in revenue, converted to 2022 prices using a 4% discount factor. The annualised cost, with a 4% discount factor is approximately £[redacted] (10-20) million. CBI 3

The applicant cannot disclose profit margin values specific to the diagnostics in scope of the AfA. In order to present an illustrative profit loss in the NUS, an indicative net profit margin will be used, based on a market survey of diagnostic companies, available online. The average net profit margin in 2021 was approximately 13%, though the year-to-day value for Q4 2021 was 24.25% [18]. Using the lower value results in a total net profit of approximately £[redacted] (1-5) million per year or approximately £[redacted] (12-60) million over the 12-year review period, discounted to 2022 prices. It should be noted that this calculation is an underestimation, as the applicant estimates the net profit from sales of diagnostics in the UK is higher than the industry average used. CBI 3

In addition to the lost profits, it is also possible that a premature cease of supply of diagnostics by the applicant will constitute a breach of contract, which could activate compensation clauses. Many of the contracts are long (5-7 years), which makes it very likely that many of them will still have several years before termination. While the penalties can be a significant cost for the applicant, which could affect their business in the UK, it is considered a transfer cost, paid to their UK customers, so it cannot be included in the assessment of overall economic impacts.

The combined economic costs and timeframe of the "non-use scenario" are compared to the "applied for use scenario" in Table 4-6.

Table 4-6 Economic Cost for the applicant

Phase	Non-Use		Applied for Use	
	Cost	Time	Cost (£)	Time
Loss of Revenue	£[redacted] (10-20) million	Annual	N/A – there would be no loss in revenue	CBI 3
Loss of Net Profit	£[redacted] (1-5) million	Annual	N/A – there would be no loss in profits	

It should also be noted that a share of the profit generated out of the revenue is used in the development of new diagnostics, meaning that introduction of diagnostics without OPnEO on the market would be delayed in the NUS.

4.4.2. Economic impacts on the supply chain

In this scenario the applicant's existing UK customers (e.g. hospitals, doctors' surgeries, blood banks and contract research organisations) would need to source new suppliers of the instruments they currently purchase from the applicant. This would mean the market would have to make up a shortfall of more than [redacted] diagnostics per year. Understanding that one diagnostic contains multiple tests, this could end up impacting > [redacted] (1-5) million tests over a year in 2026. CBI 3

The applicant is supplying their customers with both the diagnostic and the instrument to run the tests. Diagnostics and instruments have been developed in parallel and are optimised for working together. The applicant's instruments can only run the applicant's diagnostics and these diagnostics can only be used in the applicant's instruments.

When the applicant, or any other diagnostic system manufacturer, makes a service agreement with a customer, be it hospital, surgery, blood bank or testing laboratory, the agreement includes both the instrument and a portfolio of diagnostics, according to the customer's needs. When the diagnostic systems are installed, the customer needs to run some validation / calibration tests with standardised samples, to ensure reliability and reproducibility of the tests on actual patient samples. This is a standard process and may take several months, especially for large numbers of assays.

If the applicant's customers need to switch to a different diagnostic system supplier, they will need to carry out calibration of the new instruments before they can be used with actual samples. The actual costs of this cannot be determined, as it was not possible to collect this information from the applicant's customers. Nevertheless, the cost will consist of the following elements:

- Work hours for the employees that will carry out the calibration and prepare the documentation. This usually occupies 2-3 full time employees for two weeks.
- Test materials and consumables to run the tests.
- Installation and utility connections for the new instruments, after the old ones have been disconnected and removed from site.
- In addition, the time until the new platform is operational should also be considered, as it could be considered as downtime during which testing capacity will be reduced. Based on the applicant's experience, it typically takes 2-3 months to investigate and secure a new platform, approximately 3-4 days for installation and training and 2-3 weeks for its validation. Overall, it can be 3-4 months before the new platform can be fully operational.

4.4.3. Economic impacts on competitors

The applicant's competitors are expected to take over the applicant's customers in the UK if the applicant stops selling their diagnostic systems under the NUS. This means that they will see an increase in their sales and, consequently, their profits. However, the applicant does not expect that this will occur immediately after the applicant stops their sales, as the customers will still need to go through their procurement process. Furthermore, it is unknown if the competition has sufficient production capacity to increase their output and meet the demand. Typically, the main bottleneck in these situations is the manufacturing of the additional instruments required rather than the increase in production diagnostics. It is therefore expected that whatever gains the applicant's competitors make, they will most likely materialise a few years after the authorisation decision.

