ANALYSIS OF ALTERNATIVES

and

SOCIO-ECONOMIC ANALYSIS

Public version

Legal name of applicant(s):	Siemens Healthcare Diagnostics Products Ltd
Submitted by:	Siemens Healthcare Diagnostics Products Ltd
Substance:	Entry #42: 4-(1,1,3,3-tetramethylbutyl)phenol, ethoxylated, covering well-defined substances and UVCB substances, polymers and homologues (Triton™ X-100)
Use title:	Use of OPE as detergent in the production of bead components for in-vitro diagnostic kits for an immunoassay platform
Use number	1

Note

This complete version of this document includes some text and figures that are highlighted in grey. These parts of text have been blanked out in the public version of this document. Justification for confidentiality claims is provided in Section 8 of the present document.

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#D (table)

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List of acronyms and abbreviations

ADC	Americas Distribution Centre
[redacted]	#D,F (Table)
AfA	Application for Authorisation
[redacted]	[redacted]
AoA	Analysis of Alternatives
BDPE	Brominated diphenyl ether
[redacted]	[redacted]
CAI	Chemistry, Automation & Informatics
[redacted]	[redacted]
CIA	Change Impact Assessment
CMC	Critical Micelle Concentration
CRB	Change Review Board
[redacted]	[redacted]
CSR	Chemical Safety Report
[redacted]	[redacted]
DfE	Design for the Environment
DHF	Design History File
DIOH	Days Inventory on Hand
DMR	Device Master Record
DNA	Deoxyribonucleic acid
ECHA	European Chemicals Agency
EDC	European Distribution Centre
EEA	European Economic Area
ELISA	Enzyme-linked Immunosorbent Assay
EPA	Environmental Protection Agency (US)
EQS	Environmental Quality Standards
EU	European Union
FDA	Food and Drug Administration (US)
FTE	Full-Time Equivalent
GmbH	Gesellschaft mit beschränkter Haftung
GMP	Good Manufacturing Practices
HLB	Hydrophile-lipophile balance
IFU	Instruction for Use

IVD	In-Vitro Diagnostic
IVM	The Institute for Environmental Studies
LD	Laboratory diagnostics
LoB	Limit of Blank
LoD	Limit of Detection
LoQ	Limit of Quantification
MAC	Maximum allowable concentrations
NOEC	No Observable Effect Concentration
NPV	Net Present Value
NSB	Non-specific binding
OC	Operational Condition
OECD	Organisation for Economic Co-operation and Development
OEM	Original Equipment Manufacturer
OP	Octylphenol
OPE / OPnEO	Octylphenol ethoxylates
PBT/vPvB	Persistent, Bioaccumulative and Toxic Substances/very Persistent and very Bioaccumulative
[redacted]	[redacted]
PDP	Product Development Process
PEC	Predicted Environmental concentration
PHT	Product Health Team
PLM	Product Lifecycle Management
PMA	Premarket Approval
PNEC	Predicted no-effect concentration
PV	Present Value
RA	Regulatory Affairs
REACH	Registration, Evaluation, Authorisation and Restriction of Chemicals
R&D	Research and development
RMM	Risk Management Measure
RNA	Ribonucleic acid
RTM	Requirements Traceability Matrix
SBR	Sequencing Batch Reactor
SEA	Socio-economic Analysis
Siemens Llanberis	Siemens Healthcare Diagnostics Products Ltd
Siemens Marburg	Siemens Healthcare Diagnostics Products GmbH
SKU	Stock Keeping Units
STP	Sewage Treatment Plant
SVHC	Substance of Very High Concern

[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
UK	United Kingdom
US(A)	United States of America
WFD	Water Framework Directive

DECLARATION

The Applicant, Siemens Healthcare Diagnostics Products Ltd, is aware of the fact that evidence might be requested by ECHA to support information provided in this document.

Also, we request that the information blanked out in the "public version" of the Analysis of Alternatives and Socio-economic analysis is not disclosed. We hereby declare that, to the best of our knowledge as of today (07/05/2019) the information is not publicly available, and in accordance with the due measures of protection that we have implemented, a member of the public should not be able to obtain access to this information without our consent or that of the third party whose commercial interests are at stake.

Signature: FRASER HOGUE

Date, Place: Llanberis, 07/05/2019

MANAGING DIRECTOR

Signature: MARTIN GRAY

Date, Place: Llanberis, 07/05/2019.

FINANCE DIRECTOR

1 Summary

1.1 Introduction

Siemens Llanberis is part of Siemens Healthineers and is a reagent manufacturing facility based at Llanberis in North-west Wales. 4-(1,1,3,3-tetramethylbutyl)phenol, ethoxylated, (4-tert-OP) purchased by Siemens Llanberis under the trade name Triton™ X-100, is used as a processing aid at the site in the manufacture of #D in-vitro diagnostic kits (hereinafter "IVD kits") of the #D business line. The final kits do not contain Triton™ X-100 and are used on #D analysers which are used by hospitals, commercial laboratories and research centres to perform vital diagnoses of specific diseases and conditions in patient samples.

The "Applied for Use" involves the application of Triton™ X-100 as a cleaning agent (detergent) and a stabiliser in the preparation of bead components for the #D IVD kits. The kits contain reagents and beads which house the chemical and biological elements required to facilitate the biochemical reaction which is integral to the diagnostic process for each individual IVD kit.

#C, D

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1.2 Availability and suitability of alternatives

Since 2013, Siemens Healthineers implemented a policy to prevent the use of OPEs in any new product development. This requires extensive research work, reaching out to authorities and commissioning consultants, to identify alternatives which ensure that the IVD kits function effectively and deliver accurate patient results.

Siemens Healthineers is the manufacturer of #D (range: 50-500) existing products, across #D different analyser platforms, where OPEs are used and which are in the scope of REACH Authorisation; in other words, the present applied for use by Siemens Llanberis accounts for only a small part of the overall use of OPEs by Siemens Healthineers. Reformulating products to replace OPE must be done on a 'per product' basis as the technical properties of OPE, which make a diagnostic product function effectively and meet specific performance parameters, will differ between products. The only effective and compliant method of identifying an alternative is to perform feasibility testing with a number of selected substances with similar properties on a 'per product' basis to conclude which of these alternatives performs to the same repeatable standard as OPE. This must be done with the initiation of a Product Development or Design Change Project, processes strictly regulated under the EU In-Vitro Diagnostic Regulation 2017/746, as well as other global regulations. Reformulation of existing products is especially complex in the case of immunoassay reagents due to the biological elements which make product stability very difficult to achieve.

Siemens Healthineers has conducted a full analysis of the impacted product portfolio and launched a 'REACH Response Plan'. The estimated cost of reformulation is #E (range: €10-100 million). As part of this plan, certain priorities have been set for allocating resources to the reformulation task that Siemens Healthineers is facing:

- Priority is given to products that have a long lifetime ahead of them, both in terms of future profitability (and return on investment) and length of time over which potential releases of 4-tert-OP may occur; and

- Priority is given to products that contain the largest volumes of OPEs and may result in the largest theoretical releases of 4-tert-OP (i.e. wash solution products).

As a result, #D, Siemens Healthineers will not be looking into reformulating the OPE-dependent #D IVD kits in order to best allocate its R&D and other relevant resources to ensure that the most efficient route to minimising releases of 4-tert-OP is taken.

1.3 Socio-economic benefits from continued use

The continued use of Triton™ X-100 over the period 2021-2029 will confer significant socio-economic benefits within and outside Siemens Llanberis' supply chain. These can be summarised as follows:

- Siemens Llanberis will be allowed to continue the manufacture of the #D affected #D IVD kits and would avoid potential indirect adverse impacts on the sales of numerous OPE-independent IVD kits that are used on the same #D analysers;

- Siemens Marburg (a sister company to Siemens Llanberis based in Germany) would avoid disruption to its manufacture and sale of OPE-containing #D #D, the use of which must accompany the use of every single #D IVD kit;

- Siemens Healthineers would be unhindered in their continued sales of new #D analysers within and outside the EEA by virtue of the continued availability of the full range of #D IVD kits that are manufactured by Siemens Llanberis;

- Suppliers to all Siemens Healthineers operations identified above will continue to generate profits from associated sales of raw materials and services;

- Users of #D analysers will continue to have access to the full range of #D IVD kits and will thus avoid (a) operating costs increase from outsourcing of diagnostic testing, (b) the cost of validation of third-party analysers/kits and (c) the cost of premature replacement of their #D analysers. The cost of replacing a platform is approximately €#E per unit and many hospitals and laboratories run multiple analysers;

- A minimum of #D (range: 25-75) jobs in north-west Wales would be preserved, although in the case of non-Authorisation all jobs at the site might be at risk; and

- Critically, healthcare providers and patients in the EEA (but also outside the EEA) will continue to have access to the #D affected immunoassays. These IVD kits can detect severe abnormalities that affect pregnancies, can support the early diagnosis of certain cancers and other untreatable conditions (e.g. #D). The number of tests used in the EEA is significant, in the range of tens of millions per year (as of 2017). Patients who cannot undergo vital tests within the required timeframe will be significantly adversely affected; this is one of the reasons the IVD industry is so strictly regulated, to ensure healthcare providers can rely on the performance and supply of products, including the delivery of timely results.

The proportion of socio-economic benefits from continued use that can be monetised amounts to a € #C,H, E (range: €10-100 million) over the requested review period (Present Value, 4% discount).

1.4 Residual risk to the environment of continued use

26.5% of total OPE used by Siemens Llanberis is assumed to be emitted to the aquatic environment as 4-tert-OP via a municipal Sewage Treatment Plant (STP) in Liverpool (north-east England) after prior treatment at an industrial STP. No other environmental discharges occur (sludge from the municipal STP is assumed not to be spread to land). Based on a declining annual usage of Triton™ X-100 in the 10-100 kg/y range (#H,G kg for #C, a significant decrease from 2018), and under the current set of Risk Management Measures (RMMs) over the requested review period, the releases of 4-tert-OP to the aquatic environment account for a total of ca. #H,G (range: 10-50) kg. However, as will be discussed later in this document (see also Section 1.6 below), Siemens Llanberis is now committed to implement additional RMMs before the Sunset Date which will reduce releases of Triton™ X-100 by over 99%. As such, under the RMMs that will be in place by the Sunset Date, the overall releases of 4-tert-OP to the aquatic environment account over the requested review period will drastically decline to a maximum total of ca. #H,G (range: 0.1-1) kg.

The calculated worst-case local and regional PECs are significantly below the latest research values, the releases are not occurring every day since bead production occurs in batches and the assumptions made in the CSR are generally conservative. Therefore, average concentrations are expected to be lower than those indicated in the local assessment. If a half-life of eight days is assumed, then the maximum total 4-tert-OP in the environment resulting from bead manufacture is ca. #G kg. If the upper end half-life of 54 days is assumed, then 4-tert-OP stock levels peak at around #Gkg prior to declining over time due to decreased usage.

1.5 Comparison of socio-economic benefits and residual risks

The ratio of the total cost of non-Authorisation (i.e. the benefit of continued use) and the total emission of 4-tert-OP to the environment is **€ #E,G (range: €100-500 million) per kg of 4-tert-OP released**. A more conservative (but arguably unrepresentative) calculation can be performed if the total benefit (cost of non-use) is annualised and the highest annual release of 4-tert-OP (for the year #C) is considered. The ratio remains substantially high at **€ #E (€10-100 million) per kg of 4-tert-OP released**. These benefit:cost ratios are certainly underestimated for a number of reasons:

- The assumptions made in the CSR are likely to be overly conservative;
- The emission reduction that is likely to be achieved through the implementation of additional RMMs (segregation and incineration of wastewater) would probably well exceed 99%;
- The important health benefits to the patients from the continued availability of the impacted assays has not been possible to express in monetary terms; and
- Whilst benefits have been discounted, physical amounts of 4-tert-OP released over time have not been discounted.

1.6 Factors to be considered when defining the operating conditions, risk management measures, and/or monitoring arrangements

Siemens Llanberis has investigated the possibility of introducing additional RMMs towards the further minimisation of releases of 4-tert-OP to the environment. Although the use of Triton™ X-100 is planned to be discontinued in the foreseeable future, Siemens Llanberis is committed to take all action necessary to reduce the environmental impact of its use of Triton™ X-100 as much as possible. As described in Appendix 3 (Section 11), Siemens Llanberis has considered the practicality and cost of implementing a range of different RMMs and has concluded that the most appropriate additional RMM will be the implementation of a segregation system to collect fraction of wastewater from OPE-containing buffers, classify those as hazardous waste (despite the required Waste Framework Directive thresholds not being met) and send these for incineration. The implementation of this will be concluded before the Sunset Date and is anticipated to reduce emissions of Triton™ X-100/4-tert-OP by a factor of >99%.

1.7 Factors to be considered when assessing the duration of a review period

Siemens Llanberis's AfA meets the requirements set out by the ECHA Committees for Authorisation review periods longer than normal (7 years), as follows:

- An Authorisation of appropriate length is fundamental for the continued operation of the Llanberis facility. Siemens Llanberis plans [redacted] #C,D (bullet point) [redacted] business line and would make [redacted]. This could potentially leave customers unable to operate their [redacted] analysers with the full functionality and thus cause the premature replacement of these analysers with the associated wastage and future expenditure brought forward;

- Given the projected #C,D (bullet point) [redacted], reformulation of the impacted IVD kits is not planned. In any case, reformulation would take several years; there are about 80 countries with registration requirements, with varying submission requirements and approximately #C country re-registrations would be envisaged. The entire re-registration process can be expected to take 5-12 years, with 8 years being a typical duration. In addition to the cost of R&D and re-registration, implementation of an alternative substance (or combination thereof) would mean that the [redacted] affected [redacted] IVD kits would be removed from the market for several years. Siemens Llanberis' inability to supply the affected kits over a long period of time would in practice mean that this part of [redacted] IVD kit market would be irrevocably lost; and

- The continued and declining use of Triton™ X-100 is envisaged to result in modest and declining releases of 4-tert-OP to the environment; in total #G kg are estimated to be released to the Mersey estuary in the period 2021-2029. Use of Triton™ X-100 will not continue for an indefinite time period; instead releases of 4-tert-OP are predicted to cease at the end of 2029. The socio-economic benefits of this well-defined, time-limited use of Triton™ X-100 are significant resulting in a ratio of at least € #E,G **(range: €10-100 million) per kg**

of 4-tert-OP released – this figure does not encompass the important benefits to EEA patients' health which have not been possible to express in monetary terms.

Finally, the business links between the different Siemens Healthineers units should be recognised. A less than applied for outcome for Siemens Llanberis' AfA would result in a reduction to the consumption of #D IVD kits and a concomitant reduction in the demand for the #D #D that is manufactured in Marburg.

2 Aims and scope of the analysis

2.1 Aims of the combined AoA-SEA document

OPEs were identified as SVHC according to Article 57(f) of REACH as an endocrine disruptor and listed on Annex XIV (entry no. 42). This entry covers a range of individual substances. They are distinguished by the length of the ethoxylate chain that is bound to 4-(1,1,3,3-tetramethylbutyl)phenol(octylphenol) (4-tert-octylephenol = 4-tert-OP).

The OPE under discussion in this specific case is a polymeric substance with an average of 9.5 ethylene oxide units (9 or 10) and is sold under the trade name Triton™ X-100 (4-(1,1,3,3-Tetramethylbutyl)phenylpolyethylene glycol, CAS No. 9002-93-1).

4-(1,1,3,3-tetramethylbutyl)phenol, ethoxylated is on the Annex XIV Authorisation List with a Sunset Date of 4 January 2021. This means that use of the substance in the European Economic Area (EEA) after that date requires an Authorisation unless said use is exempt from Authorisation. The Latest Application Date for substances falling under entry 4-(1,1,3,3-tetramethylbutyl)phenol, ethoxylated is 4 July 2019.

This Application for Authorisation (AfA) concerns Siemens Healthcare Diagnostics Products Ltd (hereafter referred to as Siemens Llanberis) which is using Triton™ X-100 at one site in Llanberis, North-west Wales, UK. Siemens Llanberis is part of Siemens Healthineers, a medical technology company headquartered in Germany with operations across the globe. Triton™ X-100 is used in the UK in a washing and coating process to produce #B carrier materials for #C (range: 10-100) IVD kits which are used exclusively on one of Siemens Healthineers' IVD analyser platforms, called #D analysers. The OPE is used as a processing aid and is not present in the final product distributed to customers. These IVD kits test for several disease states and conditions, for example, infectious diseases, thyroid disease and infertility.

Siemens Llanberis needs to be able to continue to use Triton™ X-100 beyond the Sunset Date. This combined AoA and SEA document discusses and demonstrates the following:

- The R&D that Siemens Healthineers have been undertaking to identify feasible and suitable alternatives for Triton™ X-100;

- The technical and economic feasibility, availability and health and safety challenges in identifying an acceptable alternative reagent or technology which would provide equivalent functionality and reliability as the affected IVD kits and therefore would be approved by the relevant medical device safety authorities across the globe. #D analysers rely on the continued supply of IVD kits which contain the carrier materials manufactured at the Llanberis production facility. It would not be possible for healthcare customers who currently own #D analysers to continue using these instruments and perform the dedicated diagnostic tests undertaken on these instruments if the OPE-dependent IVD kits could no longer be supplied. This AfA is therefore submitted to enable the continued supply of IVD kits

which rely on the use of OPE as a processing aid in the production process, [redacted] #D [redacted][1];

- The socio-economic impacts that would arise for Siemens Llanberis, its upstream supply chain, its customers, patients and the healthcare systems in the EEA and elsewhere, if the applicant is not granted an Authorisation for the continued use of Triton™ X-100 with an appropriately long review period; and

- The projected emissions of OPE to the environment over the requested review period, and corresponding risks, are very low, and the costs of not granting an Authorisation are disproportionally high.

It should be noted that this AfA is part of a set of Applications that have been prepared by Siemens Healthineers for a range of different uses of OPEs by two Siemens Healthineers legal entities[2] (see **Figure 2–1**).

2.2 Summary of Siemens substitution strategy

The search for and research into alternatives for their uses of OPE takes place centrally at Siemens Healthineers, for all legal entities, and is undertaken by the parent company. Section 4.1.1. details Siemens Healthineers' efforts towards the identification of a feasible alternative for Triton™ X-100 over the last 5 years. Specifically relevant to this AfA, Section 4.1.1 explains the complexity of identifying and implementing a technically feasible alternative in a way that [redacted] #D [redacted] maintains the viability of the #D analyser range in terms of continuation of supply of IVD kits to customers who operate the impacted analysers. Siemens Llanberis demonstrates in this AfA that the "Applied for Use" Scenario will be to allow the #D [redacted], leading to a concomitant reduction in and, ultimately, the cessation of the use of Triton™ X-100 in Llanberis. Importantly, the Triton™ X-100 used as a processing aid at Siemens Llanberis is not found in IVD kits used by customers who operate #D analysers.

[1] #D [redacted].

[2] The other is Siemens Healthcare Diagnostics Products GmbH, Marburg, Germany.

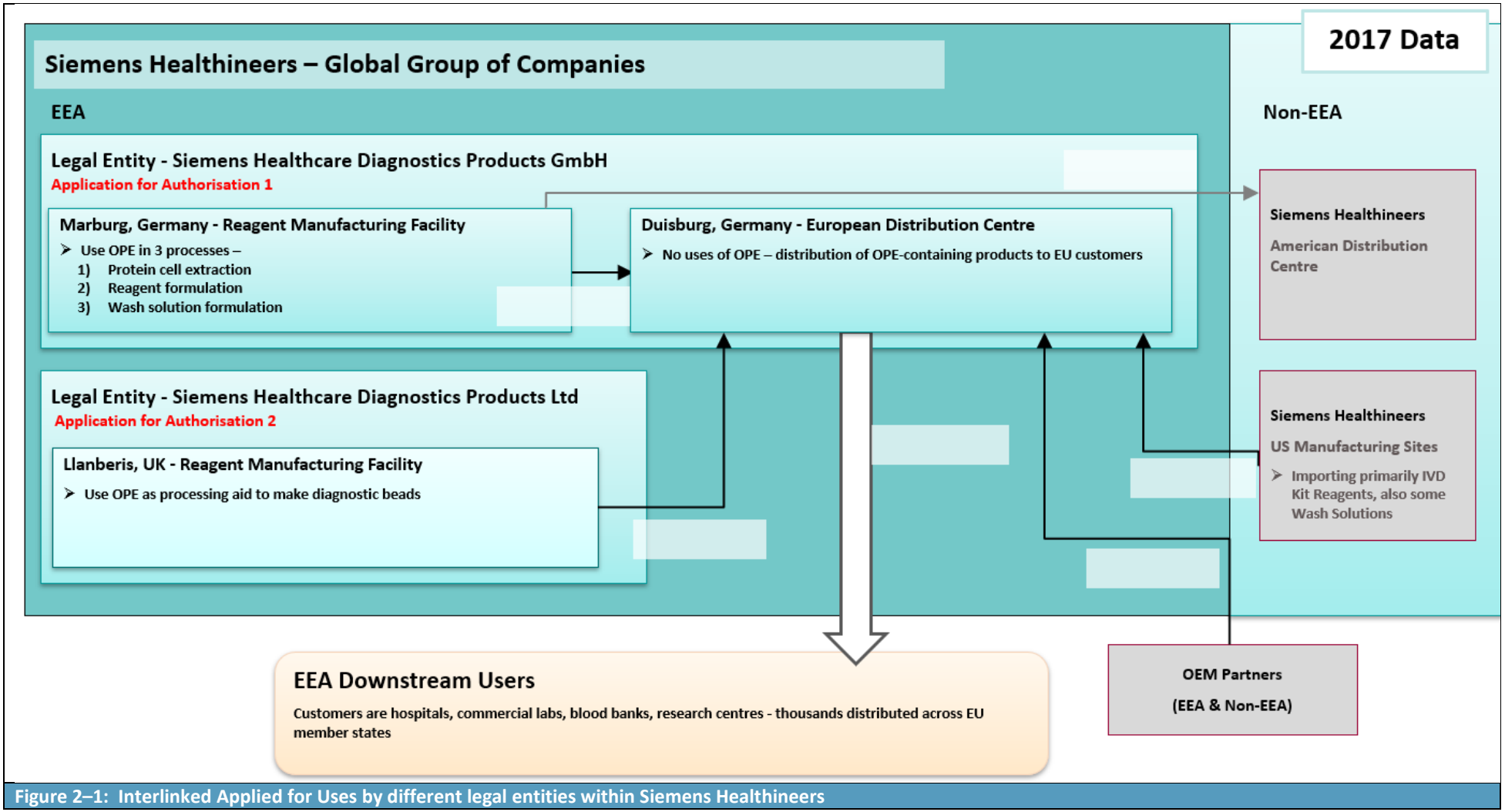

Figure 2–1: Interlinked Applied for Uses by different legal entities within Siemens Healthineers

2.3 Scope of the analysis

2.3.1 Temporal scope

The temporal boundaries of the analysis need to consider:

- When impacts would be triggered;
- When impacts would be realised; and
- For how long the continued use of Triton™ X-100 would be required by Siemens Llanberis as a minimum.

The impact assessment periods used in this analysis and the key years are presented in **Table 2–1**.

Table 2–1: Temporal boundaries of impact assessment			
Present value year			2017
Start of discounting year			2018
Impact baseline year			2021
Scenario	**Impact type**	**Impact temporal boundary**	**Notes**
"Applied for Use"	Adverse impacts on the aquatic environment	9 years	Based on the length of requested review period
"Non-use"	Loss of profit along the supply chain	9 years	Based on the length of requested review period
	Increased diagnostic costs for healthcare providers	Several months	
	Disruption to treatment of EEA patients due to loss of range of IVD kits made in Llanberis	Up to 9 years	Based on the length of requested review period
	Loss of employment	1.2 years	Average period of unemployment in the UK (Dubourg, 2016)

2.3.2 Geographic scope

Manufacturing location and distribution of relevant IVD kits

Siemens Llanberis' manufacturing facility is in Llanberis in North-west Wales, UK. This is the location where Triton™ X-100 is used. The IVD kits that are manufactured with Triton™ X-100 as a processing aid are then forwarded to Siemens Healthineers European Distribution Centre (EDC) in Duisburg, Germany. Through the EDC, the vast majority of relevant IVD kits are forwarded to the different customers (users of Siemens Healthineers analysers).

For the distribution of a small proportion of the UK-made relevant IVD kits outside Europe, the kits are sent to the American Distribution Centre, as will be discussed below.

It should be noted that there are also parts of the Siemens Llanberis operations that do not involve OPEs, e.g. manufacturing of OPE-free parts of the #D immunoassay IVD kit portfolio, as well as all the peripheral support services at a manufacturing site, e.g. warehousing, maintenance, waste management etc. These activities are closely linked to Siemens Llanberis' core operation and will suffer the same negative consequences as the OPE-dependent operations under the "Non-use" Scenario, which means that they are part of the scope of this AoA-SEA.

Finally, the analysers of relevance to this AfA also use an OPE-containing #D (a wash solution) which is manufactured in another Siemens Healthineers facility in Marburg, Germany (Siemens Healthcare Diagnostics Products GmbH, hereafter referred to as Siemens Marburg). This #D is used on all #D analysers for all tests and thus absolutely depend on the continued availability of this #D.

Given the uncertainties over the future relationship between the UK and the EU-27 at the time of writing this document (May 2019), the default position taken is that the UK is included in the list of countries which constitute the EEA.

Impacted analysers and their locations of use

Triton™ X-100 is used for the production of key components, specifically #B beads, for the #D IVD platform of #B (see **Figure 2–2**). It is essential to note that Triton™ X-100 is used in the production of the beads, but is not present on/in the beads themselves.

The #D analysers perform diagnostic tests called immunoassays in a high number of facilities in the global healthcare system, including hospitals, clinics, commercial laboratories and other health care system laboratories and research centres. Where used in the manufacture of state-of-the-art #D medical devices, Triton™ X-100 plays a critical role in enabling assays to achieve essential performance characteristics.

Figure 2–2: #D analysers #D

The focus of this analysis is primarily on the European Economic Area (EEA). In reality however, the scope of some of the impacts are global. This is because Siemens Llanberis is #D producing these IVD kits, which are distributed to analyser operators throughout the globe. The users of the #D products produced at Siemens Llanberis are located both within and outside the EEA. In terms of the number of relevant analysers in use in 2017, the majority was located outside the EEA as shown in **Table 2–2**.

Table 2–2: Number of #C, D (Table) analysers operated in different regions in 2017	
Global region	**Total number of analysers**
EEA (incl. the UK)	[redacted] (range: 1,000-10,000)
Non-EEA	[redacted] (range: 1,000-10,000)
Grand total	[redacted] (range: 1,000-10,000)

Locations of relevant suppliers to Siemens Llanberis

Siemens Llanberis has #D (range: 10-100) suppliers of relevance to the OPE-dependent activities (supply of OPE, articles and materials), of which #D (range: 1-10) are located within the EEA.

Relevant operations of Siemens Healthineers outside the EEA

Siemens Healthineers has four operational sites outside the EEA that are interlinked with the OPE-relevant operations in Llanberis and which could therefore also be impacted in the event of no authorisation being granted:

1. *Siemens Healthineers, Los Angeles, USA* – Manufacturing centre for rare reagents and critical raw materials (biological) that are supplied to the Llanberis site.

2. *Siemens Healthineers Flanders, New Jersey, USA* – Laboratory Diagnostics (LD) Systems and IT R&D site with systems manufacturing, distribution and support functions. This is the #D platform manufacturing facility and all the #D analysers are manufactured and distributed from this site.

3. *Siemens Healthineers Glasgow, Delaware, USA* – Large-scale reagent manufacturing site. They manufacture a substrate material which is supplied to the Llanberis site as well as to all Siemens' #D customers, worldwide – the substrate is required to run every #D assay.

4. *Siemens Healthineers Americas Distribution Centre (ADC)* - While most of the Siemens Llanberis #D products are distributed via the European Distribution Centre (EDC), some are also distributed via the ADC. The EDC and ADC are the two main distribution centres for all of Siemens Healthineers.

All these sites will be affected under the "Non-use" Scenario, which may, in turn, indirectly induce socio-economic impacts in the EEA. However, this SEA does not consider potential impacts to these non-EU operational sites.

3 "Applied for Use" Scenario

3.1 Analysis of substance function

3.1.1 The substance

The OPE that is of relevance to the analysis presented in this AoA-SEA document is shown in **Table 3–1**.

Table 3–1: OPE substance of relevance to this AfA				
#	Common trade name	Chemical name	Degree of ethoxylation (EO units)	CAS No.
1	Triton™ X-100	Poly(oxy-1,2-ethanediyl), α-[4-(1,1,3,3-tetramethylbutyl)phenyl]-ω-hydroxy-	9.5 (9 or 10)	9002-93-1

3.1.2 Introduction to IVD kit reagents and IVD wash solutions

IVD kits

In-Vitro Diagnostic (IVD) kits are core to modern medicine, performing qualitative and quantitative tests to diagnose a broad range of diseases and health conditions. They are also used to detect genetic mutations or the presence of certain chemicals in patient samples. IVD kits are the basis or part of about 70 % of all medical diagnoses performed worldwide.

Within Siemens Healthineers' portfolio, IVD kits #D are used in the following diagnostic fields:

- Immunoassay;
- Clinical Chemistry;
- Haemostasis (blood coagulation);
- Plasma Protein Analytics;
- Drug-Testing;
- Urinalysis;
- Cardiac; and
- Molecular Genotyping (detection of nucleic acids (DNA/RNA from viral and bacterial sources) in blood and other bodily fluids).

In the specific case of this AfA, Siemens Llanberis uses OPE as a processing aid in the manufacture of beads which are essential to the IVD kits for a specific immunoassay platform, #D. The platform also uses an OPE-containing #D which is manufactured by Siemens Marburg (the use of OPE in the manufacture of this #D is covered in a separate AfA).

The typical contents of an IVD kit differ between the various diagnostic fields, technologies and/or platforms within which they are used. They typically are comprised of several components.

An **Immunoassay** IVD kit will generally include an IVD reagent, an IVD solid phase (sometimes held in suspension in the reagent solution itself), an IVD calibrator, control and/or diluent.

Figure 3–1 provides an overview of the typical contents of an immunoassay IVD kit.

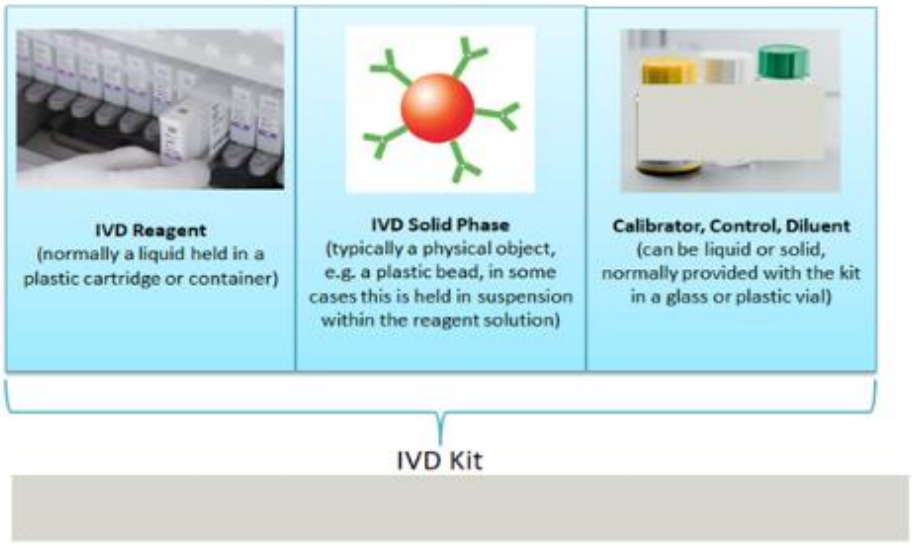

Figure 3–1: IVD kit overview

IVD kit reagent and IVD kit solid phase

The combined function of an IVD kit reagent and solid phase is to perform a chemical or biological reaction in patient samples (e.g. blood, urine) that detect, identify and/or quantify highly specific molecules, and ultimately ensure an accurate diagnosis of diseases and health conditions.

In REACH terminology, an IVD kit reagent is a formulated mixture that contains several chemicals that enable a certain function when used in an assay. Similarly, an IVD solid phase is typically a physical object, such as a plastic bead, on which are coated several chemicals that enable a certain function when used in an assay.

Key facts on IVD kit reagents:

- They are typically supplied in low volumes (in reagents manufactured by Siemens Healthineers volumes are typically <150 ml);
- Those which contain OPE typically have low concentrations (in reagents manufactured by Siemens Healthineers the average is ca. #B % (range: 0.1-1%); in formulations used in Llanberis, OPE concentration in the formulations used for washing #B beads is typically #B % with only two IVD kits requiring OPE formulations with a concentration of up to #B %. The Siemens Llanberis IVD kits do not contain OPE as sold on the market);
- An IVD kit may contain just one reagent or several; the number is normally dependent on the number of steps needed to achieve the biochemical reaction. If an IVD kit contains OPE, in some cases it will be present in only one of the reagents in that kit, in other cases it could be in multiple reagents contained within that kit;
- In a case where there are several reagents in one IVD kit, their interaction is key to the diagnostic test, one cannot function without the other;
- Some IVD kit reagents have a function in the preparation of the sample for the measurement; others play a role in the measurement itself; and

- Individual IVD kit reagents can either be bought as an IVD kit that contains all reagents needed or can be bought individually, for example, if a single reagent within a kit needs to be replenished.

Every IVD kit has a certain number of assays, i.e. tests for the specific disease or condition, that can be performed using one kit. For example, the #D kit offers up to 600 assays/tests within one kit.

Each IVD kit and the included reagents are specific for one particular parameter (e.g. the concentration of a biological molecule in a body fluid). The biological molecules that are detected can be an indicator for pathogenic changes in the patient. In some cases, these molecules are induced by a pathogen, e.g. antibodies that are produced as a reaction to a virus infection. In other cases, the molecules are always present in the organism (e.g. triglycerides, cholesterol), but if their level is increased or decreased or the ratio between two molecules changes, this is an indicator for a certain disease pattern. Such molecules are therefore also called the "target molecules" of an IVD kit. An IVD kit does not measure the molecules in a direct way, but it facilitates a reaction with another biological molecule, e.g. a receptor protein for such a target molecule. The target molecule and the receptor are highly specific to each other and follow a lock and key principle. Because of this basic principle, an IVD kit must fulfil the following functions:

- **A target molecule must be assessable for the test**: to ensure this, it must be stabilised once the body fluid has been removed from the patient. Often this is done by cooling the sample but sometimes it is also supplemented with an IVD kit reagent that stabilises molecules (e.g. protects them from enzymatic degradation), avoids unspecific binding with other dissolved structures (e.g. cell walls) or ensures the target molecule is present in the sample in a dissolved state (e.g. if it is normally inside a cell); and

- **The IVD kit is highly specific and sensitive to the target molecule**: the complete system must be optimised to detect the target molecule, only. It may also not be influenced by other molecules that can be present throughout the test (either originating from the test sample or the IVD kit components).

To summarise, the biological, and therefore highly variable, nature of these parameters from one patient sample to another, requires the development of highly specific, adaptable and sensitive test reagents and optimised test protocols. Validity and reproducibility are ensured by the extensive testing, verification and registration process applicable for in-vitro diagnostic products under the EU In-Vitro Diagnostic Regulation 2017/746 and similar regulations worldwide that entails the IVD kit design combined with the design of the relevant IVD analyser system.

IVD wash solutions

IVD wash solutions are not normally provided as part of an IVD kit, but as a separate product. Each wash solution design is specific to the IVD analyser system it is used on. IVD wash solutions are used on IVD analyser systems to clean and flush the internal parts which have come into contact with the IVD kit reagents and/or patient sample as part of the liquid-handling operation to avoid interference with subsequent tests.

How immunoassay IVD kits work

Immunoassays are analytical tests which measure the concentration or presence of an analyte through the exploitation of a highly specific antibody-antigen interaction. As the exact mechanism of

operation for immunoassays varies for different products, the commonly used 'sandwich' ELISA[3] method will be briefly discussed to illustrate the technology.

In a 'sandwich' assay/test there are two phases: a solid phase and a liquid phase. The solid phase acts as the foundation for the assay, providing a solid platform for the immobilisation of the target analyte found in a patient sample. For #D, the solid phase consists of a dry #B bead, typically coated with a specific antibody (the 'capture antibody'), which - when immersed in a patient sample (e.g. blood or urine) - captures the analyte in the sample via physicochemical binding. As discussed above, the liquid phase is known as the reagent and contains the detection system. A detection system serves to measure the binding of the analyte to the solid phase either quantitatively or qualitatively. For #D, this is typically achieved via a labelled antibody (the 'detection antibody') which, when it comes into contact with the bead-'capture antibody'-analyte complex, binds to the analyte forming a sandwich-like structure, as depicted in **Figure 3–2**. The labelled antibody initiates a chemiluminescent reaction resulting in the emission of light, the magnitude of which is measured by the #D instruments and is directly related to the presence of the target analyte.

3.1.3 Role of OPE in the production of #D IVD kits

Description of the use of Triton™ X-100

The "Applied for Use" involves the application of Triton™ X-100 as a cleaning agent (detergent) and a stabiliser in the preparation of bead components for #C (range: 10-100) #D IVD kits. In the case of IVD kits for the #D analyser range, the bead is composed of #B in diameter (see **Figure 3–3**).

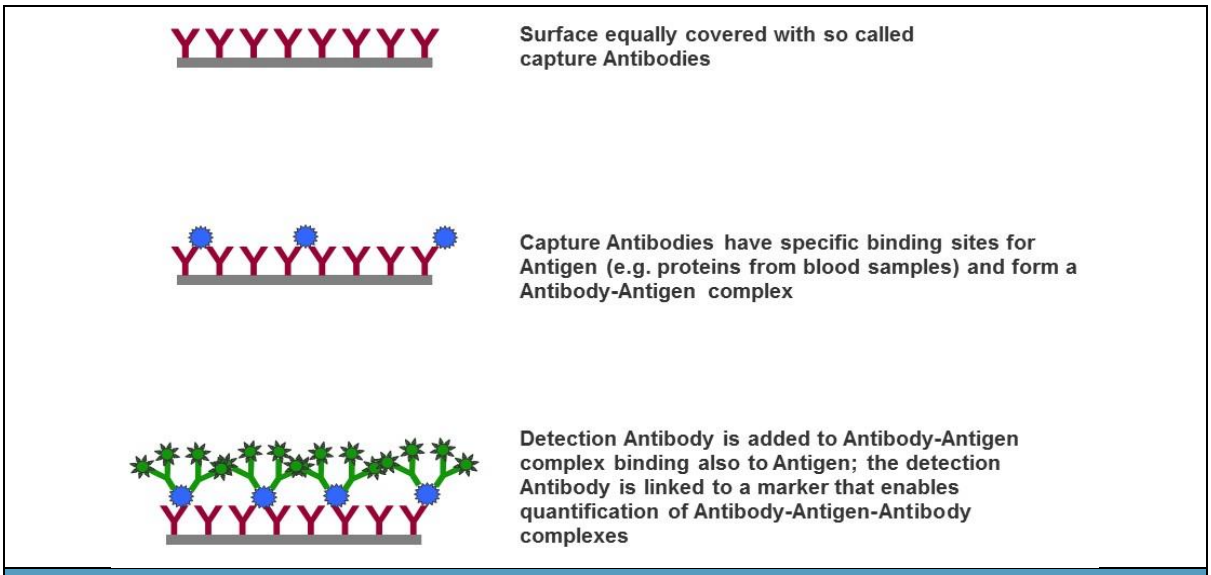

Figure 3–2: Basic principle of a sandwich ELISA

[3] Enzyme-linked Immunosorbent Assay.

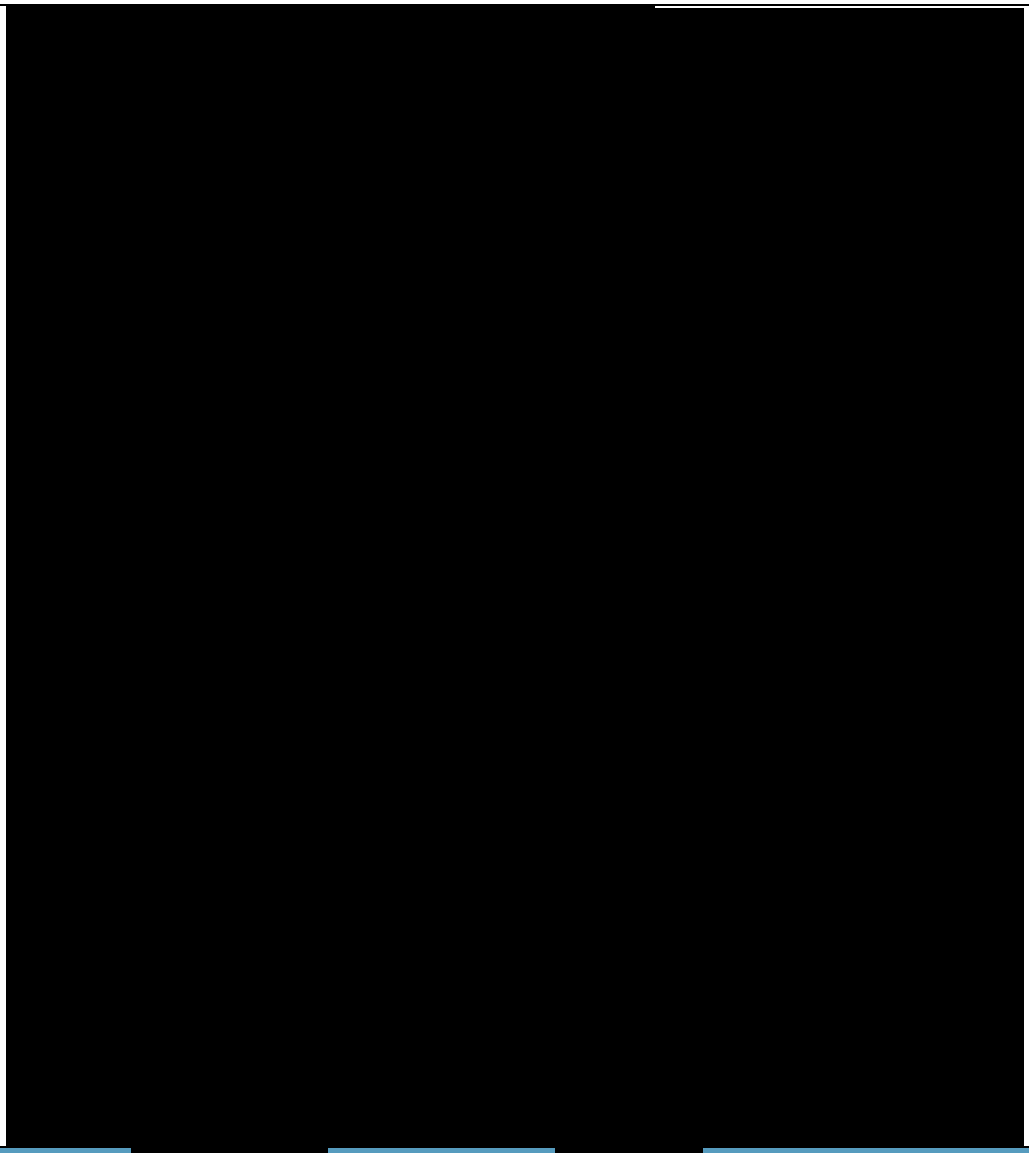

Figure 3–3: Bead, #D bead container and #D IVD kit

The actual measurement of the analyte is performed at the customers' sites (and falls within the scope of a separate AfA being submitted by Siemens Marburg). The production process and the role of Triton™ X-100 is described in further detail below. The described process applies to a range of specific IVD kits. Differences among the products arise from the different antibodies that are linked to the surface of the beads and these antibodies impart unique biological and physicochemical characteristics to the kits. As such, each IVD kit performs a different function and has different performance characteristics. The reason for this stems from molecular interactions between the chemicals and the proteins involved, where the exact mechanisms may not be fully characterised. Each product is therefore produced by following a unique and product-specific protocol. Nevertheless, the main steps are comparable.

Figure 3–4 presents the full range of assays on #D analysers. There are #C,D (range: 75-100) unique #D assays and #C,D (range: 75-100) unique #D assays.

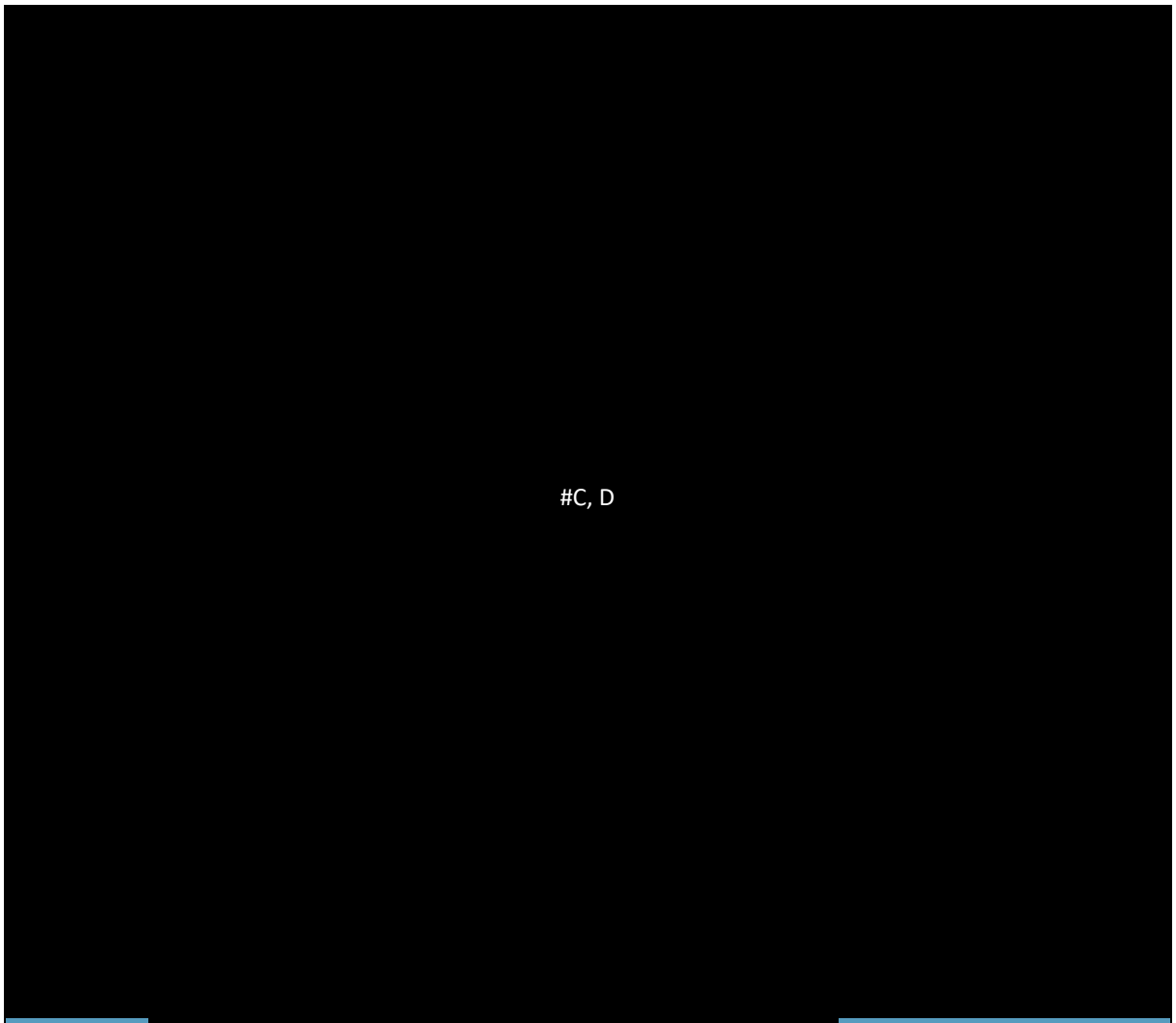

Figure 3–4: #C, D

OPE is used in the production of #B,D (range: 10-100) analyte bead components, which are bespoke to specific target analytes, as summarised in **Table 3–2**. In total, these #B,D analyte bead components are sold as part of #C,D (range: 10-100) individual IVD kit products that cover their use on the #D and #D analyser systems. There are two key parts to producing beads:

1. Bead washing: removes impurities from the surface – #B,D beads use OPE in these washes; and
2. Bead coating: where the critical raw material specific to each product/assay is coated onto the bead surface - #B,D beads use OPE in this coating process.

Table 3–2: analyte beads where OPE is used in the manufacture of bead components which are part of IVD kits

#	analyte bead name	Number of related IVD kits sold	Intended use
C, D (table)			

Table 3–2: [redacted] analyte beads where OPE is used in the manufacture of bead components which are part of [redacted] IVD kits			
#	[redacted] analyte bead name	Number of related IVD kits sold	Intended use
[redacted]			

Source: Siemens Llanberis

The manufacture of #D IVD beads in Llanberis is undertaken in batch mode and through three consecutive steps, as shown in **Figure 3–5** (NB. as explained later in this AoA-SEA document, Siemens Llanberis will be implementing additional Risk Management Measures before the Sunset Date which will allow the vast majority of OPE-containing wastewater to be segregated and incinerated).

Buffer formulation: buffer solutions are prepared for use in either bead washing or bead coating; all buffer solutions containing Triton™ X-100 that are required for bead washing and coating are prepared at this step. In most cases, Triton™ X-100 is present in the buffer solution at concentrations of no more than #C % (range: 0.1-1%).

2. **Bead washing and coating**: this takes place in a closed system referred to as the 'Bead Coating Chamber' where beads are washed and coated in the pre-prepared buffer solutions prepared in Step 1.
   - *Washing of beads*: OPE is used for bead washing during the manufacture of the first #C IVD analyte beads presented in **Table 3–2**. The surfactant action of OPE is exploited to remove impurities from the bead surface, predominantly #B, in preparation for subsequent bead coating steps where analyte-specific antibodies or antigens bind to the clean bead surfaces.

     The beads for the first #C IVD analytes listed in **Table 3–2** are first prepared by producing a #B bead known as a 'Triton Bead'. The Triton Beads are beads which have been washed in a #B% Triton™ X-100 buffer solution. Once the Triton Bead has been prepared, at a next step in the process it is turned into a specific analyte bead via the bead coating of critical raw materials specific to the products (e.g. binding of the Capture Antibody).

     The manufacture of #D products (IVD analyte bead #D in **Table 3–2**) has the Triton Bead wash step as part of its production process albeit at a reduced concentration of #B%, with subsequent coating steps being free of OPE use. In essence, the #D bead has the same production process as the aforementioned #C IVD analyte beads, the only difference being is that Triton Beads are prepared and coated in a single process, rather than in two distinct steps.

   - *Coating of beads:* the coating cycle acts to bind critical raw materials onto bead surfaces. In the context of #D beads, a critical raw material is defined as a chemical or biomolecule which forms a part of the analyte-capture system of the immunoassay (i.e. the process of binding the analyte of interest found in the patient sample to the bead surface in order to facilitate detection). For the #D products (IVD analyte bead # #C in **Table 3–2**) and the #D products (IVD analyte bead ##D in **Table 3–2**), OPE is used to facilitate the coating of a critical raw material onto the bead but is not present in the final products.

     For #D products (IVD analyte bead ##D),the critical raw material in question is #B. The #B is responsible for capturing #B,D in patient samples onto the bead so that the dose of #D can be measured by the #DX analyser (see #D for further information). In order to coat the #D onto the bead, three coating solutions containing #B % OPE are prepared in Step 1. The surfactant action of Triton™ X-100 is again exploited to stabilise the #D in the buffer medium, in order to minimise or reduce natural aggregation and disintegration processes.

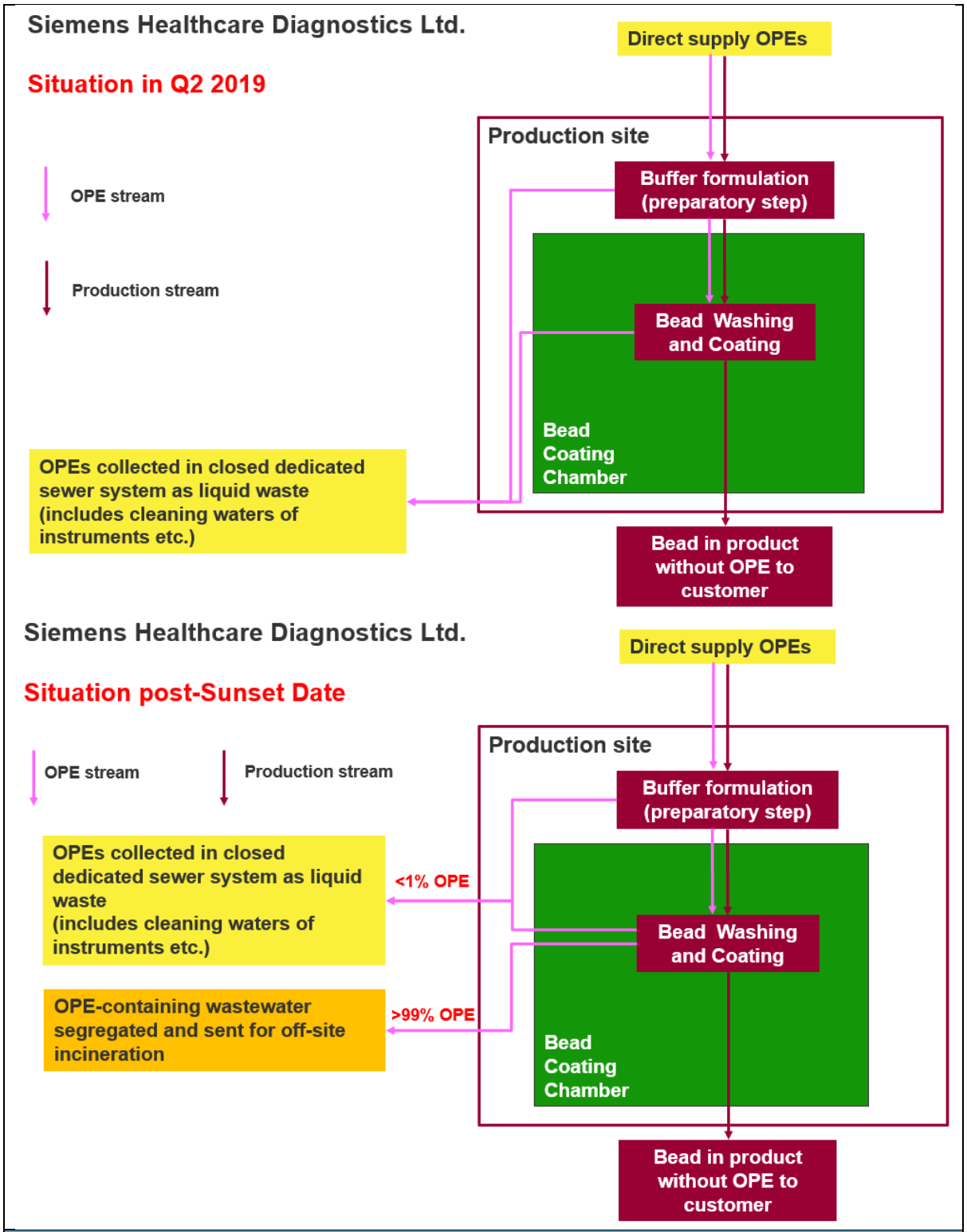

Figure 3–5: Schematic description of the use of Triton™ X-100 at Siemens Llanberis for the coating of IVD kit beads (current and post-Sunset Date)

For [redacted] products (IVD analyte bead # [redacted]), the critical raw material in question is [redacted]. The mechanism by which the [redacted] immunoassay operates relies upon the presence of this material on the bead to quantify the amount of [redacted] in serum or heparinised plasma samples. In order to coat the [redacted] onto the bead, a coating solution containing [redacted]% OPE is prepared

in Step 1. The function of the OPE in this situation is analogous to that described for the #D products, that is to stabilise the critical raw material in an aqueous environment.

Once the bead washing and coating cycles are complete, the OPE buffer solution is drained from the Bead Coating Chamber together with all other chemicals applied and collected in a dedicated closed drainage system as liquid waste.

3. **Bead drying**: to complete the process the beads undergo drying to produce dry analyte-specific beads which are inserted into the final IVD Kit. OPE is not present during this step and the dry beads produced are also OPE-free. It is important to emphasise that although OPE is absent in the final product, the use of OPE during production of the beads is nevertheless critical to the performance of the immunoassays.

Although the OPE used in the manufacture of the beads is not incorporated in the finalised dried bead component it is still a critical raw material used in the formulation of buffers used in the bead washing and coating steps. Any change to buffer formulations used in the production of #D beads would represent a change to product design, and thus any change to that design would require the initiation of a Design Change Project. This process is described further in Section 4.1.1.

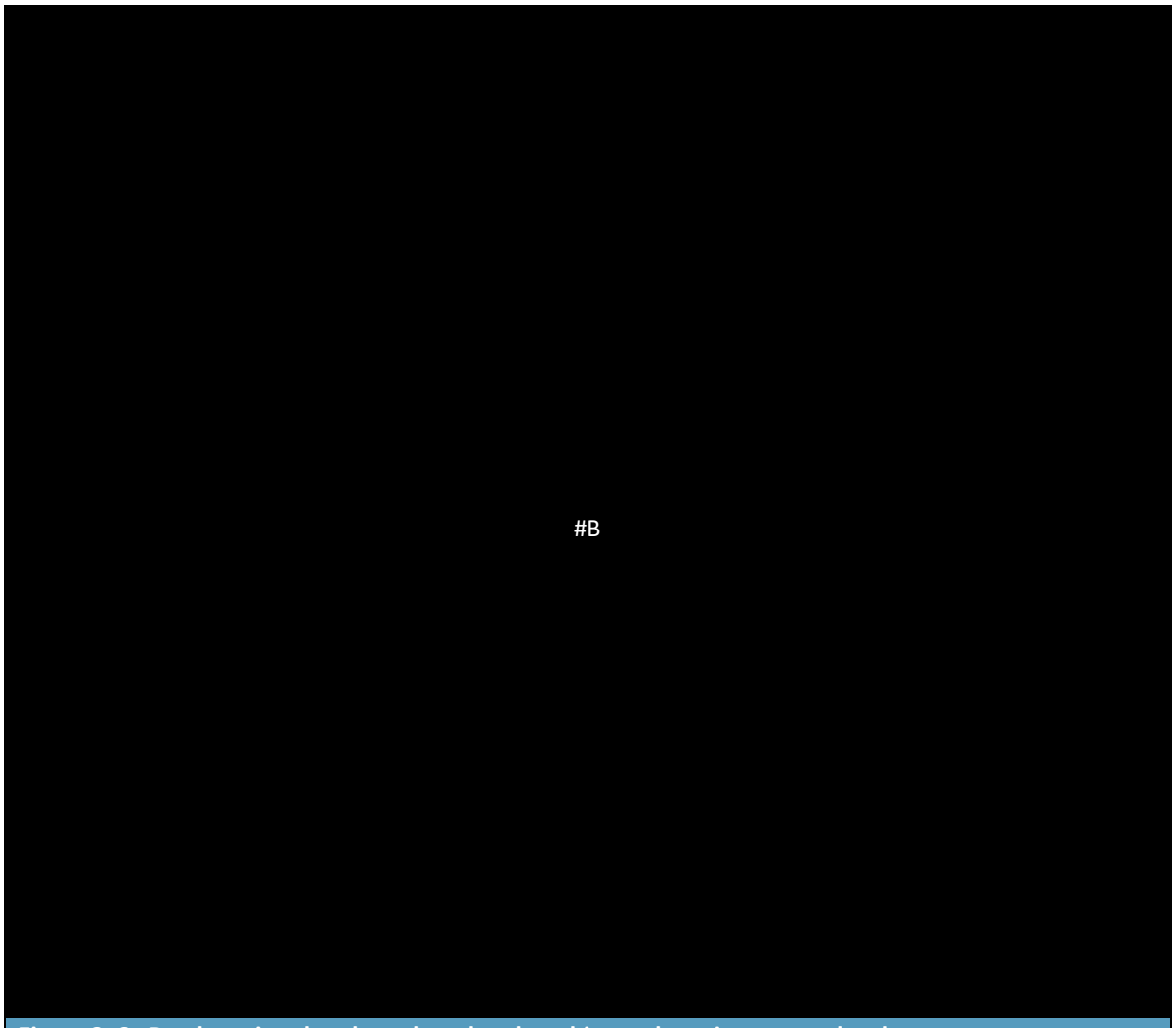

Figure 3–6: Bead coating chamber where bead washing and coating steps take place

All buffer solutions for washing and coating steps described above are prepared during the buffer formulation step and this step is identical with regards to Operational Conditions (OC) and Risk Management Measures (RMM) for all types of beads produced by Siemens Llanberis. All steps are performed in dedicated areas of the site that are connected to a separate waste-water collection system, collecting all waste liquids in a tank, which is then transported by road as waste to an industrial waste-water treatment plant in Liverpool. All steps are performed by trained personnel and in accordance with ISO 13485 and Good Manufacturing Practices (GMP) which are part of the regulatory requirements for the design and manufacture of medical devices according to FDA 21 CFR Part 820 regulation.