Furthermore, it is unlikely that any competitors with UK manufacturing facilities will take over the applicant's customers, as the applicant's main competitors are based in the EEA or in North America. This means that the UK will not have any benefit from producer surplus within its borders.

Finally, it should also be noted that many of the applicant's competitors (e.g. Siemens Healthcare Diagnostics, Ortho-clinical diagnostics) have received UK authorisations for the use of OPnEO in their diagnostic systems [19]. So, if the applicant's customers switched to a competitor's system, this would not necessarily result in a reduction to the quantities of OPnEO released to the environment, as the applicant's diagnostics may be replaced by competitor ones containing OPnEO.

4.4.4. Social impacts

4.4.4.1. Impacts on employment

As the applicant does not manufacture the diagnostics in the UK it is unlikely that there will be any employment impacts with either the applied for use or non-use scenarios. There may be employment impacts outside of the UK, but these are out of scope for this AfA.

4.4.4.2. Impacts on public health

As noted earlier, the applicant's molecular and point of care diagnostics are focused on two key areas: Infectious Disease and Women's Health and Cancer, while the Leucocount™ product is used in measuring white blood cells in leucoreduced blood products. Table 4-7 provides further detail of the very serious, and on occasion, life threatening diseases and situations the applicant's diagnostics are used to monitor. This is just an indicative list, with a more extended list presented in Table 3-5.

Table 4-7 Indicative list of Diagnostics containing OPnEO placed onto the UK Market by the applicant

Product group	Analysis	Downstream User
Molecular	• Gastroenteritis (bacterial, parasites, viruses); • Sexually transmitted infections • Vaginosis /vaginitis • Hospital acquired infections • Respiratory infections	Hospital; Laboratory
Point of care	• Influenza A & B	Point of care office
Bioscience	• White Blood Cells in leucoreduced blood products	Hospital; Laboratory; Blood bank

Removal from the UK market would have a serious impact on the lives of people dealing with these illnesses, particularly in cases when they are waiting for a diagnosis. Some of these diseases, such as respiratory infections, can be treated better with a fast diagnosis. Furthermore, a quick diagnosis allows for restrict transmission of the disease to other hospital patients or the general population. This was made evident during the Covid-19 pandemic, with the Test-Trace-Isolate approach. The emergence of diagnostics providing results quickly has helped identify positive symptomatic and asymptomatic cases and ask them to isolate earlier, limiting the number of people they could infect.

For example, the BD COR™ solution for HPV screening, which is in the final approval of acceptance by Public Health England (PHE), offers extended genotyping, which is becoming increasingly important in patient management and persistence tracking, as persistence of the same genotype has been identified as one of the highest risk factors for developing cervical cancer. In addition, the assay is CE-marked for self-collection, which is not the case for other assays currently used for HPV screening in the UK. The possibility to offer self-collection at home to women is very high ranking on the agenda in cervical cancer screening, and there are several pilot studies running currently.

In addition, the BD COR™ is a highly automated, integrated system, which can help decrease time between sampling and results.

This applies to many of the applicant's molecular products, in which use of the applicant's technology allows for much faster turnaround times for samples, with results requiring

only 3 hours, where with conventional methods it could take up to 48 hours. This is very important for patients waiting for diagnosis on infections (e.g. gastroenteritis or hospital acquired infections), as they could be diagnosed and receive treatment faster, avoiding potential complications. Furthermore, it allows the hospitals to better plan the treatment of patients and manage the available beds more efficiently. For example, the UK NHS has a 4-hour target for bed management, and the 3-hour turnaround time for the applicant's molecular products contributes towards that target.

The ease of use of the systems also frees some of the laboratory staff and biomedical scientists for other tasks, allowing better flexibility to the hospital or laboratory. The positive impact of the applicant's diagnostics for hospital operations are also concisely presented in a video by the applicant [20].

The applicant is also offering the BD Leucocount™ diagnostic system for use by blood banks and laboratories in the UK to count the white blood cells in blood samples, either for donated blood or as part of health examinations.

Table 4-8 summarises the social impacts of a refused authorisation.

Table 4-8 Social Impacts in NUS

Phase	Non-Use	Applied for Use
Quality of healthcare service	BD diagnostics would be removed from the UK market. This would have a significant impact of the quality of healthcare service provided to patients.	No impact to UK patients as there is continued use of BD diagnostic systems.