For the washing procedure, Triton™ X-100 is #B, D (paragraph) to the required concentration of [redacted]% for IVD analyte beads #[redacted] to #[redacted] and [redacted]% for IVD analyte bead #[redacted] in **Table 3–2**. For the [redacted] coating procedure (IVD analyte bead #[redacted]), three aqueous buffer solutions containing OPE at a concentration of [redacted]% are prepared and for the [redacted] coating procedure (IVD analyte bead #[redacted]), a solution containing [redacted]% OPE is prepared. The washing and the bead coating steps are subject to the same OCs and RMMs. See picture of installation below (**Figure 3–7**).

For the AoA, the bead washing and coating steps (Step 2 and 3 above) are of relevance while Step 1, the formulation, is a preparatory step that does not provide any specific technical requirements to the analysis, since the use in this step merely supplies the OPE in a medium suitable for the subsequent washing and coating of beads.

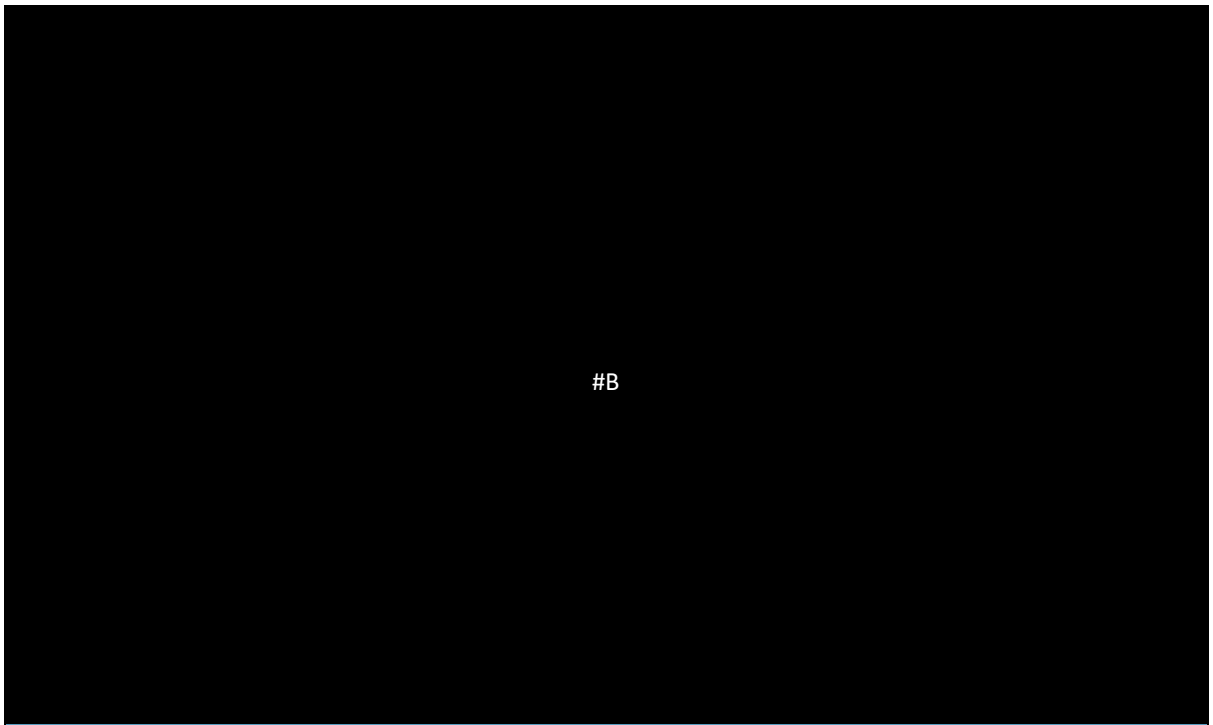

Figure 3–7: Bead manufacture buffer formulation laboratory

Function of OPEs in the relevant #D IVD kits

As previously mentioned, the purpose of an immunoassay is to generate a measurable signal to detect the presence of minute amounts of analyte in a sample. In order to do this, precision, accuracy and specificity are required and sufficient sensitivity to detect minute concentrations of an analyte. For #D IVD analyte beads listed #D in **Table 3–2**, the bead washing and coating step is critical for the test precision and sensitivity of the IVD kit produced. For #D IVD analyte beads listed

#D in **Table 3–2**, OPE is required to facilitate the bead coating of critical raw materials which are responsible for maintaining the operating mechanisms by which the immunoassays work.

Assay precision indicates the reliability of the measurement made by use of an IVD kit, i.e. acceptable precision would mean that minimal variation exists between measurements so that results from single measurements can be trusted and are consistent. A uniform coating of 'capture antibody or antigen' onto the bead surface is required to achieve acceptable precision, as non-uniformity would result in variation of the signal strength generated by individual beads.

Assay sensitivity indicates the ability of an IVD kit to measure minute concentrations of an analyte. It is the lowest possible concentration of analyte measured by the IVD kit below which assay precision would become unacceptable. Assay sensitivity is therefore dependent on assay precision performance. Acceptable sensitivity is a pre-requisite for the intended use of the IVD kit, for example, whether the IVD kit has the capability to accurately measure an analyte at the cut-off between diseased and healthy patient states.

The function of OPE in the #D relevant #D IVD analyte beads achieving their required performance characteristics can be grouped into the following two categories:

- **Acting as a cleaning agent for the removal of impurities from the #B surface of the beads (IVD analyte beads # #D to # #D)**: #B surfaces are susceptible to having surface impurities. These may derive from the production process, e.g. microscopic #B particles adhering to the surface, or from contact with the environment, e.g. airborne pollutants or dirt encountered through transportation and handling. It is essential to the production of #D IVD analyte beads ##D to # #D in **Table 3–2** that the bead surfaces are extremely clean, as any particles that remain on the surface would reduce the precision and sensitivity of the assay products that the beads support.

  When beads are coated with either antibodies or antigens, the intention is to achieve a uniform coating of the surface #B, D (Paragraph) , and on every single bead produced. This is essential, as this coating is responsible for capturing the analyte in patient samples so that the dose (e.g. concentration of the analyte in serum) can be measured by the #D analyser to meet the intended purpose of using the IVD kit, i.e. as an aid to diagnosis based on a dose cut-off point demarking disease and healthy states in patients. Variation in the coating of the 'capture antibody or antigen' would manifest in the variation of the signal generated by the IVD kit in response to the same amount of analyte sample, i.e. the precision would reduce and so would the sensitivity, leading to unreliable results and diagnoses.

  All the beads discussed in this AoA, apart from the bead (IVD analyte bead #) and the #D (paragraph) bead (IVD analyte bead #), are more acutely sensitive to bead impurity issues than the rest of the portfolio of immunoassay IVD kits, and OPE plays a critical role in achieving the level of bead cleanliness that is vital for the performance of these IVD Kits. Triton™ X-100 is a nonionic detergent and as such it serves as a cleaning agent in the process of bead washing. The main property that defines the functionality of a surfactant is the Hydrophile-Lipophile Balance (HLB) which is a measure of the degree to which the surfactant is hydrophilic (water loving molecules, i.e. polar molecular species are attracted to other polar molecules as opposed to non-polar molecules) or lipophilic (lipid or oil loving molecules, i.e. the reverse of hydrophilic where non-polar molecular species are attracted to other non-polar molecules as opposed to polar molecules). This is determined by calculating values for the polar (hydrophilic) and non-polar (hydrophobic) regions of a molecule; and

- **Acting as a stabiliser in the coating of the [redacted] bead (IVD analyte bead #[redacted]) and the [redacted] bead (IVD analyte bead #[redacted])**: the function of OPE in the manufacture of the [redacted] and [redacted] #D (paragraph) beads is that of a stabilising agent for specific critical raw materials which are to be successfully deposited from aqueous buffers onto bead surfaces. To illustrate this role, the [redacted] product is here discussed as an example.

  The role of OPE in these coatings is related to the solution-stabilisation of the key material being coated onto the bead surface, that of the [redacted] (produced by Siemens Marburg in Germany via [redacted] which is induced by OPE; note that this use is included as part of a separate but related Siemens Healthineers AfA). The [redacted] is responsible for capturing [redacted] #B,D (paragraph) [redacted] in patient samples onto the bead so that the dose of [redacted] can be measured by the [redacted] analyser as an aid to the diagnosis of [redacted] disease (refer to [redacted] for further information).

  In order to coat [redacted] onto the bead a coating solution containing OPE is prepared in Step 1. The [redacted] (as produced by the Siemens Marburg site) added to the coating solution will also contain remnant amounts of [redacted] (as a result of the [redacted] process performed at the Siemens Marburg site). These residual [redacted] stimulate the aggregation of proteins ([redacted] #B,D (paragraph) [redacted]) in solution, thus adversely impacting the efficacy of the bead coating step. OPE will act to solubilise the [redacted] and the [redacted], thereby providing a physico-chemical barrier against the aggregation process. Additionally, the micelle-type interaction between OPE and the [redacted] will protect the [redacted] from any denaturing contaminants which may be present in solution, e.g. ionic species, which may induce changes to parts of the protein structure. In summary, the non-ionic surfactant properties of Triton™ X-100 stabilise the [redacted] in the buffer medium to minimise or reduce natural aggregation and disintegration processes which would render the bead coating step ineffective.

3.1.4 Technical feasibility criteria for the role of OPE in IVD kit development

Technical feasibility criterion 1: Nonionic surfactant

Understanding the basic principles of surfactants is a prerequisite to developing formulated IVD kit reagent products. Surfactants are categorised according to use, ionic charge, and chemical structure. These substances are selected for their ability to function as detergents, wetting agents, emulsifying agents or dispersing agents. The viability of surfactants for use in the development of new products is dependent on their physicochemical properties being compatible with aqueous-based biochemical systems.

Structurally, surfactants consist of a hydrophilic (attracting to water) part and a hydrophobic (repelling to water) part. When added to an aqueous solution, the hydrophilic part arranges itself toward the water phase while the hydrophobic part tries to remove itself from the water by attaching to any surface which is less polar than water (e.g. a protein, a [redacted] #B [redacted] material surface, or cell membranes). Thus, the effect is that the surfactants adsorb onto a variety of surfaces to lower the surface tension between the different media. The major surfactant classes are anionic, nonionic, cationic and amphoteric.

Anionic surfactants have a negative charge and are considered effective in removing particulates and oils. They tend to be affected by water hardness ions (e.g. Ca, Mg, K cations) and generate higher foam levels than other surfactant classes. Therefore, such surfactants are not best suited for use in IVD kits

that are used in analysers. Foaming would strongly affect the liquid handling on the instruments. Furthermore, this property would negatively affect the stability of biological molecules that are part of IVD kits. The interaction of the charged residue with the amino acid chain of proteins might lead to a change of the shape of the protein structures (denaturation) and by this they might lose their functionality (for example, binding sites can be blocked by detergents that interact with amino acid side chains or the protein is precipitated from the solution). A precise concentration of cations present in an IVD kit solution is also very important as these cations are often co-factors for protein-protein interaction or enzymatic reactions.

Cationic surfactants have a positive charge; thus, do not react with water hardness ions, but often have similar effects on biological systems as those of anionic surfactants. These surfactants have little or no detergent properties which are needed in IVD kit reagents. Consequently, ionic surfactants can generally not be used in IVD kits.

Amphoteric surfactants simultaneously carry an anionic and cationic hydrophilic group and are therefore able to act as cations or anions according to the ambient conditions. As such, the discussions for cationic and anionic surfactants above can be applied.

Nonionic surfactants do not have an ionic charge. They foam less and are less affected by water hardness ions and are therefore well suited for use in IVD kits, where it is important that molecules remain in solution but also keep their functionality. Triton™ X-100 belongs to this class, as its molecules are neutral, i.e. possessing no charge (non-ionic).

In general, positively (cationic) or negatively (anionic) charged surfactants exhibit stronger protein denaturing effects (especially at higher concentrations) which can often alter the structure of the antibodies used, rendering them inactive.

Technical feasibility criterion 2: Hydrophile-lipophile balance

In the context of bead washing the hydrophilicity and hydrophobicity of the surfactant are important in the following ways:

1. **Hydrophilicity (water solubility)**: as antibodies are of biological origin, both bead coating and bead washing are performed in aqueous buffers (i.e. water is the solvent). If non-polar solvents were used for bead washing, unwanted solvent residues would also contaminate the bead surface. OPEs possess an ethoxylate group which makes them soluble in water.

2. **Hydrophobicity (oil solubility)**: a known contaminant of bead surfaces is [redacted] debris that adhere to the beads as a result of the raw bead manufacturing process, i.e. the formation of the spherical bead (∅ 6.35 mm) from [redacted]. [redacted] #B (paragraph) [redacted] an appropriate surfactant must have a hydrophobic region capable of interacting with the [redacted] particles. OPEs have a hydrophobic carbon chain that serve this purpose. The length of the carbon chain is responsible for the degree of hydrophobicity and varies depending on the degree of ethoxylation grade. For many proteins, Triton™ with chain length between 8 and 9 provides a good degree of hydrophobicity and this is a reason that the substance is applied in a wide range of applications. The most widely used Triton™ product has a chain length of 9.5 known and is known as Triton™ X-100.

As described above, hydrophile-lipophile balance (HLB) is a numerical system used to describe the relationship between the water-soluble and oil-soluble parts of a nonionic surfactant. HLB values can

be calculated by various methods[4]. The most commonly used is the Griffin method which divides the molecular weights of the hydrophilic portion (e.g. ethoxy groups) by that of the whole molecule, then multiplies by 20 to give an answer within a range of 0 to 20. HLB values of nonionic surfactants can be in the range 0.5 to 19.5[5]. Using the Griffin method, surfactants with HLB values of 13 to 15 make good detergents, those with HLBs between 12-18 are solubilisers or hydrotropes. So, substances with high HLB values (>12) support the removal of hydrophobic particulates (e.g. #B debris) and organic material (e.g. miscellaneous carbon-based pollutants) from surfaces in an aqueous environment. Triton™ X-100 has an HLB value of 13.4, so potential alternatives should ideally have similar values.

Technical feasibility criterion 3: Critical micelle concentration

A micelle is an aggregated unit composed of several molecules of a surface-active material. Micelles solubilise dirt and oils by lifting these soils off the surface and dispersing them into solution. Micelle formation enables emulsification, solubilisation, and dispersion of otherwise non-compatible materials. Critical micelle concentration (CMC) is the surfactant concentration at which an appreciable number of micelles are formed and thus can effectively remove particles. As such, the CMC is a measure of surfactant efficiency. A lower CMC indicates that less surfactant is needed to saturate interfaces and form micelles. Typical CMC values are less than 1% by weight (e.g. Triton™ X-100 has a CMC of 0.0189 % or 189 ppm). CMC values provide a valuable guideline for comparing surfactant detergency. Other formulation components and temperature may also affect micelle formation.

Technical feasibility criterion 4: Cloud point

The cloud point of a nonionic surfactant is the temperature above which an aqueous solution of a water-soluble surfactant becomes cloudy. Cloud points are characteristic of nonionic surfactants. Knowledge of the cloud points of nonionic surfactants is another potentially important property as wetting, cleaning and foaming characteristics can be different above and below the cloud point. Generally, nonionic surfactants produce optimal cleaning efficacy when used near or below their cloud point. Low-foam nonionic surfactants should be used at temperatures slightly above their cloud point. Finished products stored at temperatures significantly higher than the cloud point may result in phase separation and instability. The presence of other components in a formulation can depress or increase the cloud point of cleaning solutions. Cloud points are typically measured using 1% aqueous solutions of the respective surfactant. The cloud point of Triton™ X-100 under these conditions is 66°C. A cloud point should, as a consequence, be well above ambient temperatures in the countries the IVD kits are shipped to.

Technical feasibility criterion 5: Inert towards #B surfaces

For bead coating it is crucial that the detergent itself does not chemically react with the #B bead in order to avoid negative effects which may lead to the non-uniform binding of the 'capture' antibodies or antigens.

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[4] The use of different calculation methods can produce different results, meaning direct comparison is only possible if the same method is used.

[5] Some publications may quote higher values, if different calculation methods are applied.

Summary of technical feasibility criteria for potential alternatives

The following table summarises the key parameters of the selected technical feasibility criteria.

Table 3–3: Technical feasibility criteria and thresholds/tolerance ranges for alternative substances			
#	**Technical feasibility criterion**	**Result or value achieved by OPEs**	**Threshold value or tolerance (acceptable range) for technically feasible alternatives**
1	Nonionic surfactants	OPEs are such surfactants	Alternative substances need to be nonionic
2	Hydrophile-lipophile balance	Triton™ X-100: 13.4	>13
3	Critical micelle concentration	Triton™ X-100: 189 ppm	140-240ppm
4	Cloud point	Triton™ X-100: 66 °C	# B,F °C
5	Inert towards #B surfaces	Inert	Inert

3.2 Market and business trends including the use of the substance

3.2.1 Annual tonnage

The annual tonnage of Triton™ X-100 consumed at Llanberis is estimated at ca. #A (<<0.05 t/y) for the year 2018. This tonnage will decrease year on year as #D #C. At the Sunset Date (2021), the projected consumption of Triton™ X-100 in Llanberis will be #A kg/y (<<0.05 t/y).

#D,C will gradually decrease and will ultimately cease by the end of the requested review period.

The gradual decline of the volume of OPEs used is shown in **Table 3–4**.

Table 3–4: Projections of sales of IVD kits and associated consumption/use of Triton™ X-100 in Llanberis			
Year	**IVD kits sold (global)**	**OPE amount used (kg)**	**% of previous year**
2018			
2019			
2020			
2021			
2022			
2023			
2024			
2025			
2026			
2027			
2028			
2029			

Source: Siemens Llanberis
Note 1: OPE amount is calculated from volumes (litres), assuming a density of Triton™ X-100 of 1.061 g/ml at 25°C
Note 2: # A,C, H (table)

3.2.2 Market for relevant Siemens Llanberis IVD kits

Historic context

Siemens Llanberis is a reagent manufacturing facility based in the village of Llanberis in North-west Wales. Established in 1992, it is an economically significant business as the largest private employer in the county, supporting a large network of employees (#D (range: 100-1,000) members of permanent staff at present), site-based contractors, sub-contractors and suppliers.

OPE-related activities

Manufacture and sale of OPE-dependent #D IVD kits – Baseline data

OPE is used as a processing aid at the site in the manufacture of IVD kits of the #D product-line. These IVD kits are used in hospitals, commercial laboratories, research centres and by other Siemens Healthineers customers to support vital diagnoses of specific diseases and conditions based on patient samples.

#C, D

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Siemens Llanberis manufactured more than #C,H (range: 0.1-1 million) such #D IVD kits in 2017 and the corresponding profit for their sales was ca. #C,H (range: €10-100 million) in the same year. The baseline sales data (EEA and Non-EEA customers) for the year 2017 is shown in **Table 3-5**.

Table 3-5: 2017 Sales volumes and value of OPE-dependent #C,D,H (table) IVD kits linked to Use 1 by Siemens Llanberis

Sales by volume (No. kits/year)			Sales by value (€/year)			Profit after standard cost by value (€/year)		
UK	Non-UK EEA	Non-EEA	UK	Non-UK EEA	Non-EEA	UK	Non-UK EEA	Non-EEA

Projected future sale of IVD kits that depend on the use of OPE by Siemens Llanberis

The sales of the IVD kits are directly linked to the number of analysers in use as well as the frequency of use (some customers may use their analysers more frequently than others and thus buy a larger number of kits each year). The projected sales of kits over the review period is based on a strategic (# C,D (paragraph)) business plan developed by collaboration of various functions within Siemens Healthineers.

The strategic plan provides year-on-year projected changes in sales, as shown in **Table 3-6**; these can be used to estimate the number of OPE-dependent IVD kits to be sold over the requested review period and the associated revenues and pre-tax profit. As shown in the table below, Siemens Llanberis anticipates to make a present value gross profit of ca. € [redacted] (range: €10-100 million) in the period 2021-2029, [redacted] #C,H (paragraph) [redacted]. A 4% discount rate is used.

Table 3-6: Projected sales volumes and profits from sales of OPE-dependent [redacted] #D, H (table) IVD kits linked to Use 1 by Siemens Llanberis

Year	Assumed year-on year change in kit sales volumes/ value	No. of OPE-dependent kits sold on EEA market	No. of OPE-dependent kits sold on non-EEA	Discounting factor (4%)	NPV profit, € per year - EEA sales	NPV profit, € per year non-EEA sales
2018	[redacted]	[redacted]	[redacted]	104%	[redacted]	[redacted]
2019	[redacted]	[redacted]	[redacted]	108%	[redacted]	[redacted]
2020	[redacted]	[redacted]	[redacted]	112%	[redacted]	[redacted]
2021	[redacted]	[redacted]	[redacted]	117%	[redacted]	[redacted]
2022	[redacted]	[redacted]	[redacted]	122%	[redacted]	[redacted]
2023	[redacted]	[redacted]	[redacted]	127%	[redacted]	[redacted]
2024	[redacted]	[redacted]	[redacted]	132%	[redacted]	[redacted]
2025	[redacted]	[redacted]	[redacted]	137%	[redacted]	[redacted]
2026	[redacted]	[redacted]	[redacted]	142%	[redacted]	[redacted]
2027	[redacted]	[redacted]	[redacted]	148%	[redacted]	[redacted]
2028	[redacted]	[redacted]	[redacted]	154%	[redacted]	[redacted]
2029	[redacted]	[redacted]	[redacted]	160%	[redacted]	[redacted]
				Total, 2021-2029 (rounded)	[redacted]	[redacted]

Siemens Llanberis sells numerous other IVD kits for use on [redacted] analysers which do not depend on the use of OPEs. However, inability to sell OPE-dependent kits would impact upon the sales of the remaining IVD kits. Demand for those IVD kits would decrease more rapidly if the OPE-dependent kits became unavailable. This is because customers who use both OPE-dependent and OPE-independent kits would seek to replace their #D (paragraph) analyser earlier in order to operate the full range of assays they need on one type of IVD analyser. Some customers may only use OPE-independent [redacted] IVD kits and therefore they would not be affected.

Similarly, if Siemens Marburg was unable to sell the # D (paragraph) [redacted] solution that is manufactured in Germany and subject to a separate AfA, Siemens Llanberis would not be able to sell any IVD kit whatsoever as the [redacted] must be used with every single IVD kit employed on an [redacted] analyser. Non-OPE-dependent IVD kit sales are discussed below.

Non-OPE related activities

In Llanberis, there are numerous activities other than those that involve OPE and these include the manufacture of all other immunoassay kits in the [redacted] #D portfolio, as well as all the peripheral support services at a manufacturing site, e.g. warehousing, maintenance, waste management, catering, cleaning etc.

There are #D,H, (range: 50-100) unique #D assays and #D (range: 75-125) unique #D assays. Also, there is a number of additional related products /consumables such as quality control materials, diluents, etc. which are OPE-independent.

Siemens Healthineers' data indicate that in terms of profit, the OPE-dependent kits represent ca. #C % (range: 10-25%) of all profits made from sales of #D IVD kits. This makes the overall profit for 2017 sales to all markets equivalent to € #C,H (range: €0.1-1 billion) of which ca. € #C,H (range: €0.1-1 billion) was associated with sales of OPE-independent #D IVD kits across the globe.

If we use this percentage of % alongside the profit estimates for OPE-dependent IVD kit sales shown in **Table 3-6**, it is possible to estimate the Present Value gross profit that Siemens Llanberis is anticipated to make in the period 2021-2029 from sales of OPE-independent IVD kits (since #C,D,H (paragraph) no substitution activity for OPE will be carried out, this percentage can reasonably be assumed to remain constant during the review period). As can be seen in **Table 3-7**, the gross profit that Siemens Llanberis is anticipated to make over the 2021-2029 assessment period is very substantial and far exceeds the profit made from sales of OPE-dependent IVD kits, bringing the overall Present Value profit from sales of all kits to (range: €0.1-1 billion) over the 9 years of the requested review period.

Table 3-7: Net present value of profits from sales of OPE-independent # C, H (table) IVD kits, 2021-2029	
Customer group	**NPV, gross profit, 4% discount (rounded)**
EEA customers	
non-EEA customers	
All customers	

As has been noted, all the D (paragraph) kits need a wash solution, which contains OPE and is produced at the Siemens Marburg site in Germany. This wash solution is included in the scope of another AfA submitted by Siemens Marburg. If that Authorisation were not granted, sales of all kits would no longer be feasible as the kits cannot be used without , and sales would therefore cease.

3.2.3 Markets for relevant Siemens Healthineers analysers

Existing stock of #D analysers

The # D (paragraph) analysers are produced at Siemens Healthineers Flanders in the USA (New Jersey) and all analysers are distributed from that site. There are currently over instruments used by customers for diagnosing key diseases in patients in the global healthcare system, as shown in **Table 3–8**.

Table 3–8: Number of #C,D,H (table) analysers currently operated in different countries (2017)		
Customer location		**Total No. analysers**
Austria		
Belgium		
Bulgaria		
Czechia		
Cyprus		
Denmark		
Estonia		

Table 3–8: Number of [redacted] #C,D,H (table) analysers currently operated in different countries (2017)		
Customer location	[redacted]	Total No. analysers
Finland	[redacted]	[redacted]
France	[redacted]	[redacted]
Germany	[redacted]	[redacted]
Greece	[redacted]	[redacted]
Hungary	[redacted]	[redacted]
Iceland	[redacted]	[redacted]
Ireland	[redacted]	[redacted]
Italy	[redacted]	[redacted]
Latvia	[redacted]	[redacted]
Liechtenstein	[redacted]	[redacted]
Lithuania	[redacted]	[redacted]
Luxembourg	[redacted]	[redacted]
Malta	[redacted]	[redacted]
Netherlands	[redacted]	[redacted]
Norway	[redacted]	[redacted]
Poland	[redacted]	[redacted]
Portugal	[redacted]	[redacted]
Romania	[redacted]	[redacted]
Slovakia	[redacted]	[redacted]
Slovenia	[redacted]	[redacted]
Spain	[redacted]	[redacted]
Sweden	[redacted]	[redacted]
United Kingdom	[redacted]	[redacted]
Total EEA	[redacted]	[redacted]
Total Non-EEA	[redacted]	[redacted]
Grand total	[redacted]	[redacted]
Source: Siemens Llanberis		

Some general observations can be made:

- The non-EEA market is [redacted] #C as the EEA market in terms of the number of analysers currently in operation;
- The most advanced model, [redacted] #D (bullet point) is the most widely used in the EEA, while [redacted] is the most widely used model outside the EEA;
- The most important EEA Member States for Siemens Healthineers, in terms of the number of [redacted] #D analysers present are [redacted] #C. However, if we consider the relative age of the different analyser models, the countries that would most likely be severely impacted under the "Non-use" Scenario would be [redacted] #C,E because they host the highest numbers of the newest [redacted] #D model (and therefore their replacement would be the most premature);
- Importantly, [redacted] #D analysers can **only** operate with IVD kits made by Siemens Llanberis.

The expected life time of the [redacted] and [redacted] is [redacted] years and it is [redacted] years for the [redacted] and the [redacted] #C,D (paragraph). Around 10% of the analysers are operational for more than 11 years.

#C, D

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As shown in **Table 3–9**, the average age of the current stock of #D analysers is #D . The table only presents average lives across the entire stock to allow for the quantification of impacts under the "Non-use" Scenario (i.e. impacts from premature replacement of analysers by the customers). The expected remaining life time should be a reasonable approximation of the time it will take, on average, before the stock is # C , and this approximation will be used in the analysis below; this should not be taken to mean that only # D systems will remain in use #D .

Table 3–9: Remaining life time and life support of the # C,D,H (table) analysers

Analyser	Average lifetime	End of life support	Average age in 2017		Average remaining years[6] after 2020, i.e. after the Sunset Date	
			EEA	Non-EEA	EEA	Non-EEA

Projected future sales of #D analysers

and #C,D (paragraph) are no longer in production. In other words, only of the models shown above will continue to be sold until at least the end of .

Based on current business projections, in the coming years (2018-), it is expected that around (range: 1,000-2,000) new analysers will be sold of which ca. (range: 100-500) will be sold to EEA customers. **Table 3-10** shows the projected sales of analysers and the corresponding gross profits. For the period between the Sunset Date and the of and #C,D,H (paragraph) analysers, a Present Value profit of ca. € (range: €1-10 million) is expected to be made from sales of (range: 100-500) new analysers, the majority of which will be sold to non-EEA customers.

[6] Average remaining years = Average lifetime minus average age in 2017 minus 3 years (i.e. to account for the period end 2017 to end 2020).

Table 3–10: Projected sales of #C,D,H (table) analysers and associated gross profits analysers,						
Year	EEA			Non-EEA		
	Sales (No. analysers/ year)	Pre-tax profits (€ million /year)	Pre-tax profits (€ million /year) - Discounted (4%)	Sales (No. analysers/ year)	Pre-tax profits (€/year) - discounted	Pre-tax profits (€ million /year) - Discounted (4%)

3.2.4 Suppliers to Siemens Llanberis

An overview of the materials supplied to Siemens Llanberis for the manufacture of the #C,D impacted #D IVD kits and location of the relevant suppliers is provided in the table below. In total, there are (range: 1-10) relevant EEA-based suppliers and another #C (range: 10-50) located outside the EEA.

Table 3–11: Materials sourced upstream for the manufacture of OPE-dependent consumables in Llanberis				
Material	EEA		Non-EEA	
	Number of suppliers	Location (country)	Number of suppliers	Location (country)
#C,D (table)				
Total number of relevant suppliers				

The market value of the materials required for the manufacture of these kits is €#C (paragraph) (range: €1-10 million). % of this relates to EEA-supplied materials and % relates to non-EEA-supplied materials.

3.2.5 Customers of Siemens

Operators of #D analysers

Siemens Llanberis' customers are hospitals, commercial and other laboratories and testing facilities. The number of analysers presented in **Table 3–8** above is the most reliable source of information on the geographical distribution of end users of the impacted IVD kits.

Sales data for 2017 show that EEA-based customers purchased ca. (range: 10-100 million) IVD kits in 2017, of which ca. (range: 10,000-100,000) were OPE-dependent. The number of kits sold in non-EEA markets in the same year was C,D,H (paragraph) than the EEA market. As discussed above, these numbers will .

Patients

The ultimate beneficiaries of the use of the IVD kits by Siemens Healthineers' customers are healthcare systems and patients for whom the diagnostic tests are performed in hospital laboratories or other external facility or laboratory. There will be no disruption of patient care under the "Applied for Use" scenario. The tests that can be carried out with the OPE-dependent kits were described in **Table 3–2** (IVD analyte bead # is a kit used for the quantitative measurement of non-protein-bound #C,D, (paragraph) in serum, as an aid in the clinical assessment of status in).

The number of IVD kits sold in the EEA was approximately (range: 10,000-100,000) in 2017. It must be understood that each kit may deliver hundreds of different tests; for example, a kit may offer 200 tests per kit. The sales of OPE-dependent IVD kits for the #C,D (paragraph) platform in 2017 were equivalent to ca. (range: 10-100 million) tests on patient samples.

3.2.6 Employment in the "Applied-for-use" scenario

There are currently (range: 100-1,000) people directly employed at Siemens Llanberis. Additionally, there are (range: 10-100) on-site contractors and more than (range: 10-100) off-site contractors associated with the operations at Llanberis # C,D (paragraph)). Siemens Llanberis is the largest private employer in the county of Gwynedd, North-west Wales.

3.3 Remaining risk of the "Applied for Use" Scenario

3.3.1 Emission sources and existing risk management measures

Environmental classification

The environmental classifications for 4-tert-OP, a degradation product of OPE, are given in the following table.

Table 3-12: Environmental classification of 4-tert-OP		
Hazard class	**Hazard category**	**Hazard statement**
Hazards to the aquatic environment (acute/short term)	Aquatic Acute 1	H400 Very toxic to aquatic life
Hazards to the aquatic environment (chronic/long term)	Aquatic Acute 1	H410 Very toxic to aquatic life with long lasting effects

Emission sources

Triton™ X-100 is used at the site in Llanberis as part of bead manufacture. Solid waste from the site (potentially including gloves, pipettes, etc.) is incinerated, whilst wastewater undergoes the following treatment steps:

1. Wastewater is collected in a tank system on site.
2. It is pumped into a tanker and taken by road to an industrial treatment works that is permitted to take substances such as Triton™ X-100.
3. At the industrial treatment works, the wastewater undergoes treatment with lime to enable precipitation and collection of sludge. The sludge is taken to landfill whilst the wastewater is discharged to a municipal wastewater treatment works.
4. The municipal wastewater treatments works was upgraded in 2014, with a £200 million investment to increase capacity. It discharges into the River Mersey (specifically, the Water Framework Directive (WFD) waterbody named as the Mersey transitional water (GB531206908100).

The following table summarises the emissions to the environment.

Table 3-13: Summary of emission sources associated with the use of Triton™ X-100 in Llanberis	
Environmental compartment	**Release method**
Water	Via municipal STP discharge into the Mersey waterbody (ID GB531206908100)
Land	Sludge from industrial treatment works (where lime is added) is disposed of in landfill
	Sludge from municipal STP (application of sludge to agricultural land is assumed not to occur as per the exposure assessment in the CSR)
Air	There is assumed to be no release to air

Emission controls relating to the environment

Existing controls on the release of OPE/OP to the environment include environmental permitting for waste. As noted above, the industrial treatment site has an environmental permit to ensure that it can accept waste containing substances such as Triton™ X-100. Permits are also required for waste incineration, with the Industrial Emissions Directive applying to plants that thermally treat solid or liquid waste or use it as a fuel (EU, 2010).

There are also controls established under the WFD (Directive 2000/60/EC) and the need to avoid deterioration of waterbody status. The WFD waterbody that receives the discharge is the Mersey transitional water (GB531206908100). This is classed as heavily modified, with a current overall status of 'moderate' (2016, cycle 2) (Environment Agency, 2016). It has an ecological status of 'moderate' and chemical status of 'fail', driven by a 'fail' classification for priority substances (specifically lead and

its compounds). Classifications for earlier years indicate that there were previously issues with priority hazardous substances including brominated diphenyl ether (BDPE) calc, benzo(a)pyrene, mercury and its compounds, and tributyltin compounds (Environment Agency, 2016). Reviewing the classification data for individual items, octylphenol is not listed but nonylphenol is noted as being at 'good' status for 2016 (Environment Agency, 2016).

Directive 2008/105/EC on environmental quality standards (EQS) in water policy provides a list of priority substances for which EQS have been set. Octylphenol is identified as a priority substance but not a priority hazardous substance (European Commission, 2016). The Directive aims to protect against long-term exposure using annual averages and against short-term exposure using maximum allowable concentrations (MAC) (European Commission, 2016). The EQS values for octylphenol are as follows (note that there are no MAC values) (UK Government, 2015):

- Rivers and lakes (inland waters): 0.1 µg/l annual average EQS; and
- Transitional and coastal waters: 0.01 µg/l annual average EQS.

3.3.2 Exposure levels

Overview of exposure assessment

The exposure scenario is based on a declining annual usage, with #A tonnes in 2018 assumed to decrease to #A tonnes in 2021 and then to around #A tonnes by 2029. A maximum daily use volume of Triton™ X-100 of #A kg has been calculated in the CSR with a (very worst-case) maximum weekly usage of up to #A kg at the outset.

There is also expected to be variation in the amount of Triton™ X-100 used over time (i.e. use does not occur at a constant rate), however, the maximum daily use volumes of Triton™ X-100 will not decrease as quickly as the annual Triton™ X-100 consumption, since the size of the related production batches will not be reduced, but only the frequency of production lots will gradually decline.

The exposure assessment is based on a set of assumptions as listed below:

- All OPE utilised is assumed to end up in the wastewater tank at the Siemens Llanberis plant. There will be some OPE adhered to solid waste such as gloves, but this is assumed to be <0.1% of the total;

- There is no degradation of OPE during collection and transport to the industrial treatment works (this is because OPE is assumed to be stable in the absence of bacteria);

- There is minimal (if any) loss of OPE to sludge during the industrial wastewater treatment process. The exposure assessment reports that measurements taken pre-and post-treatment are near the level of detection. Thus, all OPE that enters the industrial treatment works is assumed to leave in the wastewater that goes to the municipal STP;

- Of the OPE entering the municipal wastewater treatment works, 19.5% is assumed to be adsorbed to sludge. Note that Environment Agency states that 4-tert-OP adsorbs to sewage sludge, with the result that spreading sludge containing the substance to agricultural land is a major exposure route for soil (Environment Agency, 2005). This exposure assessment assumes that the sludge is not spread to land;

- Of the OPE entering the municipal STP, 80.5% is assumed to be released within the water discharged[7], however, it is assumed to immediately degrade to OP on release. Since OP has 33% of the mass of OPE, then the OP within the discharge to the Mersey waterbody is 26.5% of the original OPE; and

- Importantly, by the Sunset Date, the Triton™ X-100-containing wastewater will be segregated and incinerated, which means that only a very small proportion of Triton™ X-100 releases will persist over the requested review period, primarily associated with the cleaning waters of instruments, etc. In the emission estimates below, a conservative emission factor of 1% is assumed.

The following figures provide an overview of the treatment process for waste from the Llanberis site indicating the proportions of the original OPE released at each stage. The exposure assessment effectively assumes a worst-case scenario, with the majority of the OPE used at the Llanberis site being discharged via the municipal STP at Liverpool into the Mersey waterbody.

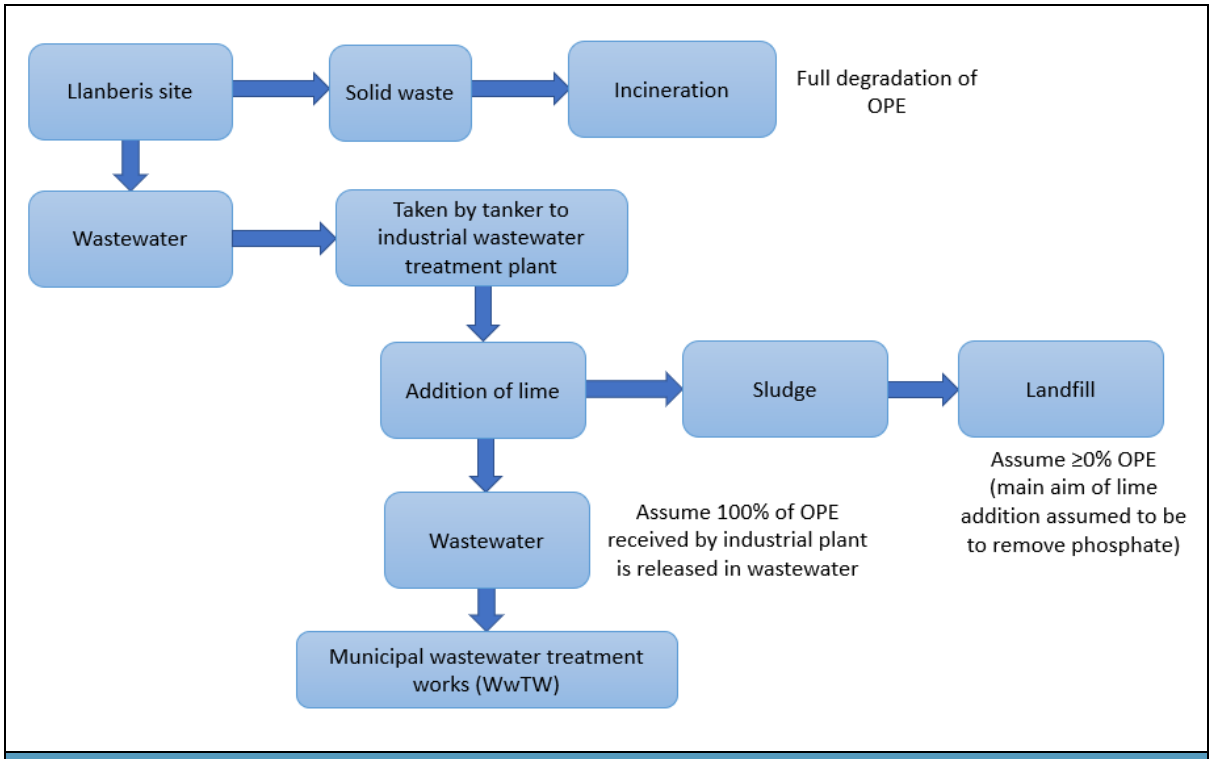

Figure 3-8: Initial treatment of waste from Llanberis site (industrial wastewater treatment plant)

[7] Note that this is a worst-case assumption, since removal levels for 4-tert-OP for a sequencing batch reactor (the type used at the Liverpool works) have been found to be greater than 95% (Zhou *et al.*, 2011).

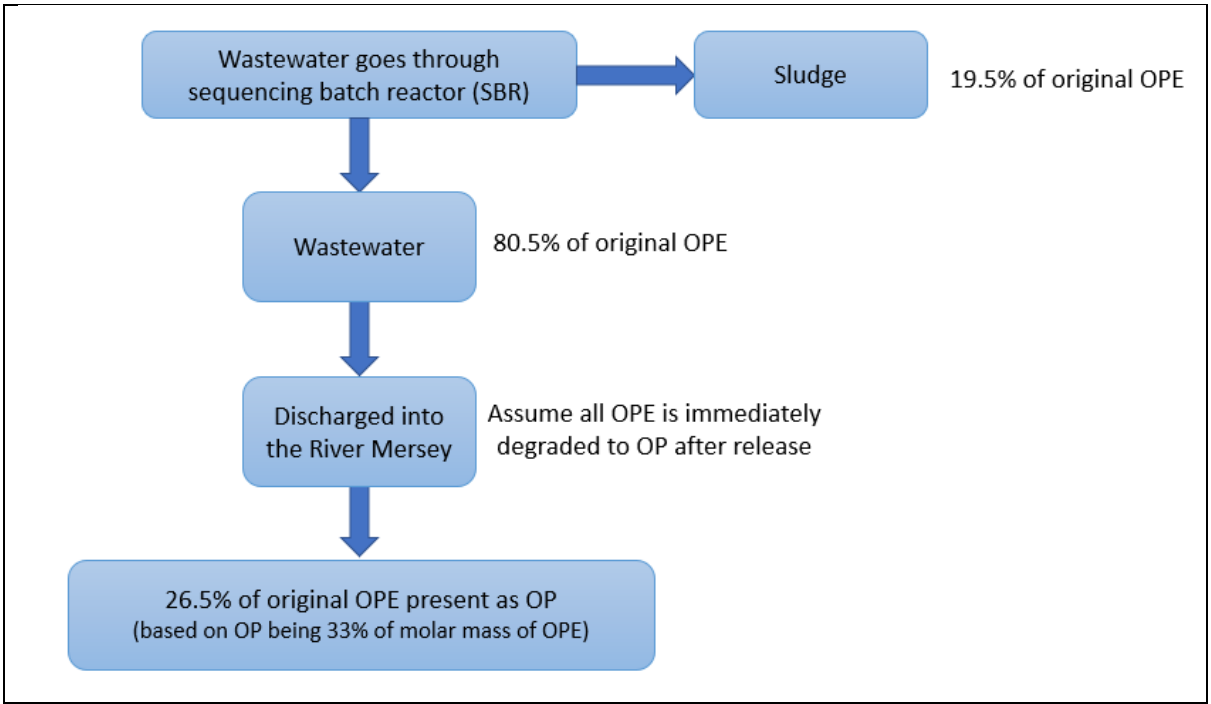

Figure 3-9: Treatment of wastewater at municipal STP in Liverpool

The following table summarises emission factors that have been used in the CSR for the estimation of releases of OPE/4-tert-OP to the environment that are associated with the use of Triton™ X-100 in the Applied for Use.

Table 3-14: Key emission parameters for the estimation of environmental impacts under the "Applied for Use" Scenario

Emission parameter		Use #1
Number of release days per year (2021) – decreasing thereafter		#B
% of consumed Triton™ X-100 released to water (as 4-tert-OP)	Current (Q1 2019)	**26.5%**
	Sunset Date and later	1% x 26.5% = **0.265%**
% of consumed Triton™ X-100 released to sludge (as 4-tert-OP)	Current (Q1 2019)	33% x 19.5% = **6.5%**
	Sunset Date and later	1% × 6.5% = **0.065%**
Is sludge applied to agricultural soil?		No

Estimated releases of 4-tert-OP under the "Applied for Use" Scenario (2021-2029)

The total emissions of 4-tert-OP to the environment under the "Applied for Use" Scenario are shown in **Table 3–15** and reflect the introduction of additional RMMs (segregation of Triton™ X-100-containing wastewater and incineration) which will occur before the Sunset Date which will reduce releases compared to the present situation by over >99%. As sludge is not applied to agricultural soil, only releases to the aquatic environment are of relevance to the present analysis. The releases to the aquatic environment account for a total of ca. #G (range: 0.1-1) kg over 9 years.

Table 3–15: Estimated environmental releases of 4-tert-OP as a result of the continued use of Triton™ X-100 in Llanberis

Year	OPE amount used (kg)	% of previous year	4-tert-OP releases to aquatic environment (kg/y)	4-tert-OP releases to sludge (kg/y)
2018	#A	#A, C		
2019				

Table 3–15: Estimated environmental releases of 4-tert-OP as a result of the continued use of Triton™ X-100 in Llanberis				
Year	**OPE amount used (kg)**	**% of previous year**	**4-tert-OP releases to aquatic environment (kg/y)**	**4-tert-OP releases to sludge (kg/y)**
2020	[redacted]	[redacted]		
2021	[redacted]	[redacted]	#G, H	#G, H
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]
		Total, 2021-2029	**[redacted] (range: 0.1-1 kg)**	**[redacted] (range: 0.1-1 kg)**

Latest research values for ecotoxicity

Table 3-16 provides the relevant latest research values on the ecotoxicity of 4-tert-OP for each of the environmental domains, as presented and discussed in the CSR. The figures in the table are only provided for comparison and orientation purposes.

Table 3-16: Latest research values (as presented in the CSR)	
Environmental domain	**Latest research values**
Freshwater sediment (Mersey transitional waterbody)	28 µg/kg dry weight
Mersey estuary long term (Mersey transitional waterbody)	0.034 µg/litre
Irish Sea - water	0.0034µg/litre
Irish Sea - sediment	0.28 µg/kg dry weight
Soil	5.6 µg/kg dry weight

Predicted environmental concentrations

Table 3-17 provides the predicted local concentrations of 4-tert-OP in the **local and regional environment** over the requested review period 2021-2029, as presented in the CSR. All values provided (for the year 2021) are well below the respective latest research values shown in **Table 3-16**. These figures consider the significant reduction in releases that will be achieved by the introduction of additional RMMs before the Sunset Date (NB. the CSR also presents PEC values without taking into account the effect of the additional RMMs; these are 100 times higher than what is shown overleaf).

Table 3-17: Predicted environmental concentrations, local and regional in 2021			
Compartment	**Latest research value**	**Local PECs**	**Regional PNECs**
Fresh water	0.034 µg/L	[redacted]E-6 mg/L	[redacted]E-10 mg/L
Sediment (freshwater)	0.028 mg/kg dw	[redacted]E-4 mg/kg dw	[redacted]E-7 mg/kg dw
Marine water	0.0034 µg/L	#G (Table) E-7 mg/L	[redacted]E-11 mg/L
Sediment (marine water)	0.0028 mg/kg dw	[redacted]E-5 mg/kg dw	[redacted]E-8 mg/kg dw
Agricultural soil	0.0073 mg/kg dw	[redacted]E-11 mg/kg dw	[redacted]E-11 mg/kg dw
Post-2021 trends		Significant decline throughout review period	Significant decline throughout review period

For both the local the regional exposure scenarios, the calculated environmental concentrations for the period 2021-2029 when the additional RMMs (segregation and incineration of wastewater) are taken into account are lower than the latest research values thus adverse effects for water and sediment organisms are not probable. On the other hand, it should be noted that it was not possible to derive a safe level excluding endocrine effects by OP for environmental organisms. Furthermore, once 4-tert-OP is bound to anaerobic sediments, it is nearly persistent and may thus expose sediment organisms or be remobilised even after the phase-out of OPEs.

Nevertheless, the estimated release and the calculation of environmental concentrations above are considered reasonable worst case. Based on the following aspects the exposure may be overestimated for the following reasons (as explained in the CSR):

- The calculated maximum use volumes of #A kg Triton™ X-100 in 2021 and the lower figures for the following years are a worst-case assumption. Events, in which these Triton™ X-100 volumes may end up in one wastewater tank, will not occur very often, if at all. Thus, the regular environmental 4-tert-OP concentrations due to discharge of Triton™ X-100 may be factor 2 or 3 lower;

- While the median net flow of the River Mersey was used for the modelling, the real dilution by tidal water will be much higher than calculated, as the Mersey Bay has a tide of about 9m. Since the release of 4-tert-OP from the use of Triton™ X-100 in Llanberis occurs maximum 3 times per week and not continuously, it can be assumed that the effective environmental concentration will be lower;

- Microorganisms present in the STP and in the local industrial environment are probably adapted to 4-tert-OP and thus environmental degradation may happen faster than considered in the CSR calculations;

- It can be assumed that the Triton™ X-100 disposed of with the wastewater is partly removed from the wastewater stream with the phosphate precipitate and thus the 4-tert-OP-load of the wastewater forwarded to the municipal STP should be lower. The effect can, however, neither be proved nor quantified; and

- The municipal STP in Liverpool is a very large and modern STP with high standards. Longer retention times than considered in the CSR calculations can be assumed and would reduce the 4-tert-OP released from the STP, while the 4-tert-OP content of the sludge will increase. Since the municipal STP sludge is incinerated, the 4-tert-OP bound to sludge will not contribute to environmental pollution.

3.3.3 Estimated 4-tert-OP stock levels in the aquatic environment

Introduction

The loadings given above indicate that of the #A kg of Triton™ X-100 that may be used per day. Using the emission factors shown for post-Sunset Date in **Table 3-14**, it can be estimated that #G kg of 4-tert-OP per kg of OPE are discharged into the Mersey transitional waterbody.

Half-lives of 8 to 54 days have been determined for 4-tert-OP in water samples within laboratory microcosms (BAuA, 2011). The following figure indicates the decay of #G kg of 4-tert-OP assuming a half-life of 8 days. It shows the amount left is approaching zero within eight weeks.

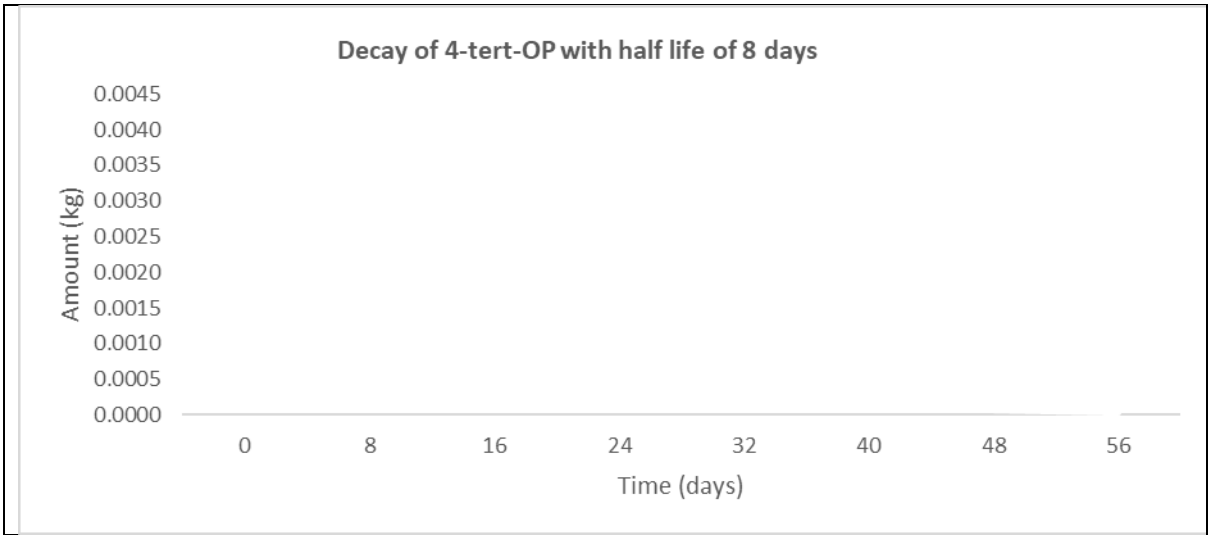

Figure 3-10: Degradation of #G kg of 4-tert-OP assuming a half-life of eight days

Stock levels of 4-tert-OP in the aquatic environment

The stock of 4-tert-OP in the environment can be considered by assuming a release of 4-tert-OP to the environment occurs every few days. This reflects the fact that the OPE is not continually discharged but is used in batches and collected prior to being taken by tanker to an industrial treatment works and subsequently discharged to the municipal treatment works.

Given that usage is anticipated to decline each year, then this decrease needs to be taken into account when considering stock levels beyond year 1. The approximate year-on-year decreases in the level of Triton™ X-100 used at the Llanberis plant for the coming years are given in **Table 3-18**. Assuming the percentage reduction in Triton™ X-100 used is the same as the percentage reduction in the amount of 4-tert-OP discharged, this results in each release containing the amount of 4-tert-OP shown in **Table 3-18**. The number of annual releases assumed is also shown and it decreases as consumption of Triton™ X-100 declines.

Table 3-18: Anticipated decrease in usage of Triton™ X-100 and release of 4-tert-OP

Year	Amount used (kg)	% change from previous year	Amount of 4-tert-OP discharged per release (kg)	Number of wastewater collections	
				Per week	Per year
2018	#A	#A, C			
2019					
2020					
2021			#G, H	#A	
2022					
2023					
2024					
2025					
2026					
2027					
2028					
2029					

The following two figures indicate the 4-tert-OP stock in the coastal and marine environment assuming a release occurs from the municipal treatment works. **Figure 3-11** indicates the stock level assuming a half-life of eight days, whilst **Figure 3-12** shows the situation for a half-life of 54 days. The figures illustrate that:

- With a half-life of eight days, 4-tert-OP stock in the environment is expected to peak at ca. #G kg. Due to degradation and declining input over the period 2018-2029, stock levels decrease to less than #G kg by end of 2029 and come close to zero by 2031; and
- With a half-life of 54 days, 4-tert-OP stock levels peak at around #G kg in 2025, but they then start to decline due to the decreasing input combined with the ongoing degradation of 4-tert-OP. By the end of 2029, the remaining stock in the environment is less than #G kg and gradually reduces to ca. 1 g by 2034.

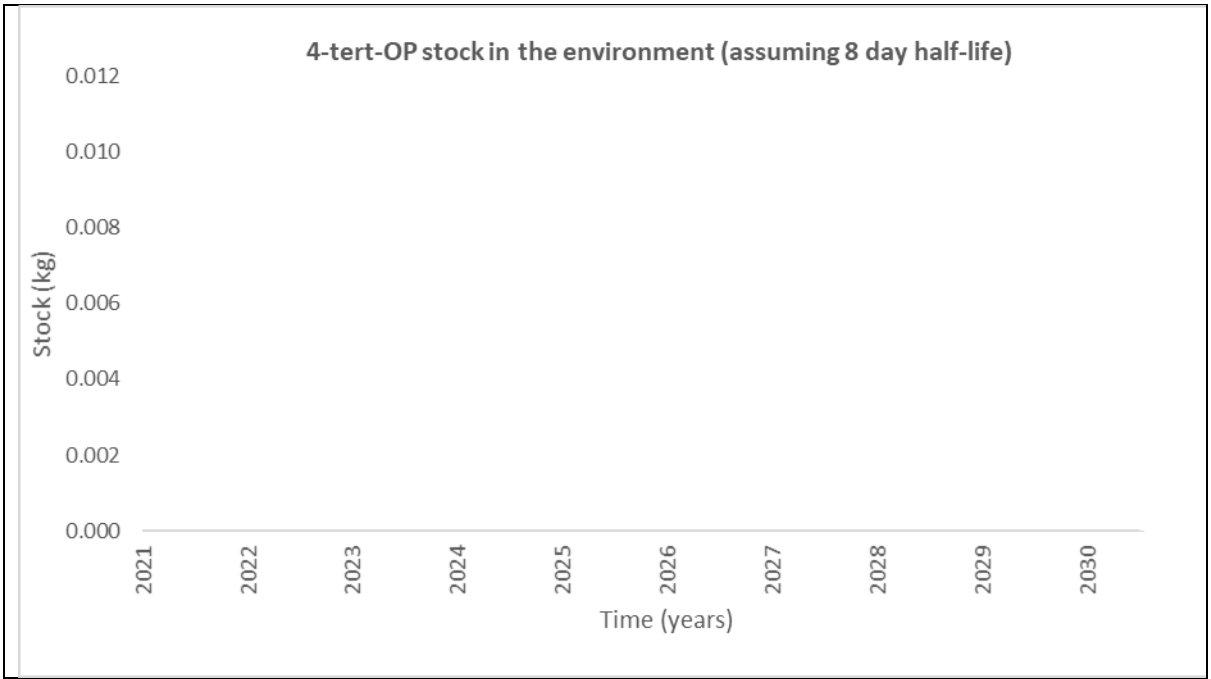

Figure 3-11: Illustrative 4-tert-OP stock in the marine and coastal environment assuming a half-life of 8 days and declining input

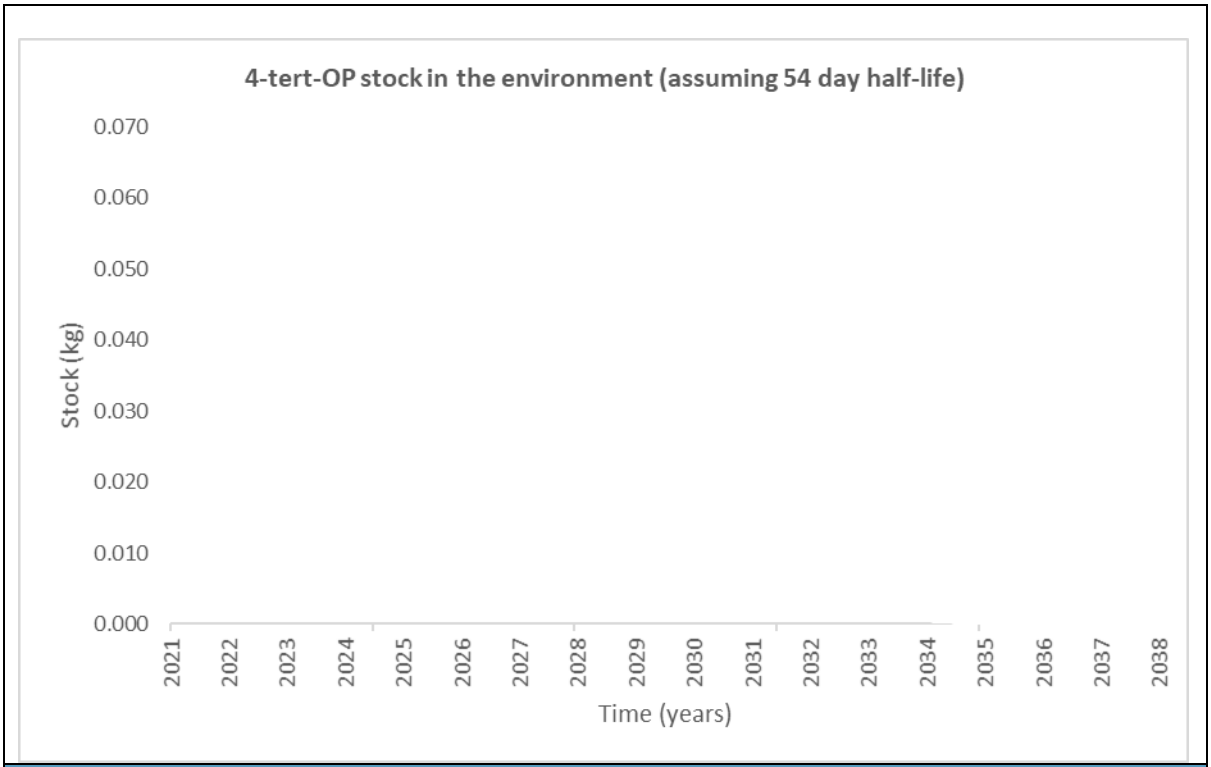

Figure 3-12: Illustrative 4-tert-OP stock in the marine and coastal environment assuming a half-life of 54 days and declining input

3.3.4 Summary

In summary, 26.5% of total OPE used is assumed to be emitted to the aquatic environment as 4-tert-OP via the municipal STP in Liverpool and post-Sunset Date a maximum of 1% of current releases will continue to occur as a result of additional RMMs that Siemens Llanberis will be implementing in the meantime. No other environmental discharges are believed to occur (sludge from the municipal STP is assumed not to be spread to land). Based on an annual usage of #A kg for 2021 (a notable decrease from the 2018 level), this equates to a total release of #G kg of 4-tert-OP to the environment. Thereafter, releases to the environment continue to decline and eventually cease at the end of 2029. Over the requested review period, the releases of 4-tert-OP to the aquatic environment account for a total of ca. #G (range: 0.1-1) kg.

Both the local and regional assessments indicate that post-Sunset Date concentrations in the water will not exceed the latest research values, the releases are not occurring every day since bead production occurs in batches and the assumptions made in the CSR are generally conservative. Therefore, average concentrations are expected to be lower than those indicated in the local assessment. As shown by the stock level curves above, total 4-tert-OP in the environment stabilises at low levels. If a half-life of eight days is assumed, then the maximum total 4-tert-OP in the environment resulting from bead manufacture is ca. #G kg. If the upper end half-life of 54 days is assumed, then 4-tert-OP stock levels peak at around #G kg prior to declining over time due to decreased usage.