4.4.5. Wider socio-economic impacts

Table 4-9 examines the wider socioeconomic impacts in the NUS. As there is little in the way of data on competitors manufacturing processes and how they may be impacted by the placing of OPnEO in the authorisation list, it is not possible to quantify the below table.

Table 4-9 Wider Economic Impacts

Impact	Applied for Use Scenario	Non-Use Scenario
Changes to competition within the UK	**No significant impact** Baseline case	**Yes – potentially significant impact** Fewer companies providing diagnostic systems in the UK could potentially affect prices for healthcare providers and patients.
Changes to competition outside the UK	**No significant impact** Baseline case	**Yes – significant impact** See above. There will be redundancies at the applicant's manufacturing facilities within the USA and Canada due to the reduced demand for the applicant's products. This could affect the applicant's competitiveness in these markets. Loss of profits could also impact R&D activities, as the applicant will not be able to reinvest in developing novel, innovative diagnostic systems.

Impact	Applied for Use Scenario	Non-Use Scenario
Changes to international trade	**No significant impact** BD diagnostic systems stay on the worldwide market providing the same level of cover to patients already using the product.	**Yes – significant impact** BD diagnostic systems are used throughout the world. The non-use scenario would mean the UK market cannot be provided with the diagnostics.
Changes to UK finances	**No significant impact** Baseline case	**Yes – low impact** Public sector customers may be faced with unplanned expenses or higher prices if the applicant leaves the market and their customers have to select replacement vendors from a smaller number of companies and at a short notice.

4.4.6. Compilation of socio-economic impacts

Table 4-10 summarises the socioeconomic impacts in the NUS. The expected monetised impacts are approximately £[redacted] (1-5) million, but the actual cost is more likely higher, if one considers the impacts to the downstream users of the applicant's diagnostic systems and the millions of patients in the UK that have their samples tested for infectious diseases or cancer. CBI 3

Table 4-10 Societal costs associated with non-use

Description of major impacts	Monetised/quantitatively assessed/qualitatively assessed impacts
1. Monetised impacts	**£ per year**
Loss of applicant's profit.	£[redacted] (1-5) million CBI 3
Sum of monetised impacts	**£[redacted] (1-5) million**
2. Additional qualitatively assessed impacts	
Costs for procurement of replacement diagnostic systems for downstream users.	Not quantified
Deterioration in quality of healthcare provided by applicant's customers.	Not quantified
Reduced competition in the UK.	Not quantified

4.5. Combined impact assessment

4.5.1. Comparison of impacts

The combined impact assessment is summarised in Table 4-11, with the comparison of socioeconomic costs and the emissions of OP to the environment from the use of the applicant's diagnostic systems.

The only emission route that is relevant to the professional use of the applicant's diagnostic systems is through the disposal of liquid waste generated by the diagnostic systems. Most of the OPnEO used by the applicant's customers ends up in solid waste, which is classified

as biohazardous waste and is incinerated. The liquid waste is treated by different methods, including incineration, but the CSR has assumed the worst-case scenario in which all of it is discharged to the sewer and is converted into OP in the WWTP and the environment. The CSR estimates a release of [redacted] (1-10) kg OP. CBI 2

The indicative annual net profit loss of £[redacted] (£1-5) million has been used for this assessment. This figure is likely an underestimate of the total impacts as it does not include unquantifiable impacts, such as the disruption to patients and the potential additional, unplanned procurement costs for the applicant's customers. Even with this underestimate the ratio of comparison of impacts is huge, showing the significant benefits of granting the AfA. CBI 3

Table 4-11 Cost of Non-Use per Kg of prevented OP emissions

	Per year
Total cost (£) (annualised to £ million per year)	£[redacted] (1-5) million in profits
Total emissions (kg)	[redacted] (1-10) kg of OP
Ratio (£/kg)	£[redacted] million per kg OP (£0.5-5 million per kg OP)

CBI 3
CBI 2
CBI 3

The cost per kg of prevented OP emissions in the NUS is approximately £[redacted] million (£0.5-5 million per kg OP). CBI 3

The acceptable values of this ratio may vary from substance to substance, based on their hazards. A study by the Dutch Institute for Environmental Studies (IVM) study proposed a benchmark of €50,000 per kg of emitted substance[7]. Furthermore, the study also benchmarks a cost of €1,000 per kg as an unacceptable ratio, with the range between €1,000 and €50,000 being a grey zone, which would require consideration of more factors.