3.4 Human health and environmental impacts of the "Applied for Use" Scenario

3.4.1 Human health impacts of the "Applied for Use" Scenario

As Triton™ X-100 falls under an Annex XIV entry that has been prioritised for risks to the environment (endocrine disruption), exposure of humans to the substance is not of relevance to this analysis.

3.4.2 Environmental impacts of the "Applied for Use" Scenario

The following information is reproduced from the CSR.

OPE is considered a substance of very high concern due to the degradation to 4-tert-OP, a substance with endocrine disrupting properties. OPE degrades to 4-tert-OP either already 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). Available information suggests that OPE and its close analogues contribute to the 4-tert-OP concentration in the environment.

Sediment organisms may be exposed to 4-tert-OP that results from the degradation of OPE either directly, downstream of the effluent, or in the longer term after its adsorption to sediment and soil. Similar holds true for pelagic organisms such as fish which may be exposed via remobilisation of 4-tert-OP from sediment to the water body.

Adverse effects on apical endpoints that are endocrine-mediated are considered crucial and most relevant for risk assessment of 4-tert-OP:

- **Fish**: the most sensitive NOEC value for fish from the different key studies investigated is related to reproductive endpoints (time to reach sexual maturity, egg production and fertilisation capacity) in *Danio rerio*, amounting to 12 µg/L;

- **Amphibians**: the most critical effect was influence on sexual development, materialising in sex ratio shifts (feminisation) and formation/delayed regression of oviducts in males. The study results from Porter *et al*. allow identification of a NOEC of 3.3 µg/L (Porter *et al.*, 2011); and

- **Gastropods**: the most sensitive endpoint describing effects of 4-tert-OP is the number of new embryos/eggs in aquatic freshwater snails. Since recent research has generated no valid NOEC concentration from an OECD Guideline study 242, a weight-of-evidence approach is described in the CSR aimed at identifying a NOEC for 4-tert-OP on the reproductive performance of *P. antipodarum*. Neither in the OECD 242 range-finding study nor in the experiments conducted in the context of an UBA validation study statistically significant effects could be observed at 1 µg/L nominal concentration. The corresponding lowest measured concentration of 0.34 µg/L has identified as the NOEC in a reasonable worst-case approach. Since this is the lowest NOEC value, 0.34 µg/L is used for the derivation of the latest research values for the risk characterisation.

4-tert-OP concentrations calculated for the local aquatic compartments and sediments are similar or slightly below the latest research values for risk characterisation, as shown in the CSR. Thus, risks for aquatic and sediment organisms cannot be excluded. According to the review of available data (see Section 7 of the CSR) the most sensitive endpoints describing effects from exposure to 4-tert-OP have been observed for gastropods and the number of new embryos/eggs. While the latest research values

have been derived based on the related NOEC, this cannot be considered a no effect concentration at all. Other endocrine effects on aquatic and sediment organisms at even lower concentrations cannot be excluded.

It is noted however that Siemens Llanberis consumes a low and diminishing volume of Triton™ X-100 (projected to be #A kg in 2021) and the annual releases of 4-tert-OP to the aquatic environment can be estimated to be #G kg in 2021 (taking into account the additional RMM to be implemented before the Sunset Date) and decreasing thereafter. The stock levels of 4-tert-OP in the environment are particularly low with a maximum level associated with Siemens Llanberis' use of Triton™ X-100 of #G kg, depending on the half-life of 4-tert-OP assumed.

4 Selection of the "Non-use" Scenario

4.1 Efforts made to identify alternatives

4.1.1 Research and development

The identification and implementation of an OPE alternative, or several combined alternatives, as a substitute in an existing commercial IVD product is an intensive, technically-challenging and time-consuming task requiring strict adherence to legally-required quality management procedures – involving extensive feasibility testing, product validation, commercialisation activities and regulatory approvals granted in each country where sold.

In this section we will describe the following processes:

- **Changing the Design of an IVD Product** - The technical considerations and methodology, also the regulatory processes which must be followed in order to change the design of an IVD Product, which would be relevant to the buffer formulations required for #D bead manufacturing operations.
- **The Challenging Nature of Identifying an Alternative Substance to OPEs –** A description of the upfront technical challenge and those which can be expected to arise as part of design change.
- **Developing and Implementing a Substitution Strategy** – A description of the plan Siemens Healthineers has mobilised to phase out OPEs from its IVD products.
- **Past and Current Research and Development** - Efforts made in recent years by Siemens Healthineers to identify OPE alternatives for use in its OPE-containing products.

It is important to note that, as previously explained in this document, Siemens Healthineers manufactures a #D number of products and thus formulations containing OPE. These products are used across many different IVD products performing a variety of functions, and therefore the technical and regulatory processes and challenges vary between projects to change the design (i.e. the formulation) of different products. While every design project must move through certain prescribed steps, there are some steps which will only apply in some cases. As such, we endeavour to present a 'typical' route below whilst also highlighting difficulties which could arise in some projects and thus affect the success and/or timeline of those projects.

Changing the Design of an IVD Product

Each product-line operated within Siemens Healthineers has a dedicated 'Product Health Team' (PHT) with representation from different functions across the business. This team assesses and verifies whether the design of a commercialised IVD Product must be changed, weighing this against other business needs and priorities. When it is agreed by the PHT that the design of a commercialised IVD Product must be changed, such as to substitute OPEs, a Design Change Project can be initiated.

When changing any aspect of an IVD Product's design it is vitally important that stringent and standardised steps are followed to ensure that any changes do not affect the performance of that product. For example, it is vital that a product which offers a diagnostic test for tumour markers must continue to detect those tumour markers within the same stated performance parameters to ensure each patient receives an accurate result, no matter what change was made. It is a legal requirement to have these procedures in place and to document that they are always followed.

The project process is stringently proceduralised, with this procedure subject to thorough audit by relevant regulatory authorities. To ensure day-to-day adherence to the procedure, there are many layers of internal approval by subject matter experts within the business, with every step documented, and which are also checked methodically through audit by regulatory authorities and as part of regulatory submissions.

The phases of a Design Change Project are shown in **Figure 4-1**, this captures the steps which are undertaken to develop a new product, and then the steps that must be taken in terms of changing a design post-commercialisation (grey box), as is the case with many of the Siemens Healthineers OPE-containing products.

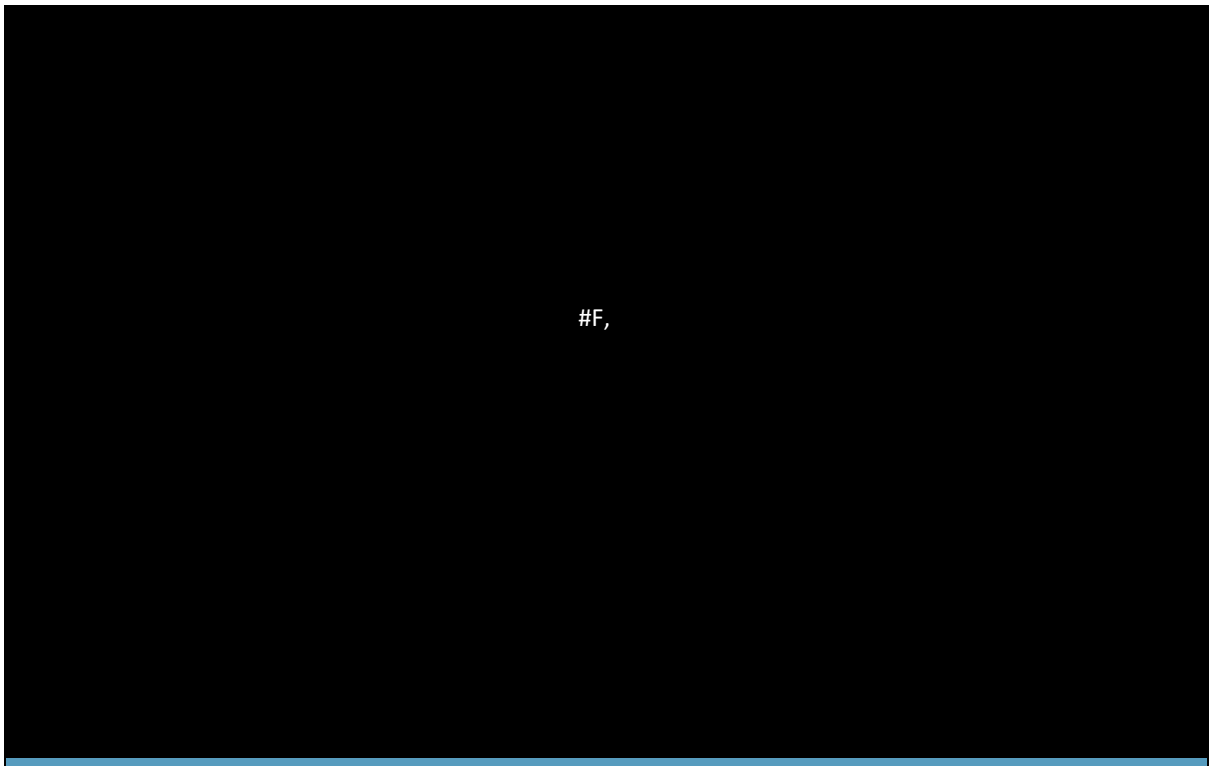

Figure 4-1: Product Design and Design Change Process Steps

It should be noted that the initial work to identify alternatives which will be tested as part of a Design Change Project is done prior to embarking on the 'Define' phase of the project (**Figure 4-2**). As previously noted, the efforts already made by Siemens Healthineers to identify potential alternatives are described later in this section and examples given of the Design Change Projects already underway to substitute OPEs in specific projects.

The different activities involved in each phase of the process are shown in **Figure 4-2**.

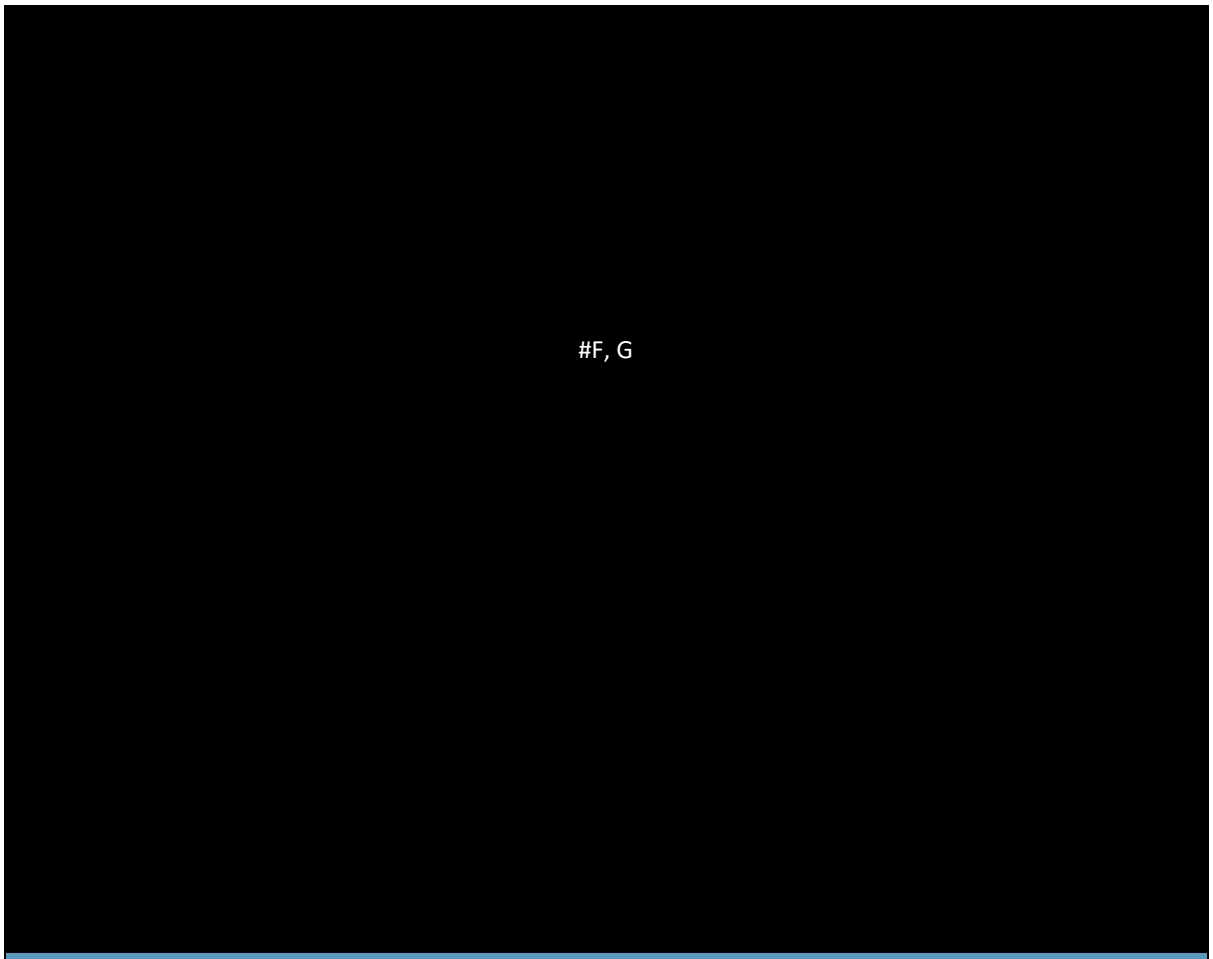

Figure 4-2: Activities involved in the different stages of a Design Change Project
Acronyms are –
DMR – Device Master Record
CRB – Change Review Board
CIA – Change Impact Assessment
DHF – Design History File

Each of the activities listed in **Figure 4-2** are specifically set out in the Siemens Healthineers extensive governing procedure for Design Change #F), and which itself has 31 supporting documents to direct and support the responsible personnel through each task in a prescribed way which can be clearly tracked and documented.

Each stage of a Design Change Project will typically involve resources from a range of business functions including Quality Governance, Quality Management, Marketing, Product Portfolio Management, R&D, Technical Operations, Procurement, Manufacturing and Regulatory Affairs; also potentially Engineering, Logistics and EHS.

In the case where a fundamental design change is undertaken, such as the change of a substance used in the formulation itself (as in the case of OPEs), the Feasibility Stage of a project is key in testing the efficacy of any alternative substance. The steps undertaken by R&D personnel in this phase are shown in **Figure 4-3**.

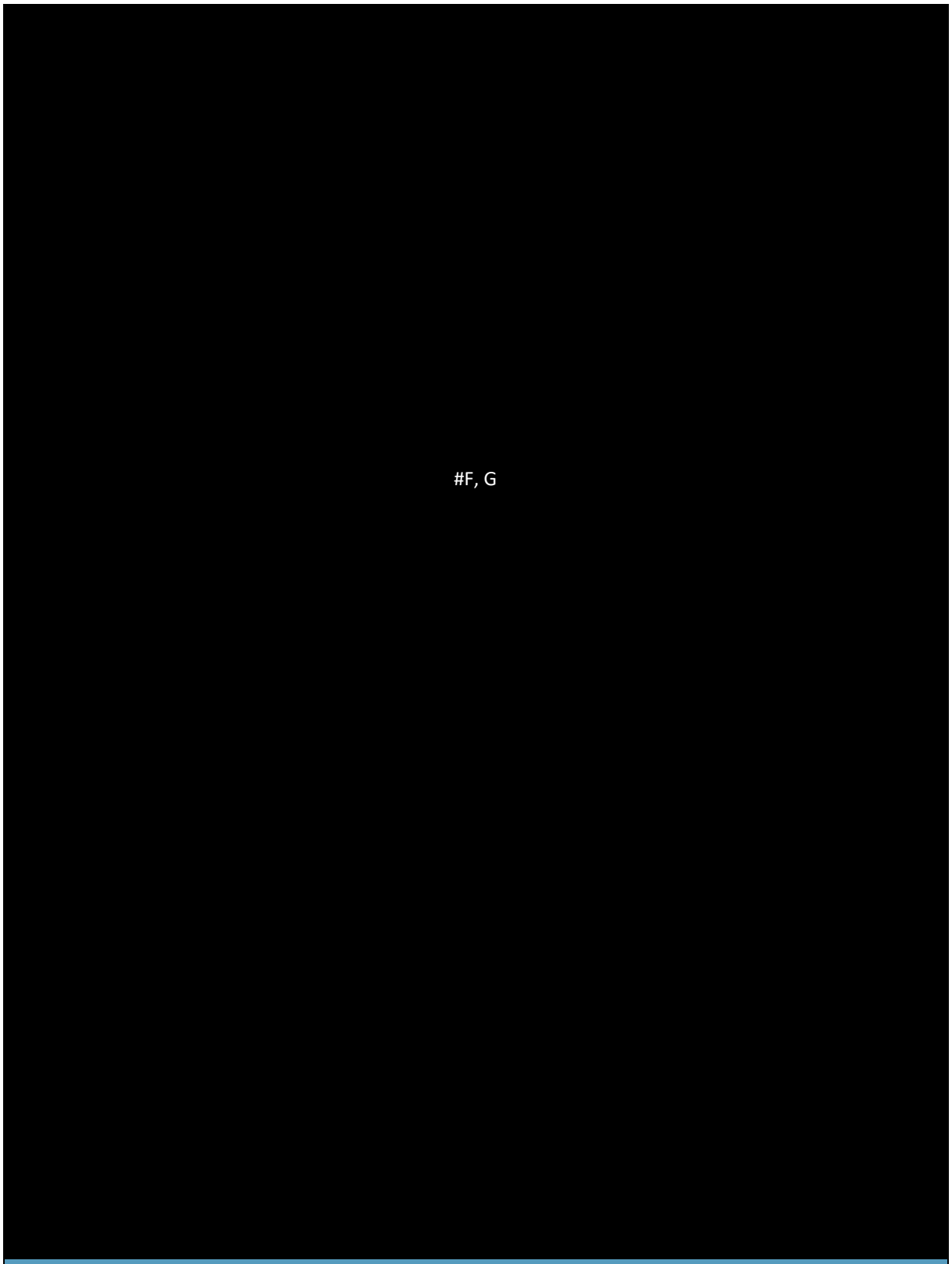

Figure 4-3: Feasibility Stage Design Phase

As noted in **Figure 4-2,** regulatory assessments must be performed to determine if the planned change will need to be submitted for regulatory approval. Depending on the assay and the extent of the planned change of design, a regulatory submission will be prepared.

Generally, at Siemens Healthineers, the process of preparing an application for the regulatory re-registration of an IVD kit and submitting it to the relevant authorities includes the following steps:

1. A Change Project initiated by the central Siemens Healthineers change team (PHT);
2. An Initial regulatory assessment is prepared by the Regulatory Affairs (RA) function;
3. A Product Change Notification is sent to all Country RA representatives to inform them of the change and request feedback on registration impact and supporting document needs;
4. The Product Change Notification feedback is then consolidated and provided back to the central change team to incorporate requirements into project planning;
5. The RA representative reviews the change verification plans and reports and prepares and collects the requested documentation to support each country's re-registrations. The Regulatory Assessment is updated based on the verification results and the Country RA feedback; and
6. Each Country RA representative prepares the applications to be submitted to their regulatory Authority. Q&A between Country RA and Headquarters RA would follow as needed to generate the required submission content.

Siemens Healthineers typically allows #B months for submission preparation in each country, this time could be exceeded if country resources are not immediately available due to other business priorities. There are about 80 countries with re-registration requirements and submission requirements to each country vary. If there are performance changes, most countries will require a re-registration; a change in formulation may require a new 510(k) in the USA and re-registration in many countries. If there is no performance change, some countries may still require re-registration due to an Instruction for Use (IFU) change related to composition. Importantly, all performance claims need to be verified. Siemens Healthineers estimates that re-registrations would generally be required in approximately 50 countries. This estimate is based on the fact that about 80 countries have applicable regulatory requirements and 31 work under EU regulations (27 EU Member States and 4 EFTA Member States). The actual number will vary because it is dependent on the number of countries where each IVD product is placed on the market.

Table 4-1 gives a non-exhaustive overview of the most important IVD regulations around the world and the timelines that are associated with a (re-)registration of an IVD-product. In China [8], one very important market, the registration of an IVD product requires 42 months, which represents the worst case; in other regions/countries, re-registration takes between 0.5 and 2 years. It should be noted that re-registration would be required in parallel in each region where #D analysers are operated.

[8] One time constraint here is China where re-registration can take 2-3 years. In China, type testing needs to be performed in accordance with the China Product Standard or the Product Technical Requirements (PTR, 3 different reagent lots; the product must be approved in either the country of the legal manufacturer or the physical manufacturer; ISO Certificate; Legal Agency Authorization Letter; Declaration of Authenticity; Declaration of Conformity for China Regulations and Standards; Instruction for Use; Outer box Label; English Product Technical Requirements; Explanation Letter For Any Inconsistency; Performance Evaluation Report and Technical Documents for Assays; Risk Management Report; Product Summary; Clinical Trial / Study Data / Method Comparison).

Overall, the entire re-registration process can be expected to take up to #B, or ca. 4 years.

Table 4-1: Worldwide IVD regulatory impact on OPE substitution timeline (non-exhaustive list of regulatory timeframes by country)			
Region	**Country**	**IVD Legislation**	**Estimated timeframe for a new product registration to be granted (in months, unless specified)**
EU & EFTA	EU countries	IVDD (87/79/EC)/ IVDR (EU 2017/746	1-6
North America	USA (including Puerto Rico)	Code of Federal Regulations (21CFR.807.81) (21CFR.814)	Class 1 or 2, Reserved (510k): 6-12 Class 2 (510k): 6-12 Class 3 (PMA/Periodic reports): 9-12
	Canada	Canadian Medical Device Regulation SOR/98-282	Class I: N/A Class II: 1 Class III: 6-8 Class IV: 12
Middle East	Russia	Roszdravnadzor Resolution No 1416	12-20
	Saudi Arabia	Saudi Food & Drug Administration - National Provisions and Requirements for Medical Devices	3
	U.A.E.	Medical Device Registration Guideline (2011)	1
Asia Pacific	Japan	Pharmaceuticals and Medical Devices Act	Class I: N/A Class II: 6 Class III: 6 - 24
	India	Drugs & Cosmetic Act and Rules	Notified: 9 Non-Notified: 3
	China	Administrative Measures for the Registration of In Vitro Diagnostic Reagents (CFDA Order No. 5 2014)	42
	Thailand	Medical Device Act 1988	General Medical Device: 1-2 Notification Medical Device: 12 Licensed Medical Device: 16
	Philippines	Administrative Order 2018-0002	9 - 12
	Australia	Therapeutic Goods Act (1989)	Class 1: 2 - 4 weeks Class 2: 4 - 6 weeks Class 3: 6 weeks - 6 months Class 4: 9 - 12 months
	Singapore	Health Products (Medical Devices) Regulations 2010	6 - 9
	Taiwan	Regulations for Governing the Management of Medical Devices	Class 1: 3-6 Class 2: 8-18 Class 3 with predicate device: 12-18 Class 3 new device: 18-24
	Vietnam	Circular 44/2014/TT-BYT and Circular 47/2010/TT-BYT	6 - 8
Latin America	Mexico	In Vitro Diagnostic Devices (IVDs): Rules 19 and 20	18
	Brazil	IVD regulation RDC 36/2015	Class I: 3-6 Class II: 3-6 Class III: 9-12 Class IV: 9-12

When taking into account the time for re-registration of product, the full Design Change process can take 5-12 years, however this can alter dependent upon the particular challenges which arise in relation to each project.

The Challenging Nature of Identifying an Alternative Substance to OPEs

There are some key factors to take into consideration when discussing the technical challenge faced by Siemens Healthineers in changing the design of its OPE-containing products -

- Each IVD formulation is designed to test for a different disease or condition and is therefore designed to interact with a different 'shape' molecule which is biologically variable;

- As an analogy – It is like manufacturing many different jigsaw puzzle designs, except the inter-locking pieces are microscopic and there are dynamic biochemical reactions happening between them and their environment which can prevent them from inter-locking and cannot always be predicted;

- An IVD product is typically a collection of raw materials and different components (the reagent formulation, a solid phase [such as a bead], controls and diluents) designed to interact with a patient sample (or in the case of a control act as a standardised sample). Each of these interact with each other and other mixtures used on the analyser such as wash solutions or substrate. Therefore, any change in design must be proven not to affect the interaction with any other raw material or component, or the patient sample itself;

- For the reasons above and the different functions OPEs mediate across the impacted portfolio we know there will be no 'one size fits all' alternative – Design Change work already undertaken has also proven this (this work is described further later in this section);

- Testing must be done on a 'per formulation' basis. While the substitution strategy described later aims to group similar or high priority products in the same project, there are no short-cuts in terms of feasibility testing. Each design of each product must be subject to its own set of feasibility testing often with a different set of OPE alternatives;

- The successful alternative cannot be known upfront. While technical feasibility criteria can be used as a guide, alternatives are primarily selected on an empirical basis and it is only through 'trial and error' testing with each identified alternative on a 'per formulation' basis that a successful alternative can be identified in the case of each IVD formulation design; and

- The impacted range of products which use OPE is significant in terms of numbers - within the [redacted] portfolio [redacted] formulations (analyte beads) use OPE (and [redacted #D (bullet point)]) and within the wider Siemens Healthineers portfolio [redacted] formulations use OPE (representing [redacted] products), the scale of the project-work and resources required to phase out OPEs is a significant undertaking and requires skilled coordination across functions, countries and [redacted] analyser platforms and extensive collaboration in terms of technological knowledge in R&D.

These factors are discussed in more detail over the following sections.

Each design is different and subject to biological variability

A significant technical challenge in substituting OPEs in an IVD reagent or a formulation used to manufacture an IVD product (such as in the case of a bead buffer formulation in scope of this AfA) is presented by the variability at the molecular level within each IVD design.

Each Siemens Healthineers platform is based on its own core technological principle or 'template', and each formulation used within that platform is unique in its biochemical function & design. This is because each formulation is biologically variable, i.e. the analyte to be detected is specific to the disease/condition it represents.

It is not possible to predict prior to testing an alternative what interaction it will have at the molecular level with the other biological and chemical components in the buffer solution and what effects, other than its intended function, it may cause and thus interfere with the final test result. See **Figure 4-4** for the description of a typical immunoassay 'Sandwich ELISA' reaction and a description of where OPE features in the case of an #D IVD Product.

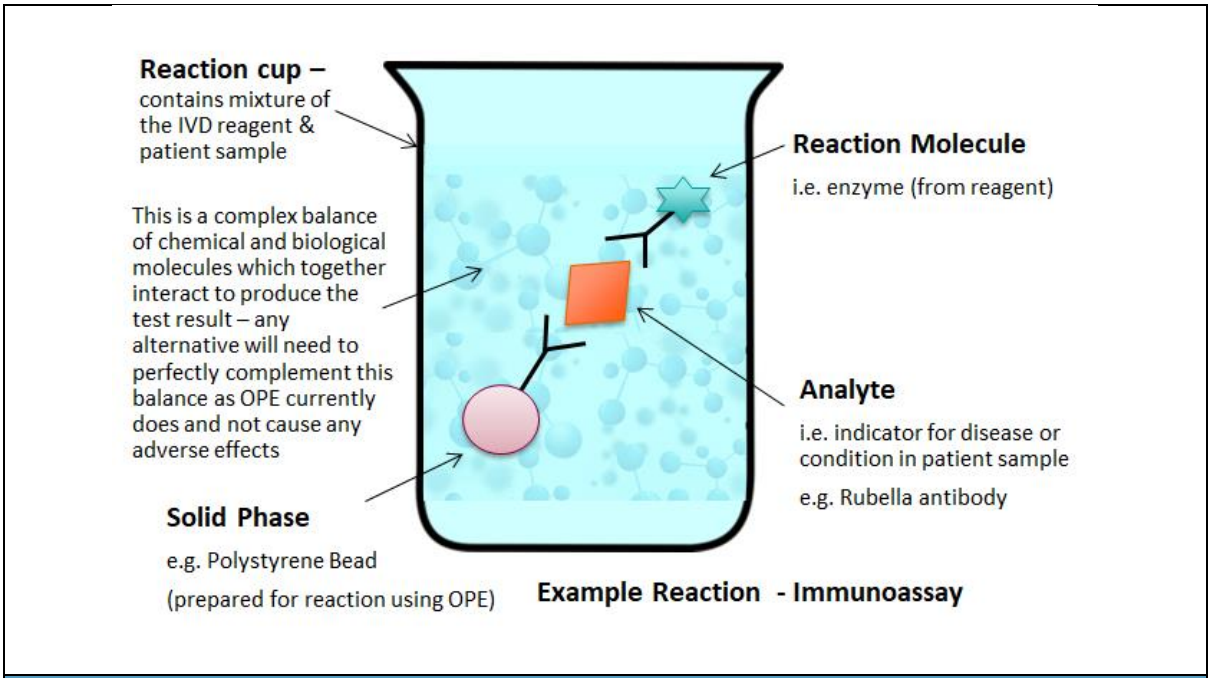

Figure 4-4: Example of the reaction in an immunoassay test
In the case of an #D IVD product where the OPE is used to bead coating and washing, OPE has a specific role in terms of ensuring that the Solid Phase adequately facilitates the detection reaction in the cup.
NB. When referring to IVD products within the wider impacted Siemens Healthineers portfolio, OPE is typically found in the IVD reagent itself.

Reaction at the molecular level

To describe the reaction shown in **Figure 4-4** in more detail, each individual IVD formulation is designed to detect a different target molecule, known as an 'analyte', in a patient sample that serves as an indication for a certain disease or physiological status, e.g. an antibody or antigen. Each analyte is detected by making use of highly specific detection molecules, which are normally proteins that have a specific binding site for the analyte. Often these are antibodies, hormone receptors, or similar proteins that can bind analytes with a high specificity. The specificity of these types of molecules is based on their potential to bind to biological structures following the lock-and-key principle. This means they have a 3-dimensional protein structure that fits to a particular complementary structure

on the surface of the target analyte. These complexes can then be used to quantify the analyte in the patient sample. For #D, this involves the initiation of a reaction which directly releases light which can be measured by the analyser.

Maintaining the balance of the design

R&D personnel are acutely aware that changing any aspect of an IVD product's fundamental design can move the test out of balance and produce erroneous results. This is another reason for the extensive Design Change Project process, which is itself designed to ensure that a change is only implemented where continued reliable performance of the test can be fully verified.

Each IVD reagent or buffer formulation contains a different set of raw materials at specific volumes and concentrations which have been thoroughly tested and proven to interact in a perfect balance in order to detect a specific analyte, i.e. disease or condition. It is important to note that the concentration of OPE and the other constituents in each IVD reagent formulation have been specifically optimised via the extensive feasibility testing conducted during their initial product development, and are typically slightly different across the various IVD product designs. Variations in the OPE concentration as small as 10 ppm range, i.e. ca. 0.001%, may affect the specificity and sensitivity of the test.