Based on the above, and considering that the cost per emission ratio is well above the €50,000 benchmark, the applicant believes that a refused authorisation will not be a cost-efficient measure to reduce OPnEO emissions to the environment and that an authorisation should be granted.

4.5.2. Distributional impacts

The table below outlines the distributional impacts of the applied for applied-for-use vs. the non-use scenario.

[7] Oosterhuis,F., Brouwer, R. Benchmark development for the proportionality assessment of PBT and vPvB substances. Available online at: https://echa.europa.eu/documents/10162/13647/R15_11_pbt_benchmark_report_en.pdf/a695a7fd-e2bd-4dc5-b69a-bc02f9f98fef, accessed on 05 April 2022

Table 4-12 Distributional impacts

Affected group	**Economic impact**	**Health and environmental impact**
Economic operator		
Applicant	High – loss of revenue and profit	Negligible
Downstream Users	High – cost to purchase and validate new diagnostic systems	Low – releases to the environment
Patients	Medium – removal of quality diagnostic systems from the market and potential delays in testing	Low
Geographical scope		
UK	Medium – loss of competition and competitiveness in market	Low – potential environmental impacts from releases of OP to the environment
North America	Potential lost jobs at the applicant's manufacturing plants.	None
Within the applicant's business		
Employers/Owners	High – lost revenue	N/A
Employees	None – no job losses expected in the UK	N/A

The applicant is expected to have the highest impacts in the NUS, as they are expected to lose their UK market for molecular products and a large share of their biosciences and point of care products. This will not be temporary, because of obstacles from the new, long contracts of downstream users with competitors (typically 5-7 years) and the negative reputation impact that leaving will have on the applicant. The applicant does not expect that there will be any employment impacts in their UK operations, but the lost sales could cause layoffs at the manufacturing sites in the US and Canada.

Most of the applicant's losses will eventually be transferred to their competition, of which the major companies are based outside the UK or even the EEA. This transition may not be immediate however, as the use of the applicant's diagnostics containing OPnEO will need to cease at very short notice, while, at the same time, procurement and calibration processes at the downstream users, mainly public organisations, can take several months. This could result in a shortage of tests and delays in testing patients to diagnose or monitor their conditions.

The downstream users of the diagnostic systems will also face negative impacts, as they will need to purchase replacement services and equipment for their testing needs. They may also face testing capacity issues in the short term, until the new supply lines are established.

Finally, the environment in the UK will not necessarily see an improvement with regards to the releases of OPnEO in the NUS. The applicant's competitors have submitted (and have been granted) UK AfAs for the continued use of the substance in their products. It is thus possible that the diagnostic systems that will be used to replace the applicant's will still contain OPnEO, which could still be released to the environment, therefore not resulting in any actual benefit.

4.6. Information to support the requested review period

The applicant is applying for a 12-year review period. This review period is based on the following criteria:

1) There is no current alternative detergent, other substance, or technique that is a technically feasible alternative to the continued use of OPnEO in the applicant's diagnostics sold into the UK, as shown in section 3.4.
2) The timelines and costs associated with any potential substitution are disproportionate to the expected benefit, due to the number of complex diagnostics currently placed on the UK market by the applicant. These timelines are driven by a regulatory burden as well as the applicant's own internal quality procedures. Any change to the reagent content for a diagnostic would be classified as a raw material change and thus be classified as a change to form, fit or function of the product. This type of change would therefore require UK Regulatory agency review. Furthermore, any R&D decision on diagnostics will be taken at a regional level, taking into consideration EEA and UK sales combined.
3) There are limited current risks to the environment. Use of the applicant's diagnostics results in very small discharges of OP to the environment across the UK (approximately 1-10 kg OP per year). This discharge is low due to overall volumes of OPnEO placed on to the market and the risk management measures (RMM) and operational conditions employed by the applicant's customers, in particular with regards to incineration of solid waste.
4) The socio-economic benefits of continued use are high, and there is clear evidence that due to high regulatory costs for re-approval of diagnostics containing any alternative substance that this situation is not likely to change in the next decade. For the applicant, the focus of the review period will be the research into finding suitable alternatives for products, so that they can ensure the continued supply of diagnostics to hospitals, doctor surgeries, blood banks and contract research organisations (CRO). Not granting the AfA for use of OPnEO by the applicant could result in a significant impact to these end users, and ultimately impact on UK patient safety and health.