OPEs, when used to optimise the performance of a certain attribute of an IVD formulation, may also maintain a fine balance regarding the optimal performance of another attribute within the same formulation. Thus, replacing OPE with another substance may move the formulation out of balance and cause inadvertent reactions which cannot be predicted.

Possible analogies which could be used to illustrate this scenario are as follows:

1. Exchanging enzymes in biological washing powder – the new enzyme cleans as effectively but inadvertently causes colour-loss

2. Two people use the same soap, both are clean but causes sensitisation in one person because of biological variability – this reaction cannot be predicted prior to effect.

As stated previously, OPEs in the #D bead washing buffer solutions act as a cleaning agent for the removal of impurities from the #B surface of the beads, while OPEs in the bead coating buffer solutions act as a stabiliser for specific biological materials coated on to the surface of the bead. If reformulation work was undertaken with these products, any alternative substance would have to be proven to fulfil these functions while not having any adverse effect on the physical and biological functions of other constituents. Performance must be proven beyond a doubt through 'trial and error' testing in the feasibility stage, followed by validation and verification activities which often involve real-time stability testing matching the shelf-life of the product, before any commercialisation activities can commence. The timelines associated with this are extensive and described elsewhere in this section.

In summary,

- Substituting OPEs with a feasible alternative may maintain the performance the OPE intended to facilitate, however may inadvertently decrease the performance of another attribute;

- It is not possible to predict prior to testing an alternative what interaction it will have at the molecular level with the biological and chemical components in the buffer solution or

subsequently in the reaction cup, and what effects, other than its intended function, it may cause and thus interfere with the test result;

- Feasibility work to identify suitable alternatives must investigate all areas of performance and involves substantial 'trial and error' testing activities to identify any potential inadvertent reactions; and

- The feasibility studies required are extensive and must demonstrate the same performance level of the overall IVD product (as defined by product design requirements and stated product claims, e.g. precision and sensitivity).

Additional Consideration – #D Wash Solution

The technical challenge described above also applies to the [redacted] solution which, while not being in scope of this AfA as it is manufactured at Siemens Marburg and subject to a separate AfA, is highly relevant to this AfA as all #D (paragraph) IVD Products (including those in scope of this AfA) must be used with this product on the [redacted] range of analysers.

IVD wash solutions such as the #D (paragraph) [redacted] are typically used on analysers as a cleaning and/or rinse agent between tests. As there could be residues from the [redacted] formulation retained on the analyser system which then interacts with the chemical and biological constituents of the reagents used in the IVD formulations which perform the tests, any change in the design of an IVD wash solution must be tested with every single IVD product used on that analyser to demonstrate that there is no adverse effect on each product's performance. If testing shows that any single IVD product is adversely affected then feasibility testing with another alternative must be initiated and the process repeated.

No 'one size fits all' alternative

Given the wide range of functionalities that OPEs mediate in IVD products, it is certain that there is no 'one size fits all' alternative which could be successfully substituted in every IVD Product in scope of this AfA (#C #D analyte bead formulations), and certainly not across the wider impacted Siemens Healthineers portfolio. An adequate substitute for one functionality will often lead to poorer performance for another key functionality, as demonstrated in the alternative testing activities already conducted by Siemens Healthineers and further described in the text later in this section entitled 'Past and Current Research and Development'.

This is further demonstrated by the fact that other detergents are already in use in IVD products within the Siemens Healthineers portfolio and across the industry, this is because they have proven to be the most effective detergent substance of all those tested for the particular IVD product design they are used in. Just as OPE has proven itself to be effective in the IVD product designs in which it is currently used, Triton™ X-100 has historically been very effective in a wide-range of applications, hence its use in the large number of Siemens Healthineers products. However, this detergent does not work in all IVD kits that follow the exact same test principle regarding the test set up and detection method. Once again, this is based on the need for different target and detection molecules.

The development of an IVD product involves a high degree of empirical observations as it is not always possible to determine the substance property or a set of substance properties that are responsible for the particular function that needs to be realised. Some physicochemical properties, such as those listed in Section 3.1, can be used as indicators that a potential alternative detergent might qualify as an alternative and that makes them a candidate for further empirical studies.

This means that 'trial and error' testing of a range of alternatives must always be performed on a 'per formulation' basis to prove the efficacy of an alternative in its intended function while not causing the adverse reaction with other molecules already described.

Technical Resource Challenge – Wider Portfolio

When taking into consideration the wider Siemens Healthineers product portfolio (including all products in scope of this AfA and the other Siemens Healthineers linked AfAs), the technical challenge increases in scale and complexity.

As noted, each platform is based on its own core technological principle or 'template', and each formulation used within that platform is unique in its biochemical function & design. Typically, R&D personnel are allocated to and specialise in specific technologies within the business. With over #C IVD products (representing #C formulations) affected across #C analyser platforms the technical challenge in terms of initiating multiple Design Change Projects with only a certain availability of technical resources significantly increases.

This limitation, along with a number of other factors described in this section in terms of Design Change Project requirements and timelines, also the anticipated life-cycle of platforms and specific products, has been taken into account when developing the Substitution Strategy for phase out of OPE's. This strategy is described in the following text.

Developing and Implementing a Substitution Strategy - The 'REACH Response Plan'

As noted previously, the Siemens Healthineers product portfolio is #C by the inclusion of OPEs on the REACH Authorisation list. As well as the technical challenge described in the preceding text, transitioning to alternatives requires significant investment in terms of monetary spend, the time and technical resource required to complete Design Change Projects, regulatory registration requirements and other commercialisation activities.

As a result, in order to develop a thorough and appropriate substitution strategy, Siemens Healthineers has conducted a full analysis of the impacted product portfolio and launched what is known internally as a 'REACH Response Plan'.

A key strategy in regard to this plan is that all OPE-dependent products which are connected to the platform (e.g. , & products where the same reagent formulations are used on the #D (paragraph) platform) or which are expected to have a longer life-cycle[9] are being given the highest priority in terms of Design Change, and plans to reformulate these products are underway on a per product basis. Other products, such as those within the platform, which will over time be replaced by the , for evident reasons and as described above, are being given a lower priority. Another key objective of the Siemens Healthineers REACH Response Plan is to ensure that the transition to alternatives for OPE-dependent products with a longer life-cycle, like the more numerous IVD kits produced by Siemens Marburg in Germany, will be prioritised so as to ensure that the products with the highest potential for emissions to the environment (due to their number and

[9] For example: #D analysers which are relevant to the Siemens Marburg Downstream User AfA.

long life-cycle) become OPE-independent as soon as possible, thus minimising OPE environmental emissions.

An overview of the full Siemens Healthineers 'REACH Response Plan' is shown in **Figure 4-5**.

Past and current research and development

In 2012, Siemens Healthineers initiated work to establish the role of OPEs across its global portfolio and pursue the identification of potential alternatives which could be used in its IVD kit reagents and wash solutions. With the knowledge that OPEs were widely used across the global operating units and supply chains, 3 main work-streams were initially identified and initiated:

1. The identification and quantification of OPEs used across the global operating units and global supply chains
2. The development of a strategy to prevent the use of OPEs in any new product development
3. The identification of alternative surfactants which could be used in new product development and potentially in any future re-design of existing products.

These are further expanded below.

1) Identification and quantification of OPEs across Siemens Healthineers

The initial project to identify the uses of OPE throughout the global operating units and supply chains was significant, to not only confirm the uses and concentrations of OPE at or greater than 0.1% across a portfolio which includes thousands of saleable products, and which are often combinations of various liquid components, but also the use of OPEs in any raw materials from suppliers or OEM partners. This work took 6 months to complete, across all business-lines, and with many updates, additions and amendments made in the years following. This project ultimately identified the use of OPEs in more than #D saleable products, representing #D formulations of IVD kit reagents and IVD wash solutions.

2) Development of R&D strategy to prevent use of OPEs in new product designs

A global R&D policy was implemented in what was originally the CAI (Chemistry, Automation & Informatics) business division (representing the majority of uses of OPE) to ensure that no diagnostic IVD method achieving final design status post-2013 would contain OPEs. This approach was incorporated into the company's Product Development Process (PDP) and successfully implemented at a global level in the relevant R&D programmes. A communications programme was initiated, with a senior R&D Director in the CAI division given responsibility to ensure that all R&D personnel were aware of the status of OPEs, the policy that they were no longer to be used in any new product-design, and an introduction to identifying suitable alternatives when initiating a Product Development Process (PDP) project. This latter part tied in closely with the third work-stream, the identification of suitable surfactant alternatives.

Detailed examples of the subsequent R&D projects undertaken to replace OPEs in newly-designed products and in existing products are described later in this section.

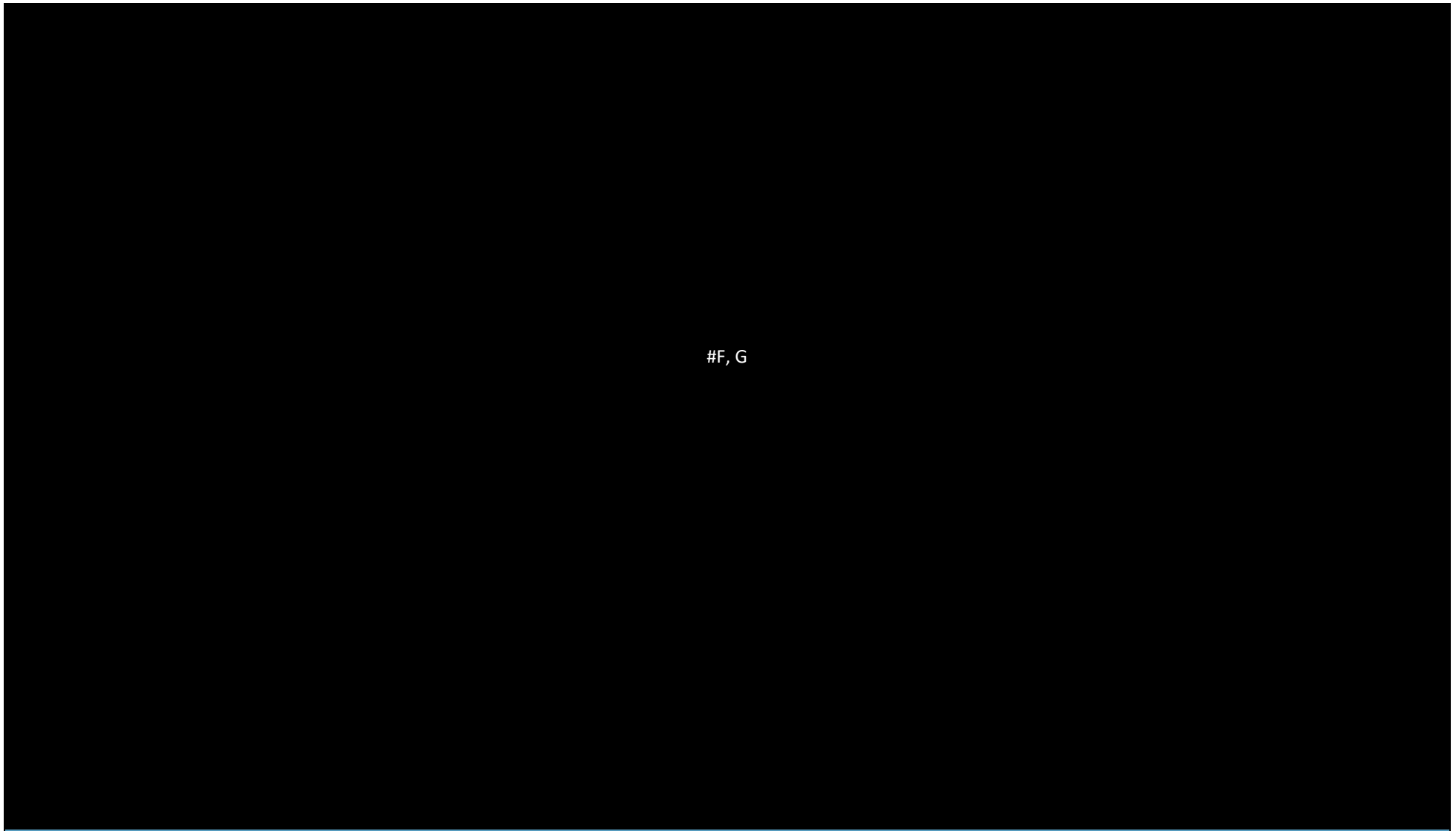

Figure 4-5: Siemens Healthineers REACH Response Plan overview

3) Identification of alternative surfactants for use in IVD products

To support the above policy and to support anticipated future work to phase out OPEs from existing products through re-design, work was initiated to identify surfactant alternatives. It was the assumption at the outset that given the #D of products affected, and the range of functions that OPEs perform across the global portfolio, a selection of potential alternatives would need to be identified. Subsequent research has confirmed that there is no single alternative which is suitable as a replacement for OPEs in every new or existing IVD product.

Also, given the significant and strictly regulated protocol that must be followed in order to re-design any existing IVD Product, a process which can take 5-12 years (a typical duration of 8 years may be assumed) to complete per product design, it was recognised that any alternative surfactant needed to be 'future-proof' in terms of having a low likelihood of being restricted or subject to Authorisation under REACH, or under any other regulatory chemicals framework in the #C, D that Siemens Healthineers ships health care diagnostics products to.

Within this work-stream, and taking into account the above recognised factors, the following work was undertaken:

- Consultation was undertaken with the US Environmental Protection Agency (EPA) to collate further data on chemicals with similar technical functionalities but which were not considered hazardous from an environmental or human health perspective. In 2012, the EPA had released a publication entitled Design for the Environment (DfE) Alternatives Assessment of Nonylphenol Ethoxylates on potential alternatives to OPEs, therefore approaching the EPA seemed a logical choice (Siemens Healthineers R&D is also primarily based in the USA and therefore had good visibility of initiatives such as this). The EPA were able to issue information on chemicals which may be considered as suitable alternatives, an excerpt from their communication is shown in **Figure 4-6**.

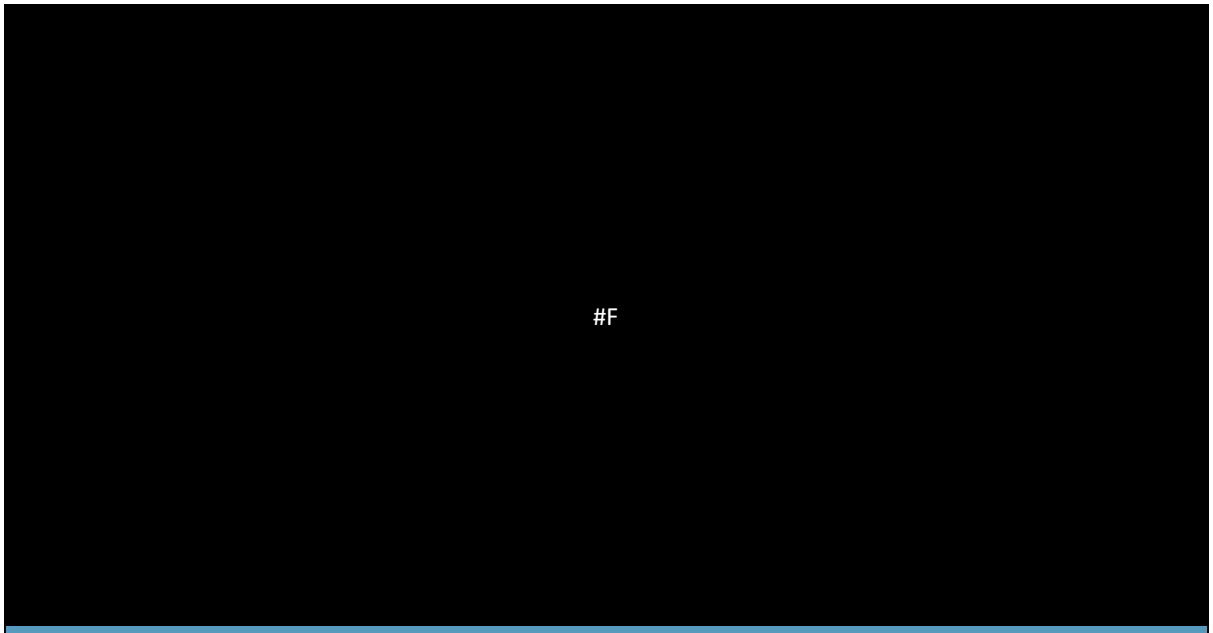

Figure 4-6: Excerpt from communication with US EPA in efforts to identify suitable low or non-hazard alternatives to OPE

- In May 2014 Siemens Healthineers initiated a collaborative project with the [redacted][10]. The challenge presented by OPEs in terms of the widely impacted Siemens Healthineers product portfolio, and the strong interest in identifying alternatives and potential partners in managing chemicals of concern was presented to a technical team at [redacted] The institute presented the [redacted] and groups of interest ([redacted]) who could potentially support on this topic. While these links did not initially prove fruitful, dialogue with [redacted] continued, and in May 2015 Siemens Healthineers presented its case at the [redacted] on May 19, 2015. Further discussion was held with [redacted] #F (bullet point) [redacted] to discuss work he and his students had already conducted around OPE substitution in other applications.

  This work culminated in the set-up of a research project in 2016. The project was entitled [redacted] # F (includes Phase 1 and Phase 2) [redacted] and its goals were to:

  Phase 1
  - Develop novel [redacted] surfactants as alternatives to replace OPEs;
  - Demonstrate [redacted] methods using principles of '[redacted]; and
  - Evaluate performance of the [redacted] surfactant in immunoassay applications.

  Phase 2
  - Compare final properties of these [redacted] surfactants to OPEs in the Siemens Healthineers immunoassay product line;
  - Establish overall safety and long-term viability of these [redacted] surfactants in [redacted] tests on primary human [redacted] cells and [redacted]; and
  - Compare biodegradation studies to establish a biodegradation profile.

  The project focused on the synthesis of [redacted] surfactants, i.e. those based on [redacted], and a material was provided for testing in assays at the Siemens Healthineers R&D site at [redacted]. The substances developed and assessed are displayed in **Figure 4-7**.

#F

Figure 4-7: [redacted] **#F**

[10] #F [redacted]

[redacted] and [redacted] were chosen to pursue due to their surface tension properties and more favourable toxicity and biodegradation results. This was later narrowed to octyl glucoside due to a safer, more environmentally friendly and simpler manufacturing process. A summary of the work is included in the report provided in Appendix 4 (Section 12). The first substances supplied were not successful in the testing conducted at the Siemens Healthineers [redacted] R&D site.

This work with [redacted] is still ongoing and it is not yet clear if it will lead to the commercial introduction of a viable alternative, however this will continue to be pursued, as it is seen as a long-term project and thus there is currently no set timeline for completion;

- In 2016 a study was commissioned by Siemens Healthineers, working with [redacted], to focus specifically on the substitution of octylphenol ethoxylates in IVD kit reagents and IVD wash solutions. [redacted] performed a desk-based analysis of alternatives using information supplied by Siemens Healthineers regarding the function of OPEs in the IVD kit reagents and IVD wash solutions containing OPEs and their technical properties.

  The result of this work was a list of potential surfactant alternatives which Siemens Healthineers R&D were able to use to inform their ongoing work to develop and design new products without the use of OPEs, and to initiate work to reformulate existing products containing OPEs. The list of potential alternatives generated from this work is included in the long-list of potential alternatives established by Siemens Healthineers for consideration in new and existing product design in **Table 4-2** (at the end of this sub-section). [redacted] report is provided as Appendix 4 (Section 4) to this document; and

- Internet-based data searches and communications with chemical suppliers were undertaken to understand what alternatives were available on the market, including Merck Millipore & Dow. In recent years, chemical suppliers have released communications based on work undertaken to identify alternatives which offer similar properties to OPEs; Siemens Healthineers R&D teams have been actively monitoring this work and lists resulting from this to initially create a list of alternatives and to continuously update that list.

Of the alternative surfactants identified, profiling of the hazardous properties of each identified substance was conducted with the aim of giving preference to substances which would reduce the overall risk profile. An example of how substances were profiled is presented in **Figure 4-8** below.

		Hazard Class. - ECHA						
Name	CAS.	skin	eye	aquatic	Goodman*	EPA*	Internal	Notes
1-Oleoyl-rac-glycerol	111-03-5	N	N	N			N	
Brij®L23	9002-92-0	Y	Y	N	5			
Brij® O10	9004-98-2	Y	N	Y				
Na Cholate	206986-87-0 361-09-1	N	N	Y			Y	
Decaethylene glycol monododecyl ether	9002-92-0							
Decyl β-D-maltopyranoside	82494-09-5						Y	
Digitonin	11024-24-1	Y	N	N	N	N/A	N	biological, VERY toxic. Avoid
ECOSURF™ EH-9	64366-70-7							
ECOSURF™ SA-9	-							
Genapol® x-080	9043-30-5	N	Y	N	5			aka BRIJ 35
Genapol® 26-L-80	68551-12-2							HLB = 13.4; biodegradable; alcohol ethoxylate
Glucopone	170905-55-2	N/A	N/A	N/A	4			
Kolliphor® P 188 – (3)	9003-11-6	N/A	N/A	N/A	3		N	aka Lutrol® F68
Kolliphor® EL	61791-12-6	Y	Y	N				aka castor oil, ethoxylated
Lauryl Glucoside	110615-47-9	Y	Y	N	4			
Lutensol® XP 80	160875-66-1							
Methoxypolyethylene glycol 350	9004-74-4							
N,N-Dimethyldodecylamine N-oxide	1643-20-5							

Figure 4-8: Example of substance profiling to identify alternatives with a lower hazard category

From the consultation work carried out above with chemical suppliers, the [redacted], and known experts in the field of OPE study, combined with the professional knowledge of Siemens Healthineers Method Chemists and their understanding of the performance of other surfactants in other IVD products, the list in **Table 4-2** presents those surfactant alternatives which Siemens Healthineers has actively considered and/or actually tested in certain IVD Products. It is important to note again that no single one of these would be suitable for all impacted IVD Products due to the range of technical functions of the surfactant and the biological variability an IVD product must adapt itself to when testing for certain diseases or conditions.

Table 4-2: List of OPE alternatives which could be suitable for IVD Products based on the various branches of work conducted by Siemens Healthineers to identify suitable alternative surfactants

Name	CAS Number	Tested in Siemens Healthineers IVD product?
Triton™ X-100	9002-93-1	Reference
1-Oleoyl-rac-glycerol	111-03-5	[redacted]
Brij® L23	9002-92-0	
Brij® O10	9004-98-2	
Brij® 35	9002-92-0	
Decaethylene glycol monododecyl ether	9002-92-0	
Digitonin	11024-24-1	
ECOSURF™ EH-9	64366-70-7	
ECOSURF™ SA-9	-	
Genapol® X-080	9043-30-5	
Kolliphor® P 188	9003-11-6	
Kolliphor® EL	61791-12-6	
Lutensol® XP 80	160875-66-1	
Methoxypolyethylene glycol 350	9004-74-4	
N,N-Dimethyldodecylamine N-oxide	1643-20-5	
n-Dodecyl β-D-maltoside	69227-93-6	
n-Nonyl-β-D-Glucopyranoside	69984-73-2	
n-Octyl-β-D-thioglucopyranoside	85618-21-9	
Nonaethylene glycol monododecyl ether	3055-99-0	
Pluronic® F-127	9003-11-6	
Pluronic® F-68	9003-11-6	
Pluronic® 25R2	9003-11-6	
Pluronic® 31R1	-	
Pluronic® L64	-	
Poly(ethylene glycol)	25322-68-3	
Polyoxyethylene (10) tridecyl ether	78330-21-9	
Saponin	8047-15-2	
Silwet 7604	-	
Silwet 7606	-	
Span® 80	1338-43-8	
Span® 85	26266-58-0	
TERGITOL™	68551-14-4	
TERGITOL™ 15-S	68131-40-8	
TERGITOL™ NP	127087-87-0	
TERGITOL™ TMN	60828-78-6	
Tetramethylammonium hydroxide pentahydrate	10424-65-4	
Thesit®	9002-92-0	
Triton™ X-100, Reduced	92046-34-9	
Triton™ X-114, Reduced	92046-34-9	
Triton™ X-405, Reduced	92046-34-9	

Table 4-2: List of OPE alternatives which could be suitable for IVD Products based on the various branches of work conducted by Siemens Healthineers to identify suitable alternative surfactants		
Name	**CAS Number**	**Tested in Siemens Healthineers IVD product?**
Tween® 20	9005-64-5	[redacted]
Tween® 60	9005-67-8	[redacted]
Tween® 80	9005-65-6	[redacted]

A number of the alternatives listed above have been actively tested by Siemens Healthineers R&D in a number of new product development projects and in the re-design of existing products. The following are examples of the extensive R&D projects which were undertaken specifically to design new, or re-design existing, IVD products with the aim of making them OPE-free.

OPE Alternatives Project – Example 1

IVD Product Name	[redacted] #B, D, F (table) [redacted] Assay
Product Description	The [redacted] assay is for *in vitro* diagnostic use in the quantitative measurement of [redacted] in human serum or plasma using the [redacted] system. The assay can be used to aid in the diagnosis of [redacted].
New or Existing Product?	New, however design had already been completed using Triton X-100 and therefore a re-design was undertaken
Year Development Initiated	2010
Development Location	Siemens Healthcare, [redacted]
Development Team	Assay Development Team, R&D, [redacted]
Background	During development of this reagent, Triton™ X-100 was used as the initial surfactant and delivered the required performance parameters. As a result, design was completed with Triton X-100 as a constituent. As Siemens Healthineers became aware of concerns that Triton™ X-100 could be added to the Annex XIV list, a re-design project was initiated to replace the OPE with an alternative surfactant.
Alternatives Tested	Pluronic 25R2 Triton X-100 Reduced (please note this is the chemically reduced form and not an OPE and not a reduced concentration of the OPE).
Summary of Analysis	In the initial experiment, [redacted]% Triton™ X-100 was substituted by either Triton X-100 reduced (please note this is the chemically reduced form and not an OPE and not a reduced concentration of the OPE) or Pluronic 25R2 [redacted] Triton X-100 reduced has very similar detergent characteristics to Triton™ X-100, which makes it a natural candidate for substitution experiments. The only difference on a molecular level is a reduced ring structure of the octylphenol, which leads to a slightly different 3-dimensional conformation of the molecule. Pluronic 25R2 has a somewhat lower HLB than Triton™ X-100. Since it is non-toxic[11] and has an acceptable HLB value the substance was included in the experiments, but the outcome showed this substance was not a good candidate to replace Triton™ X-100. IVD kit performance, including detection of the [redacted], was not sufficient to meet the quality standards of Siemens that had to be met to achieve authority approval of the IVD kit

Summary of Results	[redacted] was determined to be an acceptable alternative. This assay successfully demonstrated meeting all Design Requirements as defined in the Requirements Traceability Matrix (RTM) necessary to be commercially available in the EU and recently gained approval with the US Food and Drug Administration (FDA)

OPE Alternatives Project – Example 2

IVD Product Name	[redacted] #B, D, F (table) [redacted] Assay
Product Description	The [redacted]) assay is for *in vitro* diagnostic use in the quantitative measurement of [redacted] in human serum or plasma ([redacted]) using the [redacted] Analyzer. The assay can be used to aid in the diagnosis of acute [redacted])
New or Existing Product?	New
Year Development Initiated	2011
Development Location	Siemens Healthcare [redacted]
Development Team	Assay Development Team, [redacted]
Background	The initial reagent design contained [redacted]% (w/w) Triton™ X-100, which performed excellently, however, as with the previous example, the anticipated inclusion of OPE on the Annex XIV list led the R&D team to initiate a project to identify an alternative.
Alternatives Tested	Tween® 20 Brij® 35 Silwet 7604 Silwet 7606 Pluronic 25R2 Pluronic 31R1 Pluronic L64 Tween® 80
Summary of Analysis	Several candidate alternatives initially worked well during early screening, but additional testing proved more challenging. The basic screening consisted of [redacted]. The idea was to maximise the [redacted] and [redacted] the assay [redacted], removing [redacted] as well. A few low end [redacted] were also added to collect [redacted] and [redacted]. Background [redacted] was also an important consideration, there should not be any non-specific binding (NSB) that generates signal in the absence of analyte. In comparing assay performances with the OPE and with an alternative, examination of several fundamental metrics/behaviours were undertaken, such as [redacted]) with the two formulations and sample recovery comparisons. A portion of each detergent formulation was also set aside to check [redacted] and [redacted]. When another critical IVD performance parameter, [redacted], was checked with the formulation containing Silwet 7604, the new formulation did not pass. Unfortunately, this was the only OPE alternative to show acceptable performance for many of the other critical parameters. This issue was finally remedied by switching to the [redacted]. Finally, it was necessary to label [redacted] with all available [redacted]s and understand the influence of [redacted] and [redacted]. [redacted] was the only one that was effective but it also incurred issues - the [redacted] stuck to the [redacted] as it was not [redacted] completely. As a result, over time on replicate measurement using [redacted], the [redacted] reagent became irreversibly [redacted] raising the background. The addition of [redacted]

	[redacted] to the [redacted] whose [redacted] mimic [redacted] and increasing the probe's [redacted] at the wash station solved the problem
Summary of Results	Replacing Triton™ X-100 not only required finding an acceptable alternative, but also resulted in a new detection label ([redacted] and further [redacted]. In total, all these efforts to identify an alternative to the OPE added a year to the development of the [redacted] assay.