4.7. Uncertainties and sensitivity analysis

4.7.1. Uncertainty analysis

The key assumptions and sources of uncertainty within this report, and their importance to the overall conclusions of the SEA are provided in the table below.

Table 4-13 Key Assumptions and Sources of Uncertainty

	Assumption / Uncertainty	Importance
1	Availability of alternatives for all of the applicant's products is not certain. The applicant has identified two potentially suitable alternatives (Alternatives 3 and 4), which are evaluated for use in a number of new molecular diagnostic components. However, these alternatives are not considered suitable for some Point of care and possibly other diagnostics so more work is needed, which could take longer than the requested review period.	The substitution plan was prepared under an assumption that suitable alternatives will be available for all of the applicant's products. However, if this would not be the case, a review report will need to be submitted and some products may reach their end of life without substitution.
2	The environmental emissions calculations are based on a worst case scenario that all liquid waste from the applicant's diagnostics are directed to the environment via sewer. The applicant's customer survey has shown that there are a number of disposal pathways for liquid waste.	This figure is an overestimate of the total discharge volume of OP attributable to BD diagnostics. As the figure is very small, at most [redacted] (1-10) kg OP a year across the whole of the UK, this overestimation is unlikely to alter the findings of the SEA. CBI 2
3	The environmental emission calculations are based on all solid waste generated by the applicant's diagnostics being classified as biohazardous (EWC Code 18 01 03*) and as such disposed of in a manner (i.e. incineration) that removes the possibility of OPnEO and its breakdown products entering the environment.	This assumption is confirmed by the applicant's technical documents that provide guidance on waste, and waste management legislation in the UK.
4	Revenues and volumes are difficult to fully predict due to the healthcare market being unstable particularly with the COVID-19 pandemic.	The applicant has offered a forecast of future sales in the UK to the best of their current knowledge. Actual sales for different product groups and as a total may be different than what has been forecasted, which could affect impact calculations and the total volume of OPnEO used. Nevertheless, the applicant considers the impact assessment to be robust in that potential economic impacts are also positively correlated with the volume of OPnEO in diagnostics.
5	The total cost of impact, approximately £[redacted] (£1-5) million in profits, is likely an underestimate of the total impacts as it does not include costs to customers to switch diagnostic system suppliers and other, unquantifiable impacts, such as the disruption to patients and the operation of hospitals.	This potential underestimate of the total cost of the non-use scenario will not alter the findings of the SEA, which already show that benefits of continued use vastly outweigh the costs. CBI 3
6	The net profit margin that was used is a publicly available figure from a survey on a number of companies in the applicant's sector. It is unclear whether this survey is representative for the whole sector, and the applicant's net profit margin is higher than what is used.	The economic impacts of a refused authorisation for the applicant are underestimated, by the use of a lower net profit margin. This gives a conservative calculation of economic impacts. However, as the cost per emitted kg ratio is high, it is not expected that this would affect the findings and conclusions of the SEA. A sensitivity analysis is carried out to evaluate the impact of different profit margins to the overall conclusions of the SEA.

4.7.2. Sensitivity analysis

Table 4-14 shows the expected economic impacts for the applicant and the resulting cost per emitted kg of OP for different net profit margins, if said profit margins applied to the whole portfolio.

Table 4-14 Sensitivity analysis on economic costs for the applicant

Economic impact (net profit margin)	Base NUS	5% profit margin	20% profit margin
Lost profits (£ per year)	£[redacted] (1-5) million	£[redacted] million	£[redacted] million
Cost per kg emitted OP	£[redacted] (£0.5-5) million	£[redacted] (£0.1-2.5) million	£[redacted] (£0.5-5) million

CBI 3

The IVM benchmark study, suggested that a ratio of €50,000 per kg of prevented emissions is a good indicator that the suggested measure, in this case a refused authorisation, is not cost effective. This can be achieved only with very low profit margins, which are unlikely to materialise for the whole of the applicant's operations.

The benchmark value for a cost effective measure is at €1,000. The applicant would need to have practically zero profits for this scenario to materialise. It should be noted, however, that the actual value of the threshold for cost effectiveness depends on the substance in question.

5. CONCLUSION

The assessment of alternatives has shown that there will be no technically feasible alternative available to the applicant at the expiry of the transitional period for OPnEO. The applicant is actively working on identifying potentially suitable alternatives for their diagnostics. For example, Alternative 3 has received regulatory approval in the EU for use in some diagnostic components. Alternative 4 is also evaluated in at least one molecular diagnostic component. Furthermore, both Alternative 3 and 4 may be considered for use in other diagnostics.

However, even if a suitable alternative for all diagnostics was available, the validation and regulatory approval procedures, in combination with the large number and complexity of the affected diagnostics, would mean that it would take several years, many more than 12, to complete substitution. The applicant currently focuses on using alternative detergents in new product development, which are easier to incorporate changes to, but also plans to work on existing products as well. However, strategy on the latter does not depend only on the UK sales and any decisions must be taken having the whole EEA, if not the global operations, in mind.

The continued use of the applicant's diagnostics in the UK will result in limited releases of OPnEO to the environment. Most of the OPnEO in the applicant's diagnostics ends up in solid waste, which is sent for incineration by the downstream users. The approximately 30% of OPnEO that ends up in the liquid waste is expected to result in emissions of [redacted] (1-10) kg OP to the environment in a worst case scenario with the maximum expected OPnEO usage. This is probably an overestimation, as it does not consider alternative methods of treating liquid waste by the downstream users (e.g. incineration). CBI 2

In the NUS, the applicant will cease their UK sales of diagnostics containing OPnEO. The monetised impacts in the NUS are estimated at approximately £[redacted] (1-5) million per year and they only consider the applicant's lost net profits. This results in approximately £[redacted] (£0.5-5) million per kg of prevented OP emissions per year. CBI 3

Apart from the economic impacts for the applicant, downstream users may also face impacts from having to switch suppliers of diagnostic systems, and there may be shortages in diagnostics, resulting in delays of patient sample testing. Furthermore, competitors that could take over the applicant's UK market share may have also applied for and received an authorisation for the use of OPnEO, which means that the quantities of OPnEO that will be placed on the UK market and released to the environment will not necessarily be lower in a NUS.

Overall, the applicant is of the opinion that the lack of suitable alternatives for all diagnostics at the sunset date, largely driven by the validation and regulatory approval processes, the low expected emissions of OP and the high impacts of a refused authorisation justify a long review period of 12 years.

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CBI 1

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ANNEX I – JUSTIFICATIONS FOR CONFIDENTIALITY CLAIMS

Blanked out item reference	Justification for confidentiality
CBI 1	**Demonstration of Commercial Interest:** Substitution strategy, including potential alternative names, evaluation results and timelines is proprietary knowledge and indicative of the applicant's commercial and development strategy. **Demonstration of Potential Harm:** Dissemination of this information could reveal R&D and marketing details to competitors of the applicant and allow them to engage in aggressive commercial tactics using proprietary knowledge to gain an unfair competitive advantage. This would severely harm the commercial interests of the applicant. **Limitation to Validity of Confidentiality** This claim is valid indefinitely
CBI 2	**Demonstration of Commercial Interest:** Volumes of 4-tert-OPnEO imported and used are confidential information that are only to be used for the applicant's planning and operations. Sharing them publicly may also breach anti-trust and competition laws in the UK. This also applies to emission volumes, which can be used to back-calculate to volumes of 4-tert-OPnEO used. **Demonstration of Potential Harm:** If competitors got hold of this information, they could use it to determine the applicant's output and market share or the weight of the particular products on their overall business. Competitors could use such sensitive information to gain a competitive advantage over the applicant. Some of the redacted information could also be used to back-calculate sensitive information. **Limitation to Validity of Confidentiality:** This claim is valid indefinitely
CBI 3	**Demonstration of Commercial Interest:** Information on business commercial performance, such as manufacturing output, sales, revenue and profit margins, as well as employment, are commercially sensitive information and are only supposed to be known by the company. If they become publicly available, they will distort competition and may even be in breach of anti-trust laws in the UK and the EU. **Demonstration of Potential Harm:** If marketing (production, sales, revenue and profits) information were to be released, it will provide the applicant's competitors with proprietary

Blanked out item reference	Justification for confidentiality
	knowledge of information on the applicant's market share and would give them an unfair competitive advantage. **Limitation to Validity of Confidentiality:** This claim is valid indefinitely