OPE Alternatives Project – Example 3

IVD Product Name	# B,D,F (table) [redacted]
Product Description	The [redacted] method used on the [redacted] clinical chemistry system is an *in vitro* diagnostic test intended for the quantitative determination of [redacted] in human serum and plasma
New or Existing Product?	Existing
Year Development Initiated	2017
Development Location	Siemens Healthcare, [redacted]
Development Team	Assay Development Team, R&D [redacted]
Background	Examples of Siemens studies where OPEs were experimentally evaluated within a Siemens Healthineers [redacted] chemistry assay include: 1. for the [redacted] Assay, the necessity of Triton™ X-100 is described as follows: *"Triton™ X-100 was found to be essential for the activity of [redacted]. Linear optimization in the presence of the total reagent system also showed this surfactant to be an essential reagent… In a typical experiment with Triton™ X-100 as a variable in the presence of other optimized reagents ([redacted]) the final absorbance values with and without the optimum concentration of this surfactant were [redacted], respectively. Similarly, upon [redacted] of Triton™ X-100 from the reagent system the time required for reaction completion was prolonged from [redacted] to more than [redacted]* 2. a study into Surfactant inhibition of [redacted]: *"Using the rate at which [redacted]s converted to [redacted], the reaction was followed directly by monitoring the increase in absorbance at [redacted] nm. Inhibition of [redacted] was demonstrated with three surfactants, [redacted]. A fourth, Triton™ X-100, produced high enzyme activity, although low concentrations resulted in incomplete substrate dispersal and high concentrations caused high blank values. [redacted] was studied more closely and the mechanism of inhibition is suggested as poor substrate dispersal at low surfactant concentration and a competitive inhibition at higher concentrations…."*. In 2017 Siemens initiated internal experiments to investigate the technical option of a substitution of Triton™ X-100 by **Triton™ X-100 Reduced**
Alternatives Tested	Triton™ X-100 Reduced This was initially chosen based upon the literature as well as the physicochemical similarity (as well as the fact that it is not an OPE nor NPE)
Summary of Analysis	The following experimental reagents were produced, all identical except for the surfactants used: [redacted] **Condition A** [redacted]

	Condition B **Condition C** As expected, all requirements regarding solubility in water and in oil in the appropriate concentration were fulfilled. The reagents were then tested on-board the Clinical Chemistry analyser using commercial reagents including the calibrator and , alongside a commercial lot to test for congruity. The main questions addressed were the ability to generate a calibration curve and the accuracy of the test upon substitution, the effect on the activity on other involved components, especially the enzyme
Summary of Results	Following extensive evaluation, the following conclusions were made: • Lowering the concentration of Triton™ X-100 to a concentration of w/w did not produce accurate results; • Preparations in which Triton™ X-100 Reduced or a mixture of Triton™ X-100/Triton™ X-100 Reduced both yielded acceptable results; • It is believed that Condition A, , is the better of the options because it poses the least risk for human error during manufacturing and eliminates the Triton™ X-100 completely from the products resulting in the removal of risks associated with the substance. • Condition A was chosen as the best option and a full design change project is now in progress

OPE Alternatives Project – Example 4

IVD Product Name	#B, D, F
Product Description	The assay is for *in vitro* diagnostic use in the quantitative determination of) in human serum and plasma ( ) using the Analyser. Measurements of produced by the are used in the diagnosis of disorders. The commercial assay in an important test and requires one of the lowest in the portfolio
New or Existing Product?	Existing
Year Development Initiated	2016
Development Location	Siemens Healthcare,
Development Team	CPS Team, R&D,
Background	This product contains OPE in each of three separate reagents that constitute the product. In this example, therefore, three reagents need to be reformulated and very stringent acceptance criteria must be met.
Alternatives Tested	Alternative concentrations of OPE Removal of OPE Tween® 20 Tween® 60 Silwet 7604 Triton™ X-100 Reduced

Summary of Analysis	The initial experiments tested three conditions; to lower the OPE concentration to below the REACH threshold level ([redacted] to use [redacted] the threshold level and to [redacted]. The results clearly demonstrated that none of these conditions were acceptable due to poor precision, LoD failures and loss of Functional Sensitivity. Importantly however, these initial studies demonstrated that one reagent of the three was the main contributor to the performance failures. The development chemist then focused on the reagent having the greatest impact on performance and tested four different concentrations of the following surfactants: Tween® 20, Tween® 60, Silwet 7604 and Triton™ X-100 Reduced. Overall, optimal concentrations were identified for each of these alternatives that at this preliminary stage yielded similar, or in a couple of instances better, performance for LoD and Functional Sensitivity. Multiple candidate formulations will be prepared in the next stage of this project and these will be subjected to much more thorough testing, including real-time stability studies
Summary of Results	Although preliminary studies were promising, additional assay performance characteristics will also be addressed in the re-formulation process so a new study was initiated in 2018

OPE Alternatives Project – Example 5

IVD Product Name	[redacted] #B, D, F (table)
Product Description	The [redacted] Assay is a homogeneous enzyme immunoassay intended for use in the quantitative analysis [redacted] in human serum or plasma. [redacted] assays are designed for use with a variety of chemistry analysers. This assay monitors [redacted] patients prescribed therapeutic doses of the drug [redacted] Monitoring serum [redacted] concentrations, along with careful clinical assessment is the most effective means of ensuring safe and effective therapy
New or Existing Product?	Existing
Year Development Initiated	2017
Development Location	Siemens Healthcare, [redacted]
Development Team	CPS Team, R&D, [redacted]
Background	This assay is comprised of two separate reagents, one reagent contains [redacted] w/w OPE. Initial acceptance criteria for this method were the generation of a calibration curve, a known sample concentration recovery and estimated precision
Alternatives Tested	Tween® 20 (1%); Tween® 20 (2%); Tween® 20 (1%) with OPE (0.094%); Tween® 20 (2%) with OPE (0.094%); Tween® 80 (1%); Tween® 80 (2%); Tween® 80 (1%) with OPE (0.094%); Tween® 80 (2%) with OPE (0.094%); Triton™ X-100 reduced (1.6%); Triton™ X-100 reduced (1.6%) with OPE (0.094%); Triton™ X-100 reduced (0.8%) with Tergitol (0.8%); and Brij® 35 (1.6%) Tergitol™ 15-S (1.6%); Tergitol™ 15-S (1.6%) with OPE (0.094%); Brij® 35 (1.6%) with OPE (0.094%); and Thesit® (1.6%).

Summary of Analysis	Based upon the information on potential alternatives provided to the method development chemist (and as outlined above), several candidate formulations were investigated. Surfactants (concentrations) that did pass calibration curve specifications for the product included: [redacted]
Summary of Results	These later four formulations will soon begin additional preliminary acceptance criteria testing

OPE Alternatives Testing – Example 6

IVD Product Name	[redacted] #B, D,F (table) [redacted] Assay
Product Description	The [redacted] assay is another important blood test measuring [redacted], improving patient care in individuals suspected of having [redacted]). Measurements of [redacted] are used as an aid in the diagnosis and assessment of [redacted] severity. The test is further indicated for the risk stratification of patients with acute [redacted] [redacted].
New or Existing Product?	Existing
Year Development Initiated	2017
Development Location	Siemens Healthcare, [redacted]
Development Team	Assay Development Team, R&D, [redacted]
Background	This product is composed of four separate reagents, three containing [redacted] w/w OPE (Reagents [redacted]) and the other reagent (Reagent [redacted] containing [redacted] w/w OPE.
Alternatives Tested	Triton X-100 Reduced Tergitol™ 15-S-9
Summary of Analysis	The following formulations were produced and tested, and the summary results are outlined: **Revision A ([redacted])**: Lowered OPE to [redacted]% w/w within Reagents [redacted]; and Replaced OPE [redacted]% w/w with Triton™ X-100 reduced [redacted]% w/w (Reagent [redacted]). Results Summary: [redacted] patient samples were tested for method comparison showing [redacted]% shift in patient sample recovery vs commercial reagents. There is a much greater shift (under recovery for test lot) for samples above [redacted] [redacted] units. Assay range is [redacted]/mL. **Revision B ([redacted])**: Replaced OPE [redacted]% w/w with Triton™ X-100 reduced [redacted]% w/w within Reagents [redacted]; and Replaced OPE [redacted]% w/w with Triton™ X-100 reduced [redacted]% w/w (Reagent [redacted]). Results Summary: [redacted] patient samples were tested for method comparison and showed [redacted]% shift in the patient sample analyte values vs commercial reagent - similar analyte recovery to Revision A. Samples greater [redacted] [redacted]/mL showed a much greater shift (low patient sample analyte values for the test reagent). Since Reagent [redacted] is formulated with the greatest OPE concentration [redacted]%), the team has now focused only on Reagent [redacted] in the short-term. **Revision C ([redacted])**: Lowered OPE to [redacted]% w/w; and Replaced remaining OPE with Tergitol™ 15-S-9 [redacted]% w/w. Results Summary: [redacted] patient samples were tested for method comparison against commercial reagents. A familiar recovery of [redacted]% shift in patient samples occurred (under recovery). It cannot be determined if the under

	recovery is better or worse in each experiment, as it varied. For the most part the under-recovery was much greater for samples above [redacted]/mL in each instance and shared a similar pattern. **Revision D ([redacted])**: Lowered OPE to [redacted]% w/w; and Replaced remaining OPE with Tergitol™ 15-S-9 [redacted]% w/w and Triton™ X-100 reduced. Results Summary: method comparison testing was completed with [redacted] samples showing ca. [redacted] patient sample shift between test and commercial reagents. Again, the familiar pattern of patient samples higher than [redacted]/mL show greater under-recovery for the test reagent. It was noted that the separation was closer than previous experiments. **Revision E ([redacted])**; **Revision F ([redacted])**: Lowered OPE to [redacted]%; and Replaced remaining OPE with Triton™ X-100 reduced [redacted]% w/w.
Summary of Results	Feasibility Testing Stage ongoing. From the experiments performed to date, results from patient sample and QC recoveries demonstrated that modifying the Triton™ X-100 concentration in Reagent [redacted] has a significant impact. Lowering the Triton™ X-405 concentration in Reagents [redacted], however, had an insignificant impact. It is clear that the Triton™ X-100 at [redacted]% w/w in Reagent [redacted] has a complex effect on the reaction, and a more systematic, further fact-finding approach to identifying an acceptable alternative is needed

Below is a list of Siemens Healthineers IVD Products that have successfully achieved final design since 2013 with the use of an OPE alternative and referencing the specific surfactants chosen:

[redacted] #D, F

[redacted]

[redacted] #D, F

[redacted]

– [redacted].

Overall summary of alternative testing

Note that for commercial OPE-containing products or those that have already obtained final design status (as described above), only select feasibility testing has been conducted by Siemens Healthineers. The strategy is now to determine the efforts required to identify potential alternatives to Triton™ X-100 in [redacted] #D [redacted]. While there are examples of this being completed successfully, there are also examples where it has been demonstrated that known and tested alternatives are not acceptable substitutes.

Each immunoassay product's design is unique and each one must be fully tested to confirm that an alternative is acceptable. There are no guarantees of success at the outset of this process, even if an alternative substance has been successfully (or unsuccessfully) proven for a similar assay. As described above, therefore, physicochemical properties and toxicological classification of potential alternatives are aids in prioritising the order in which alternatives are evaluated. This has been used in practice. However, due to the complex and unique nature of each milieu, as well as the potential multiple effects that OPEs convey to IVD assay performance, there is no single alternative that has been shown to be a universal replacement. Differences among the IVD products arise from the different critical raw materials (i.e. antibodies, signal technology, etc.) which manifest unique biological and physiochemical characteristic to the products. As such, each product behaves in a different way and has different performance characteristics. The reason for this is due at least in part to molecular interactions between the chemicals and the proteins involved, but inadvertent reactions cannot always be predicted as explained earlier in this section when describing the technical challenges. Each product is therefore produced by following a unique and product-specific protocol.

The efforts undertaken as part of the extensive work done by the Siemens Healthineers organisation to identify alternative substances to OPE continually benefit future efforts. Consequently, after careful consideration of the above parameters, it is concluded that several alternatives, alone or in combination, must be systematically and experimentally evaluated on a 'per product' basis so as to be able to successfully implement alternatives across the #D Siemens Healthineers portfolio.

4.1.2 Data searches

The website/data searches conducted to identify OPE alternatives are listed below. It should also be noted however that many of the aforementioned alternatives were identified based on the expert knowledge of R&D technical staff from their experience in using a wide range of surfactants in IVD products.

- Siemens Healthineers internal databases, i.e. SAP, R&D databases;

#F

4.2 Identification of known alternatives

4.2.1 Introduction

Based on the R&D undertaken in the past, the literature searches undertaken and on consideration of market conditions, and realism of switching to an alternative, the following theoretical alternatives to the use of OPE for the manufacture of beads in Llanberis could be considered:

1. Substitution of Triton™ X-100 by an alternative substance.
2. Replacement of OPE-dependent IVD kits by an alternative technology.
3. Sourcing of third-party IVD kits for the #D platform.
4. Relocation of production of beads outside the EEA and import of coated beads.
5. Discontinuation of supply of OPE-dependent IVD kits for the #D platform.
6. Discontinuation of supply of all IVD kits for the #D platform.

4.2.2 Alternative 1: Substitution of Triton™ X-100 by a potential alternative substance

Starting from the "long list" of alternatives shown in **Table 4-2**, the most important requirement is a similar (or higher) HLB value. Furthermore, the CMC of potential alternatives should be in a similar range to that of Triton™ X-100 and (known) toxicological properties should be, at the very least, less "problematic". This means the exclusion of substances with a classification as CMR, acute or chronic effects on the aquatic environment cat. 1 according the CLP Regulation and "other" properties that might give reason to have equivalent concern, as well as the exclusion of those similar substances of concern that are likely to be classified as such in the next 10-15 years. In particular, this list includes substances that are suspected of having endocrine disrupting properties. A list of potentially relevant substances is shown in **Table 4-3** below, alongside Triton™ X-100 which is included for comparison purposes. The substances shown here are substances that already have been involved in generic or specific reformulation processes for products in the Siemens Healthineers portfolio, as described in Section 4.1. Within **Table 4-3** (see below), substances with a slightly lower HLB are shown in orange.

The table identifies some promising potential alternative substances. Nevertheless, whilst physicochemical properties and toxicological classification of potential alternatives can help towards prioritising the order in which alternatives are evaluated, due to the complex and unique nature of each milieu, as well as the potential multiple effects OPEs convey to IVD assay performance, selecting a single alternative substance to replace Triton™ X-100 across all IVD kits manufactured in Llanberis is unlikely to be successful, as has been described above in this report, particularly in Section 4.1.1. In practice, several alternatives, alone or in combination, must be experimentally evaluated on a 'per IVD kit' basis.

Importantly, elimination of the use of OPE without substitution is neither technically nor economically feasible; there is a reason why Triton™ X-100 is used for the bead washes. Even if it was removed, the process of proving/re-validating/re-registering the products would not be economically feasible given the overall Siemens Healthineers business #D

4.2.3 Alternative 2: Replacement of OPE-dependent IVD kits by an alternative technology (i.e. alternative analyser plus IVD products)

Siemens Healthineers does offer an alternative technology to #D, as is discussed later. This is the #D. However, this still relies on legacy IVD kits some of which contain OPE and for which Siemens Healthineers is very actively trying to switch over to alternative substances. This option cannot deliver the elimination of the use of OPE on the Sunset Date; thus, it is not considered a realistic immediate-term alternative to the continued use of OPE by Siemens Llanberis in the manufacture of beads used in OPE-free IVD kits.

4.2.4 Alternative 3: Sourcing of third-party IVD kits for use on the #D analysers

Siemens Llanberis confirms that there are no third-party IVD kits in the market that would be compatible with the #D platform. Therefore, Siemens Llanberis cannot source such third-party IVD kits on behalf of existing customers with whom they have contractual obligations, nor could the customers obtain them directly and use them as replacements for the affected #D IVD kits that are dependent on the use of OPE in the production process. This alternative is impossible to implement and thus it is not considered further.

4.2.5 Alternative 4: Relocation of production of beads outside the EEA and import of OPE-free coated beads

The production equipment used to manufacture beads at Siemens Llanberis, and described in Section 2, is bespoke. They are specifically designed for the #D bead manufacturing process. To move all bead production out of the EEA to another Siemens Healthineers site would require re-validation of the equipment, production processes and the production environment. This process normally takes several months to complete, during which time supply of the OPE-dependent products to customers worldwide would stop. The Legal Manufacturer of the IVD kits would also need to be changed; this normally results in re-registration of the IVD products in the countries where they are sold. This process can take up to 41 months in some countries. Moving the production process would also lead to job losses at the Llanberis site; there are currently #D (range: 10-100) people employed directly in the bead manufacture process, with other peripheral functions supporting this process.

For these reasons, this alternative is technically very challenging and is discussed below primarily for completeness.

4.2.6 Alternative 5: Discontinuation of supply of OPE-dependent IVD kits for the #D platform

This alternative would simply envisage the cessation of sales of OPE-dependent kits for the #D platform in the absence of a feasible alternative for Triton™ X-100 on the Sunset Date. This alternative is, in principle, possible to implement (at significant cost and impact to healthcare provision, as will be shown) and will be discussed further in this analysis.

4.2.7 Alternative 6: Discontinuation of supply of all IVD kits for the #D platform

This alternative would simply envisage the cessation of sales of all IVD kits for the #D platform in the absence of a feasible alternative for Triton™ X-100 on the Sunset Date. In other words, Siemens Llanberis would stop supporting its customers-users of #D analysers with consumables on the Sunset Date. This alternative is, in principle, possible to implement (at significant cost and impact to healthcare provision, as will be shown) and will be given further consideration.

4.2.8 Shortlisted alternatives

Based on the screening process above, the following potential alternatives for Siemens Llanberis use of OPE will be considered in more detail in this AfA:

- Alternative 1: Substitution of Triton™ X-100 by an alternative substance;
- Alternative 4: Relocation of production of beads outside the EEA, and import of coated beads;
- Alternative 5: Discontinuation of supply of OPE-dependent IVD kits for the #D platform; and
- Alternative 6: Discontinuation of supply of all IVD kits for the #D platform.

4.3 Assessment of shortlisted alternatives

4.3.1 Alternative 1 – Substitution of Triton™ X-100 by an alternative substance

The discussion on this option is based on a general approach to substituting Triton™ X-100 in the applied for use with another substance.

Substance ID, properties, and availability

There is currently no example of a successful substitution of Triton™ X-100 in an existing IVD kit that is produced under the applied for use in this AfA. Past research and development activities in regard to other products within the overall Siemens Healthineers portfolio that were introduced to the market after the Siemens Healthineers' decision to eliminate Triton™ X-100 (and other OPEs) in new products in 2013, has shown that it is possible to substitute Triton™ X-100 by several non-ionic detergents available on the market or under development. Nevertheless, there is no known substance that can directly substitute Triton™ X-100 in the applied for use under consideration here and no actual trial has been initiated to date to screen for substances that might qualify as alternatives. The reasons are further explained in the sub-sections "actual plans for reformulation of #D IVD kits" and "The Siemens REACH Response Plan" below. Therefore, the discussion here on potential alternative substances is by necessity kept to a hypothetical level.

From a very general perspective, a substitution process of Triton™ X-100 in the processes within the scope of the applied for use would cover the following steps:

1. A long list of non-ionic detergents would be screened for substances that have similar properties as Triton™ X-100. Besides an indication that the substance might work on a technical level, there should be some indication that the alternative is less problematic regarding its intrinsic properties;

2. An initial testing series would be performed to see if the shortlisted alternative substances perform satisfactorily under the conditions of the current process/IVD test;

3. Alternative substances that give promising results in initial testing might be used for further optimisation; and

4. Selected alternative substances would have to undergo extensive quality testing including verification of assay performance.

As previously noted, no existing processes or products within the scope of this AfA have undergone an active substitution process. The closest experience in this regard are examples shown in Section 4.1.1 (for instance, #D), where an IVD kit reagent has been changed (reformulated) after it was close to product release.

Based on their substance properties and their performance in some research activities Tween® 20 (or potentially also other Tweens) or Triton™ X-100 Reduced, might qualify as alternatives in the Applied for Use for one or more products. Also, other substances that have been used successfully in new product development since 2013.

Table 4-3 below provides a wider overview of non-ionic surfactants that in principle can be used in IVD buffer media that are applied in bead coating processes. The substances shown in this table have been already used successfully in product development or have been subject to screening tests. The colours of the fields show whether the key parameters presented in Section 4.1 are met.

Technical feasibility of Alternative 1 (substitution by an alternative substance)

Comparison to technical feasibility criteria

As indicated above, the assessment of the technical feasibility of any potential alternative substance requires several successive steps to be taken. It is paramount that the substitution of Triton™ X-100 in the production of the #C #D analyte beads must not impact upon product quality. To better understand the technical feasibility requirements for any Alternative 1, some additional detail is provided below.

- Step 1 – Theoretical Identification: the first step in the process of identifying a feasible alternative substance would be the generation of a list of nonionic detergents that would be screened for their properties against those of Triton™ X-100. Some indicators that could identify detergents that might qualify as replacements to Triton™ X-100 are the physicochemical parameters discussed above (HLB, CMC, solubility etc). Nevertheless, it should be noted that these parameters provide no guarantee that a substance will perform as required in the manufacturing of any specific IVD test. Therefore, any substitution activity in the field of IVD kit manufacture must include a large amount of expert judgement and must focus, at least on a high level, on the specific IVD kit concerned.

- Step 2 – Initial Screening: the second step involves the testing of the most promising, well-characterised and available alternatives. If none of these alternatives pass initial screening, the scope would be extended to test substances which are more novel in terms of characterisation and availability.

  Given the large number of potential alternative substances and the unpredictably of the performance of a substance in the manufacturing of a specific IVD product and in the subsequent performance of the IVD product itself, these two steps are likely to take a

significant amount of time; for the #C #D analyte bead formulations an estimate of #C years has been calculated[12].

- Step 3 – Optimisation: the third step in the process would focus on potential alternatives which had demonstrated promising results in Step 2. Application of those alternatives as replacements to Triton™ X-100 in bead formulations would require the need for technical optimisation to ensure that the performance of the IVD kits were maintained to that of current performance.

- Step 4 – Product Validation: once an alternative was proven to reproduce the performance of Triton X-100, the fourth step would commence to complete extensive product validation testing, including real-time stability testing over the shelf-life of the product (18 months). This activity would need to be performed by the manufacturing site and would therefore be in competition for resources required for maintain product supply to customers (for both OPE-dependent and OPE-independent #D products). Resources for such trials are limited since production facilities are limited and capacity is dedicated to normal manufacturing activities. It is necessary that these trials are performed under the same technical conditions as the actual production of the beads, as the production process itself needs to be under strict control and this may also take several years (#C).

  Only when this process has been successfully finalised can equivalent product performance be verified as being acceptable. The modified process and the products that result from the substitution process could be subject to subsequent regulatory re-registration (see below). The re-registration process impacts the time before any alternative to Triton™ X-100 can be introduced to the market and products produced with the alternative substance (or combination thereof) can be sold to customers that operate #D analysers.

[12] Assumption based on other trials to reformulate products not linked to #D products.

Table 4-3: Key information on detergents that have been tested as alternatives in comparison to Triton™ X-100[13]							
Name	**CAS No.**	**Trade name (s)**	**HLB**	**CMC[14]**	**Cloud Point [°C]**	**Classification Supplier safety data sheets**	**H-phrases**
4-(1,1,3,3-Tetramethylbutyl)phenylpolyethylene glycol	9002-93-1	Triton™ X-100	13.4	0.23 mM (189 ppm[15])	66	• Acute Tox. 4 • Skin Irrit. 2 • Eye Dam. 1 • Aquatic Acute 1 • Aquatic Chronic 1	• H302 • H315 • H318 • H400 M-Factor-Aquatic Acute: 10 • H410
Polyethylene glycol sorbitan monolaurate	9005-64-5	Tween® 20, Polysorbate 20	16.7	0.059 mM (72 ppm)	76	Not classified according to suppliers	
Polyethylene glycol sorbitan monostearate	9005-67-8	Tween® 60	14.9	0.0055-0.022 mM (7 – 29 ppm)	> 60[16]	Not classified according to suppliers	
Polyethylene glycol sorbitan monooleate	9005-65-6	Tween 80	15	0.012 mM (15 ppm)	65	Not classified according to suppliers	
1-[4-(2,4,4-trimethylpentan-2-yl)cyclohexyl]-1,4,7,10,13,16,19,22-octaoxatetracosan-24-ol	92046-34-9	Triton™ X-100 Reduced	13.5	0.2-0.9 mM (113 – 508 ppm)	65	• Skin Irr. 2, • Eye irritation, • STOT SE 3 • Aquatic Chronic 2 • Unknown ED effect due to reduced ring	• H315 • H319 • H335 • H411
C_{16}-C_{18}-Fatty alcohol ethoxylate	No data found	Lutensol® AT 50	18	No data found	92	Not classified according to supplier	
Tricosaethylene glycol dodecyl ether	9002-92-0	Brij®L23	16.9	0.091 mM (109 ppm)	>100	Not classified according to supplier	

[13] If not specified otherwise, the data were taken from (Bhairi *et al.*, 2017).

[14] Both units are used by suppliers, in case the mM were given, ppm values were calculated if necessary.

[15] Taken from a product data sheet of Dow Chemical Company (Dow Chemical Company, no date).

[16] Supplier's information taken from (Croda, no date).

Table 4-3: Key information on detergents that have been tested as alternatives in comparison to Triton™ X-100[13]							
Name	**CAS No.**	**Trade name (s)**	**HLB**	**CMC[14]**	**Cloud Point [°C]**	**Classification Supplier safety data sheets**	**H-phrases**
Ethoxylated lauryl alcohol	9002-92-0	Brij® 35	16	0.091 mM[17] (109 ppm)	No data found	• Acute Tox. 4 • Skin Irr. 2, • Eye Dam. 1	• H302 • H315 • H318
Polyethylene glycol dodecyl ether	9002-92-0	Thesit	13.3[18]	0.09 mM (53 ppm)	No data found	• Acute Tox. 4 • Skin Irr. 2, • Eye Dam. 1	• H302 • H315 • H318
Ethylene Oxide/Propylene Oxide Block Copolymer	9003-11-6	Pluronic ® 25R4	7 – 12	No data found	40	Not classified according to supplier	
Ethylene Oxide/Propylene Oxide Block Copolymer	9003-11-6	Pluronic® 31R1	1 – 7	No data found	25	Not classified according to supplier	
Siloxane Polyalkyleneoxide Copolymer	68937-54-2	Silwet 7604	10.6	40 ppm[19]	50	• Repr Category 2	• H361f
Siloxane Polyalkyleneoxide Copolymer		Silwet 7606	No data found	No data found	No data found	No data found	No data found
Secondary Alcohol Ethoxylate	60828-78-6	Tertigol (MW538)	13.1	800 ppm	36	• Skin Irr. 2, • Eye Dam. 1 • Aquatic Chronic 3	• H315 • H318 • H412
Secondary Alcohol Ethoxylate	60828-78-6	Tertigol MW 683 avg.)	14.4	1313 ppm	76	• Skin Irr. 2, • Eye Dam. 1 • Aquatic Chronic 3	• H315 • H318 • H412
Secondary Alcohol Ethoxylate	60828-78-6	Tertigol (MW 570)	14.0	930 ppm	65	• Skin Irr. 2, • Eye Dam. 1 • Aquatic Chronic 3	• H315 • H318 • H412
Secondary Alcohol Ethoxylate	68131-40-8	TERGITOL™ 15-S-9	13.3	52 ppm	60	• Acute Tox. 4 (oral / inhalation) • Skin Irr. 2, • Eye Dam. 1	• H302 + H332 • H315 • H318

[17] Supplier's information taken from (Serva, 2019).

[18] Supplier's information taken from (Sorachim, 2019).

[19] Supplier's information, own calculation from that information (Momentive, 2011).

Regulatory re-registration of IVD kits

All IVD kits must be registered for use in the relevant jurisdiction where they are used, according to the relevant regulations of that country. Generally, at Siemens Healthineers, the process of preparing and submitting to the relevant authorities an application for the regulatory re-registration of an IVD kit includes the 6 steps described in Section 4.1.1.

Siemens Healthineers typically allows two months for submission preparation in each country. There are about 80 countries with re-registration requirements and submission requirements vary by country. If there are performance changes, most countries will require a re-registration, for example a new 510(k)[20] in the USA. If there is no performance change, some countries may still require re-registration due to a composition-related change to the Instruction for Use (IFU). Importantly, all performance claims need to be verified. Siemens Healthineers estimates that re-registrations would generally be required in approximately 50 countries. This estimate is based on the fact that about 80 countries have regulatory requirements and 31 work under EU regulations. The actual number will vary because it is dependent on the number of countries where each IVD product is placed on the market.

Table 4-1 gives a non-exhaustive overview of the most important IVD regulations around the world and the timelines that are associated with a (re-)registration of an IVD-product. In China, a very important market, the registration of an IVD product requires 42 months, which represents the worst case; in other regions-countries, re-registration takes between 0.5 and 2 years. Re-registration would be required in parallel in each region where #D analysers are operated.

Overall, the entire re-registration process can be expected to take up to #B,F months, or ca. 4 years[21].

Economic feasibility and economic impacts of Alternative 1 (substitution with another substance)

Actual plans for reformulation of #D IVD kits

#C,D (whole paragraph)

[20] A **510(K)** is a premarket submission made to FDA to demonstrate that the device to be marketed is at least as safe and effective, that is, substantially equivalent, to a legally marketed device (21 CFR §807.92(a)(3)) that is not subject to premarket approval.

[21] As shown above, the key time constraint here is China where re-registration can take 2-3 years. In China, type testing needs to be performed in accordance with the China Product Standard or the Product Technical Requirements (PTR, 3 different reagent lots; the product must be approved in either the country of the legal manufacturer or the physical manufacturer; ISO Certificate; Legal Agency Authorization Letter; Declaration of Authenticity; Declaration of Conformity for China Regulations and Standards; Instruction for Use; Outer box Label; English Product Technical Requirements; Explanation Letter For Any Inconsistency; Performance Evaluation Report and Technical Documents for Assays; Risk Management Report; Product Summary; Clinical Trial / Study Data / Method Comparison).

[redacted]. Therefore, OPE-dependent [redacted] IVD kits should remain available for a minimum 9 years from the Sunset Date and this is the core of Siemens Llanberis' justification for the requested review period. In addition, discussed above, substitution to alternatives would take 5-12 years at considerable cost including the cost of Siemens Healthineers resources diverted from R&D on alternatives for long lifecycle and high-volume products. [redacted]

The Siemens REACH Response Plan

The Siemens Healthineers product portfolio is #C [redacted] by the inclusion of OPEs into the REACH Authorisation list, with #C [redacted] affected products. Transitioning to alternatives will require significant investments #C [redacted]. It is important to note that the successful substitution of Triton™ X-100 in any one IVD kit by a safer alternative substance does not necessarily mean that this alternative will be appropriate as a substitute for the next kit, even within the same IVD kit line. The properties which make Triton™ X-100 effective in one kit may be completely different to what makes it effective in another, and this is generally only proven through 'trial and error' feasibility testing. As a result, Siemens Healthineers has conducted a full analysis of the impacted product portfolio and launched a 'REACH Response Plan'. As part of this plan, all OPE-dependent products which are connected to the #D [redacted] (e.g. with its #C [redacted] products being #D [redacted], #D [redacted] and #D [redacted] products) or which are expected to have a longer life-cycle[22] are being given the highest priority in terms of Design Change, and plans to reformulate these products are underway on a per product basis. On the other hand, the #D [redacted] platform, which will over time be replaced by the #D [redacted], for evident reasons and as described above, is being given a lower priority. One key objective of the Siemens REACH Response Plan is to ensure that the transition to alternatives for other OPE-dependent products with a longer life-cycle, like the more numerous IVD kits produced by Siemens Marburg in Germany, will be prioritised so as to ensure that the products with the highest potential for emissions to the environment (due to their number and long life-cycle) become OPE-independent as soon as possible, thus minimising OPE environmental emissions. For Siemens Healthineers #D [redacted], the requested review period of 9 years #C, D [redacted], and the knowledge that it would take 5-12 years to implement an alternative (or combination of alternatives), engaging in substitution efforts would make little business sense and would make a poor investment of funds and resources.

Calculation of the theoretical costs of reformulation of OPE-dependent #D [redacted] IVD kits

The time that would in theory be required for re-designing the OPE-dependent #D [redacted] IVD kits is uncertain. Siemens Llanberis have not developed specific estimates of the potential R&D costs of reformulating its OPE-dependent #D [redacted] IVD kits as this is not prioritised by the Siemens "REACH Response Plan". For orientation, the theoretical analysis presented above estimates an implementation period of 5-12 years.

[22] For example: #D [redacted] in analysers which are relevant to the Siemens Marburg AfA.

By way of comparison, if the substitution plan that has been developed for Siemens Marburg (see its separate AfA) could be used as a proxy, one could consider the timeframe of substituting OPEs in Use #2 of the Siemens Marburg AfA (reagent reformulation) as having some high-level similarity to the Siemens Llanberis' situation. For the #C affected Siemens Marburg formulations, an estimated 12 years will be required in Marburg for substituting OPEs. During this period a total of #D,E FTEs are expected to be needed to complete the substitution process. It is assumed that each FTE is equivalent to a cost of #E. This would bring the overall cost for Siemens Marburg to #E (range: €1-10 million).

As #C,D formulations would be involved in such R&D project if Siemens Llanberis were to follow the re-formulation route, it can be confidently stated that the cost of reformulating the #D IVD kits would cost several millions of Euros. Such expenditure would be incurred in the context of a steadily decreasing sales of OPE-free kits #C,D

As far as the cost of re-registration of the impacted kits is concerned, the effort that would be needed and the associated cost are difficult to estimate with a minimum degree of accuracy. On the other hand, downtime costs, described below, will be far more critical.

Potential losses of profits from sales of OPE-dependent #D IVD kits

It was explained above that reformulation of the OPE-dependent IVD kits would take several years, possibly 5-12 years (for instance, the Siemens Marburg REACH Response Plan for Marburg's Use #2 (see separate AfA) assumes 8 years). It has also been explained that for well-founded business and operational reasons (lack of spare R&D capacity), Siemens Healthineers have decided to prioritise other business lines, not the #D platform, within the scope of their REACH Response Plan. As such, no substitution activity is to be undertaken at Siemens Llanberis.

If no Authorisation is granted, substitution will not be feasible. If substitution efforts were to theoretically start in 2021 and were to take an estimated 5-12 years, #D, it is entirely unrealistic that a substantial part of this business would survive the lengthy process of OPE substitution implementation. In other words, in the event of a negative decision from the European Commission, if the OPE-dependent #D IVD kits were taken off the market for a minimum of 5 years (most likely longer) years from the Sunset Date, it cannot reasonably be expected that their commercialisation using alternatives would be possible, let alone successful for a very short period of time afterwards, before Siemens Healthineers #D analysers.

It therefore seems reasonable to assume that beyond the cost of reformulation, Siemens Llanberis would lose the vast majority of the profit from sales of the OPE-dependent #D IVD kits that is projected to be made under the "Applied for Use" Scenario. **Table 3-6** shows that the projected Present Value profit that is anticipated to be made over the requested review period, 2021-2029 is ca. #C,E (range: €10-100 million). Siemens Healthineers typically maintains a very limited stock of kits (for some kits only #C Days Inventory on Hand (DIOH) is maintained at the EDC), thus under Alternative 1 sales of the impacted IVD kits would practically cease soon after the Sunset Date. The Present Value profit losses for the period 2021-2029 can be estimated to be ca. € #C,E (range: €10-100 million). From Siemens Healthineers' perspective, it would thus be a better business decision and more prudent use of resources to discontinue the supply of OPE-dependent kits on the Sunset

Date, rather than pursue alternatives for the affected #D IVD kits [redacted] #D.

Profit losses as a result of erosion on the customer base during the substitution activities

Even if it were assumed that implementation of alternative substance(s) could be achieved in a much shorter timeframe and thus some market for #D IVD kits could be preserved, the anticipated actions of Siemens Healthineers' customers could still render the manufacture of the #C impacted #D IVD kits redundant.

On the Sunset Date and with the #C,D IVD kits unavailable, the customers using the #D analysers would have to seek alternatives, at least for the period of reformulation. These alternatives could, in principle, be:

- Siemens Healthineers' #D Solution analysers, if the EEA-based use of OPEs by Siemens Marburg and its customers have been granted separate Authorisations for Uses #1-5 applied for by Siemens Marburg (assuming that customers would still consider Siemens Healthineers as a reliable business partner following the abrupt loss of #D); or

- Competitor products run on competitor analysers and diagnosing the same/similar range of diseases in patients as those diagnoses provided by the #D whole bullet pt range (the reader is reminded that [redacted] analysers cannot run on third-party IVD kits). It is not known whether any competitor analysers diagnose the identical set of diseases as the [redacted] range, so multiple competitor analysers might be required to provide the same range of patient healthcare diagnostic services.

In either case, in addition to a long tendering and installation process, customers need at least 6-24 months for the validation of a new analyser. If disruption to the supply of #D IVD kits were to last substantially longer, customers would be strongly encouraged to move on to an alternative platform where there is certainty of supply of the IVD products required for their diagnostic testing operations. The uncertainty over the future Authorisation of #D-related OPE-dependent IVD products would probably strongly encourage customers to seek third-party alternatives.

Assuming customers made this change to competitor IVD kits and analysers, it is quite probable that most, if not all, customers would continue to use these alternatives rather than switch back to the OPE-dependent #D kits. Therefore, sales of the #C IVD kits would permanently cease, even if Siemens Healthineers could place them again on the market after the full process of substituting to an alternative substance was complete, i.e. after a minimum of 5 years.

Based on the analysis above, Alternative 1 is not considered economically feasible for Siemens Llanberis.

Availability of Alternative 1

Market availability of potential alternative substances

The availability of potential alternative substances may vary since, as has been explained, it seems very likely that no "one size fits all" solution can be found for the OPE-dependent production process of all #D IVD beads relevant to this AfA. Given that variation, the time required for the implementation of an alternative substance would also vary (see discussion above).

While there are some potential alternative substances which are well-known commercial solutions in the field that can be sourced from several suppliers, other alternative substances have not passed the laboratory level. On the other hand, relatively small amounts of an alternative substance would be needed per year to substitute the current volumes of use of Triton™ X-100. The amount needed for substitution of Triton™ X-100 in all production at Llanberis can be assumed to be below 100 kg (even if concentrations would need to be adapted). As such, market availability of an alternative substance might not prove to be a major stumbling block, regardless the identity of the alternative (unless it is an entirely novel solution).

Operational availability of potential alternative substances

As a consequence of the description of the substitution process described above, a substitution of Triton™ X-100 by another substance in the Applied for Use for Llanberis would require 5-12 years to be complete across all relevant countries. If laboratory testing and validation proves to be complex, the time needed until products can be introduced to the market would be towards the high end of this range.

The substitution process described above has to be seen in the light of the overall Siemens Healthineers' strategy linked to the #D platform. #C,D . Therefore, there will be a need to be able to supply #D . If substitution of Triton™ X-100 were to take a minimum #C years, the newly OPE-independent IVD kits would only become available for a very short period #D . It should also be noted that the future of the applied for use is also tied closely to the outcome of the separate AfA that is submitted by Siemens Marburg for the use of OPE in the #D #D which is used on every #D analyser alongside the IVD kits that are manufactured in Llanberis. Without certainty that Siemens Marburg is granted an Authorisation, committing funds and effort in the substitution of OPE in the manufacturing processes of Siemens Llanberis could not be contemplated.

Availability of necessary resources for reformulation of OPE-dependent #D IVD kits

As noted earlier, the #D business line does not have the additional R&D resources required to initiate the reformulation of the impacted IVD kits as available R&D resources are mainly assigned to work on the #D platforms.

Overall, both the availability of resources and the timeline of implementing an alternative substance in IVD kits #D limiting factors for the substitution of Triton™ X-100.

Hazard and risk of Alternative 1

A general evaluation of a Triton™ X-100-independent alternative kit reagent is very difficult, since the selected alternative substance would be highly reagent-specific. Whether or not an alternative reagent has less hazardous properties cannot be evaluated on a generic level as there is no "one size fits" all solution for the substitution of Triton™ X-100 in the Applied for Use.

For the substances discussed in **Table 4-3** their hazard classification indicates that a reduced hazard profile compared to the OPEs could be achievable.

Conclusions on Alternative 1

Alternative substances are an important component of the overall Siemens Healthineers' OPE substitution strategy under their REACH Response Plan. Given the broad range of diagnosis parameters and analyser systems in the corporate portfolio, it is a core part of the strategy to reformulate solutions that contain OPEs to maintain the broad diagnostic capacity of Siemens Healthineers' analysers.

The above is only a theoretical discussion of the challenges of substituting OPE in the #D applied for Uses use in Llanberis as Siemens Healthineers is in #D transitioning customers to a new platform, the #D #D. The #D offers an assay menu providing many of the same tests currently provided by the #D IVD kit range.

Given the significant effort that Alternative 1 would involve #D, this alternative cannot be viable for Siemens Llanberis. The phasing out #D will lead to the gradual reduction in volumes of use of OPEs in the production of the #C IVD kits relevant to this AfA. These resources would best be used in the development of alternative products and platforms that do not rely on OPEs anymore while consumption of OPEs in Llanberis gradually diminishes and eventually ceases #D.

In conclusion Alternative 1 is not a feasible alternative for Siemens Llanberis.

4.3.2 Alternative 4 – Relocation of production of beads outside the EEA, and import the coated beads

Description of Alternative 4

Alternative 4 would entail the relocation of the bead manufacturing equipment to a location outside the EEA from where bead washing and coating processes would continue after the Sunset Date.

Technical feasibility of Alternative 4

Finished beads do not contain any Triton™ X-100, they can therefore be manufactured with OPE-containing buffers outside the EEA and then imported into the EEA without their end use requiring an Authorisation[23]. This assumes that the use of Triton™ X-100 in the place where bead coating and washing would be relocated to is permitted under local legislation.

Siemens Healthineers has production sites in the USA, where manufacturing operations are also performed to produce IVD kits on other platforms. This also involves antibody technologies for the manufacture of beads. Before 2008, about 50% of the bead production was undertaken by Siemens

[23] This again is only true for the beads; note that the IVD kits that contain the beads would need to be used alongside the OPE-containing #D #D (which is subject to a separate AfA submitted by Siemens Marburg).

Healthineers in its Los Angeles facility in the USA. A decision was taken in 2008 to transfer almost all manufacturing of #D products to the Llanberis site. Due to their current operations and past experience with #D, it can be assumed that there is sufficient expertise and experience available at the Los Angeles site to make the production of beads for #D IVD kits feasible.

It would also be feasible to consider the involvement of a third-party manufacturer in a non-EEA country who would perform the bead coating process (potentially even using the bead coating chambers from Siemens Llanberis' plant).

Beyond the practical implementation of relocation, this alternative may well have regulatory implications; a change of the legal entity of the IVD kit manufacturer would also require re-registration in almost all countries. To minimise this potential regulatory burden, Siemens Llanberis could aim to remain the Legal Manufacturer.

To provide an estimate of the anticipated period required for the implementation of this alternative, the following activities would be envisaged:

1. Pre-submission enquiry to US FDA (advisable step): 3 months.
2. Physical relocation of equipment, acquisition of new staff, training: 3-6 months.
3. Validation of equipment, process and product: 12 months.
4. Pre-Market Notification to US FDA: 8 months (worst-case).

Thus, implementation of a relocation strategy and re-registration of the process and the IVD kits would possibly take 2.5 years, a period during which Siemens Llanberis would be unable to manufacture the OPE-dependent #D IVD kits. This production gap could not be closed by building up a stockpile of the #C IVD kits. Their shelf-life at 2-8 °C is only 18 months, which is not sufficient for building a 'bridge' until the technical process is established at the other site and re-registration is finalised.

Overall, this alternative is technically implementable but would by necessity require a lengthy period of downtime during which global sales of the OPE-dependent #D IVD kits would have to be suspended.

Box 4-1: Would stockpiling of beads be an option?

Theoretically, manufacturing of larger volumes of beads prior to the Sunset Date for the purposes of stockpiling would be an option. However, it would not offer a viable solution to non-Authorisation as beads are not stockpiled on their own but only as components on IVD kit reagents. These reagents have a shelf-life of 18 months. Manufacturing beads worth a longer period of time would be pointless as the reagents would go out of date by mid-2022 at the latest. Other considerations include the introduction of a night shift to increase capacity (requiring consultation) , availability of beads is not a given as #C, D; planning ahead could be complex. In conclusion, any attempts at stockpiling would have a minimal effect towards alleviating the adverse impact of non-Authorisation

Economic feasibility and economic impacts of Alternative 4

A change of legal manufacturer would require re-registration in almost all countries – see Section 4.3.1 on Regulatory re-registration. The costs of re-registration would be those described above for Alternative 1. Part of these costs could be avoided by keeping Siemens Llanberis as the Legal

Manufacturer, which is feasible. The engineering/start-up cost of re-location itself is estimated to be at least € #E .

We may further assume that:

- It would take 2.5 years for before beads manufactured outside the EEA could start to be shipped to Llanberis;
- Stockpiles of Llanberis-manufactured coated beads would only be available for a period of 1.5 years, thus leaving a gap in the supply of the #C impacted IVD kits for a period of one year; and
- #D customers could not wait for a year without the supply of these IVD kits. For reasons for business continuity and in order to meet their own contractual obligations, these customers would be strongly motivated to validate and switch to a third-party analyser.

Overall, keeping the OPE-dependent #D IVD kits off the market for one year or longer would mean that the customer base would be eroded. Customers would be very unlikely to return to the #D platform after having invested money and time in switching to an alternative analyser platform. With reference to the assumptions made for Alternative 1, it can be assumed that Siemens Llanberis would lose the profit from sales of the #C,D IVD kits over the period 2021-2029. **Table 3-6** shows the projected Present Value profit that would be lost would be ca. € #C, E (range: €10-100 million).

Based on the analysis above, Alternative 4 is not considered economically feasible.

Availability of Alternative 4

Currently, there is no Siemens Healthineers facility anywhere in the world where the Siemens Llanberis bead manufacturing process could be relocated without any adaptations. The most likely relocation site is the Siemens Healthineers site in Los Angeles, USA.

On the other hand, as presented above, it would not be possible to commence bead manufacturing outside the EEA for a substantial period due to engineering requirements and regulatory obligations. As such, this alternative cannot be available at the Sunset Date.

Hazard and risk of Alternative 4

Relocating the manufacture/coating of the beads would eliminate the use of Triton™ X-100 in the EEA in the applied for use without introducing any potential risk from the use of an alternative surfactant. In this respect, this alternative would therefore have no hazard and a lower risk than the "Applied for Use" Scenario.

Conclusions on Alternative 4

This alternative is technically possible but #C unrealistic. Importantly, it would be accompanied by significant length of downtime, loss of sales and a concomitant erosion of Siemens' customer base. As such, it is not economically feasible. #D , engaging in major operational changes would be accompanied by disproportionate costs and poor business justification.

4.3.3 Alternative 5 - Discontinue supply of OPE-dependent IVD kits for the #D platform

Description of Alternative 5

Alternative 5 for the use of Triton™ X-100 by Siemens Llanberis would be to bring the manufacturing of the OPE-dependent #D IVD kits to an end and stop supplying these kits to the customers.

Technical feasibility of Alternative 5

This alternative is technically feasible in that it can be readily implemented by Siemens Llanberis making the decision to discontinue the manufacture of the OPE-dependent #D IVD kits.

Economic feasibility and economic impacts of Alternative 5

If sales of the OPE-dependent #D IVD kits stopped on the Sunset Date, the profits that Siemens Healthineers would have gained from the sales of the OPE-dependent kits thereafter would be lost. In accordance with estimates shown earlier, profit losses under Alternative 5 for the period 2021-2029 would be ca. € #D (range: €10-100 million).

It is of note that of the #D analyte types which cover the #D impacted #D IVD kits, #D are part of the #D and #D are part of the #D). These are of economic importance to Siemens Llanberis:

- The #D (paragraph) disease state[24] was Siemens Llanberis' largest in terms of revenue in 2017 (range: €10-100 million)) representing approximately % (range: 10-50%) of total IVD reagent revenue. The assays are typically run as a panel, the discontinuation of the affected assays would have an adverse impact on sales for the rest of the assays;

- Of the affected assays, four are part of the #D (paragraph) disease state . The disease state was Siemens Llanberis' second largest in terms of revenue in 2017 (€ (range: €10-100 million)), representing approximately % (range: 10-50%) of total reagent revenue. The assays are typically run as a panel, the discontinuation of the affected assays would have an adverse impact on sales of the rest of the assays.

Overall, sales of IVD kits within these states represented approximately #D % of the #D reagent revenue, amounting to € #D, E (€10-100 million) in 2017. If Siemens Llanberis stopped supplying the OPE-dependent IVD kits, it is likely that the customers currently carrying out these tests would stop running the panels all together, which would have a large impact on Siemens Healthineers global business.

[24] Disease state = the circumstances or attributes of a state of health; panel = when several different assays/kits are used in parallel to determine a disease state.

Another risk with discontinuing the supply of the #D impacted IVD kits is that the customers who are relying on the continuation of the supply of #D IVD kits until the end of life support could choose to move to a different platform earlier than originally planned. This might not be a replacement Siemens Healthineers platform #D in which case customers might choose to move to a competitor's platform[25]. In any case, this would lead to additional a profit loss for Siemens Llanberis, as only #D products are manufactured on the Llanberis site.

The lower bound of the profit lost for Siemens Llanberis will be related to the lost sales of the OPE-dependent #D IVD kits over the period 2021-2029 (€ #D , E , (range: €10-100 million), NPV, 4% discount), but as explained above, the actual loss may be substantially higher, due to a likely reduction in the sales other IVD kits in the overall #D portfolio.

Based on the analysis above, Alternative 5 is not considered economically feasible and would naturally have a severe impact on employment at the site

Availability of Alternative 5

This criterion is not relevant to the analysis. Cessation of production could be implemented (but at significant cost and impacts on the applicant and their employees and customers).

Hazard and risk of Alternative 5

Cessation of the processing of the beads and the manufacture of the OPE-dependent #D IVD kits would eliminate the use of Triton™ X-100 in the EEA in the applied for use without introducing any potential risk from the use of an alternative surfactant. In this respect, this alternative would therefore have no hazard and a lower risk than the "Applied for Use" Scenario.

Conclusions on Alternative 5

This alternative is technically feasible but economically infeasible. It would result in significant loss of profit and would be certain to precipitate the termination of the entire #D business in Siemens Llanberis and the loss of hundreds of jobs.

4.3.4 Alternative 6 - Discontinue supply of all #D IVD kits

Description of Alternative 6

Alternative 6 for the use of Triton™ X-100 by Siemens Llanberis would be to bring the manufacturing of the all #D IVD kits to an end and stop supplying these kits to the customers.

[25] The end use of the OPE-containing reagents and wash solutions by customers is also subject to a separate AfA submitted by Siemens Marburg (Uses #4 and #5), therefore, the feasibility of a switch to the #D will depend on the outcome of other AfAs too.

Technical feasibility of Alternative 6

This alternative is technically feasible in that it could be implemented by Siemens Llanberis making the decision to discontinue the manufacture of all #D IVD kits. This should not, however, be considered an easy decision to make.

Economic feasibility and economic impacts of Alternative 6

Under Alternative 6 the entire #D product portfolio would be removed from the market. This means Siemens Healthineers would lose the profits from the sales of all #D IVD kits which are produced at the Llanberis site. **Table 3-7** shows the volumes and corresponding profits from the sales of IVD kits in the period 2021-2029. If Alternative 6 were to be implemented, the profit that would be lost would be € #D, E (range: €0.1-1 billion).

#D, E

Based on the above analysis, Alternative 6 is not considered economically feasible and would be much costlier than the other three alternatives investigated above.

It should be clear that if an Authorisation was not granted for Use 3 of OPE (#D formulation) in the Siemens Marburg's separate AfA, the whole Llanberis site would have to shut down since all IVD kits made in Llanberis (whether they contain OPE or not) can ultimately only be used alongside the #D IVD wash solution (#D). In addition, the actual downstream use by Siemens Healthineers' customers of the #D is also subject to a separate AfA by Siemens Marburg (this is Use 5). If that applied for use was not authorised, again, Siemens Llanberis would be forced to shut down, irrespective of the outcome of the present AfA.

Availability of Alternative 6

This criterion is not relevant to the analysis. Cessation of production could be implemented (but at significant cost and impacts on the applicant and their employees).

Hazard and risk of Alternative 6

Cessation of the manufacture of all #D IVD kits would eliminate the use of Triton™ X-100 in the EEA in the "Applied for Use" Scenario. In this respect, this alternative would therefore have no hazard and a lower risk than the "Applied for Use" Scenario.

Conclusions on Alternative 6

This alternative is technically feasible but economically not feasible. It would result in significant loss of profit, certain closure of the Llanberis facility and job losses.

4.4 The most likely "Non-use" Scenario

There are common elements among the shortlisted alternatives considered above, these are:

- Long implementation periods and associated downtime/suspension of sales;
- Inability of #D customers to source third-party IVD kits for these diagnostic tests for use on their #D analysers; and
- Inability (but also reluctance) of #D customers to endure reduced/impaired functionality of their #D analysers whilst Siemens Healthineers implements an alternative.

Realistically, current users of the #D impacted #D IVD kits would most likely replace their #D analysers with third-party replacements (the #D analysers would still rely on the use of OPE and the continued use of OPE-containing IVD kits and wash solutions is contingent to an Authorisation being granted for two separate uses applied for by Siemens Marburg on behalf of their customers). Once the analysers of those customers are replaced, market demand for the #D impacted #D IVD kits would permanently cease. Having made a transition to a new analyser, these customers would be extremely reluctant to return to #D products. Moving to another platform requires significant effort to tender for, acquire and validate a new immunoassay system as well as to re-baseline many patients being monitored for various diseases including cancers. As such, it is safe to assume that once customers move away from #D they will stay away permanently.

For this reason, the most likely "Non-use" scenario would be Alternative 5, that is, cessation of the manufacturing and sales of the OPE-dependent #D IVD kits.

On the other hand, a reduction in the portfolio of tests that can be carried out by the #D analysers and a reduction in the overall number of users of #D analysers could mean that the entire #D business line becomes unviable and thus, ultimately Alternative 6 becomes the end-state, that is, cessation of the manufacturing and sales of all #D IVD kits. As described above, this means that the entire Llanberis site would shut down, including all supporting services.

To ensure that the benefits of granting an Authorisation are not overestimated, Alternative 5 will be taken forward as the "Non-use" Scenario.

5 Impacts of granting authorisation

5.1 Economic impacts – benefits of continued use

5.1.1 Introduction

The main assessment period used in this analysis is 9 years, the period 2021-2029 (inclusive), to reflect the requested review period. A short consideration of potential impacts of a shorter review period will also be presented for illustrative purposes.

Under the "Non-use" Scenario, Siemens Llanberis would cease its use of Triton™ X-100, but continue to produce non-OPE dependent #D (paragraph) IVD kits. Note that this is only feasible if Siemens Marburg is granted an Authorisation for (a) its own use of OPE in the formulation of the [redacted] (Use #3) and (b) the customer use of the OPE-containing [redacted] which is used on all [redacted] analysers (Use #5). This would mean that Siemens Llanberis would no longer manufacture beads using Triton™ X-100 and the OPE-dependent [redacted] IVD kits currently containing these beads could no longer be supplied. Consequently, suppliers of raw materials would no longer be able to supply their products to Siemens Llanberis and customers/users of the [redacted] impacted IVD kits would not be able carry out the affected diagnostic tests using the [redacted] analyser. The customers would have to seek alternatives or discontinue these tests.

5.1.2 Economic impacts for Siemens Llanberis

Section 3.2.2 provides an overview of the profit Siemens Llanberis is expected to earn over the requested review period. This profit represents parts of the benefits to society from granting an Authorisation, as opposed to the "Non-use" Scenarios in which the manufacturing of beads using OPE in the EEA in the manufacturing process would have to cease.

By way of summary, it was discussed in Section 4.3.3 that the costs to Siemens Llanberis under the "Non-Use" Scenario cannot be fully quantified, but as a lower bound, losses are assumed to equate to the "Applied for Use" projected profits from the sales of the OPE-dependent IVD kits over the period 2021-2029. For the "Non-use" Scenario, it should be noted that the reduced diagnostics portfolio for the #D (paragraph) analysers may lead to customers moving away from Siemens [redacted] products, both analysers and kits, altogether. This would mean that profits from sales of <u>all</u> [redacted] IVD kits to these customers could be lost. If a substantial proportion of the customers abandoned Siemens Healthineers' [redacted] analysers, the continued operations at Llanberis might no longer be profitable, in which case operations would cease and all profits related to the [redacted] platform would be lost (corresponds to profit loss under Alternative 6 in Section 4.3.4).

Table 3-6 shows the profit loss from loss in sales of the #D impacted products; the Present Value of this loss for sales to both EEA and non-EEA-based customers over the period 2021-2029 (4% discount) is € #D, E (range: €10-100 million). For illustrative purposes, the lost sales and profits for all #D [redacted] IVD kits over the same period would be € #D, E (range: €0.1-1 billion), based on the figures shown in **Table 3-7**.

It is possible that Siemens Llanberis may face legal penalties if the company is unable to distribute products it is contracted to supply. However, this could depend on the customer, the contract and the country, as laws may vary. There is no way to estimate/quantify the potential impact (if any) on the early discontinuation of #D products #C, D [redacted]

5.1.3 Economic impacts for other Siemens Healthineers operations within the EEA

Two key sites are of relevance to the operations of Siemens Llanberis:

- Siemens Marburg (in Germany) manufactures the #D which is used with all #D assays; and

- The Siemens European Distribution Centre (EDC) in Duisburg (Germany) which distributes IVD kits and #D manufactured in Llanberis and Marburg respectively (as well as IVD kits or their components that are made by third parties (OEMs)).

Clearly, in the event of non-Authorisation, the inability of Siemens Llanberis to manufacture and place on the market a series of #D IVD kits would have an impact on sales of the #D. Ultimately, any non-Authorisation for either the present Applied for Use or that discussed in the Siemens Marburg AfA would have repercussions for the other Applied for Use. Such impacts are quantified in the separate AfA submitted by Siemens Marburg. By way of demonstration, Section 3.2.2 has explained that the OPE-dependent kits represent ca. #D % (range: 10-50%) of all profits made from sales of #D IVD kits. Assuming that the same percentage applies to sales of #D #D "Non-use" Scenario, the losses in profits for Siemens Marburg from a reduction in the global sales of the #D #D would be #D, E (range: €0.1-1 million) (Present Value, 4% discount, 2021-2029) – see Table 3-18 in the Siemens Marburg AfA for Use #3.

On the other hand, impacts on the EDC specifically arising from the non-Authorisation of the present Applied for Use would be minimal.

5.1.4 Economic impacts for other Siemens Healthineers operations outside the EEA

If Siemens Llanberis were unable to continue producing and selling the impacted IVD kits, this would reduce the number and volume of critical raw materials required from the Siemens, Los Angeles site. As noted earlier, the Siemens Manufacturing Center in Los Angeles produces rare reagents and critical raw materials (biological) which are supplied to the Llanberis site. At the same time, demand for #D analysers made in Flanders, New Jersey (USA) could be impacted if non-Authorisation would result in a reduction in the #D assay portfolio. As explained in Section 3.2.2, for the critical period (after the Sunset Date), a Present Value profit of ca. € #D, E (range: €1-10 million) is expected to be made by the US manufacturer from sales of (range: 100-500) new #D analysers; for the EEA in particular, the relevant figures are (range: 50-100) analysers and € #D, E (range: €0.1-1 million) profit. If #D % of these sales were to be impacted, the profit loss for Siemens Healthineers associated with lost sales arising within the EEA would be #D, E (range: €0.01-0.1 million). Profit losses associated with sales to non-EEA customers are assigned to the US operations and thus is not considered a relevant impact for the present analysis.

On the other hand, the Glasgow, Delaware (USA) site of Siemens Healthineers supplies only one material to Llanberis; as such the impacts on its operations from non-Authorisation would be small. Similarly, while most of the Llanberis #D products are distributed via the European Distribution Centre (EDC), some are also distributed via the American Distribution Centre (ADC) but impacts on the ADC operations from non-Authorisation would be minimal.

5.1.5 Economic impacts for suppliers

Suppliers materials to Siemens Llanberis

The suppliers of Siemens Llanberis are likely to experience reduced profits, if they can no longer supply (a proportion of) their goods to the Llanberis plant. Section 3.2.4 shows that the value of relevant contracts to EEA-based suppliers is very small and thus losses for suppliers under the "Non-use" Scenario can be disregarded.

5.1.6 Economic impacts for Siemens #D customers

This sub-section first considers possible "Non-use" Scenarios specifically for Siemens #D customers, then discusses the impacts of granting an authorisation for these customers.

Introduction – "Non-use" Scenario for customers

If Siemens Llanberis is not granted an Authorisation for the continued use of OPE in the manufacturing of beads, none of the #D IVD kits that contain these beads can be supplied to their customers. **It is not possible to use 3rd party kits in an #D analyser**, which means that none of Siemens Healthineers' impacted customers would be able to carry out the tests facilitated by the affected IVD kits using their #D analyser and supply results back to healthcare providers and, ultimately, patients. In some cases, customers are specifically using the analyser for the impacted kits, which would render the analyser totally unusable.

Dependent on whether OPE-free IVD technology is available on market, the customers may choose to:

- Prematurely invest in a new analyser which can replace their existing #D analyser – this might be a Siemens Healthineers one or a third-party one;
- Potentially outsource some of the tests to other laboratories; or they
- Discontinue the affected diagnostic testing until such technology has been developed.

It is currently not known whether other actors on the EEA market can provide OPE-free technology which can be used to diagnose the same health conditions instead of the #D OPE-dependent IVD kits. Consequently, it is not possible to establish a single "Non-use" Scenario for Siemens #D customers. The range of possible "Non-use" Scenarios is presented below.

Scenario 1: Switch to a Siemens Healthineers #D analyser

Siemens Healthineers' #D (paragraph) analysers aim to gradually replace analysers on the market. (at the manufacture and the end-user level) and as such the future of the is dependent on the outcome of AfAs that are separately being submitted by Siemens Marburg. In any case, as of early 2019, the , e.g. there is no assay available and currently no other platform that offers equivalent testing (which is a significant part of the offering).

It would also be fair to assume that if Siemens Llanberis failed to obtain an Authorisation for its use of modest volumes of OPE in the manufacture of the OPE-dependent IVD kits, it would be most likely that the prospects of Authorisation for the more voluminous and dispersive uses of OPE applied for by Siemens Marburg would face a similar unfortunate non-Authorisation outcome.

Moreover, if Siemens Healthineers were to suddenly become unable to service the running stock of #D analysers in January 2021 (and note that some of those analysers would only be a few months or years old), the reputational impact on Siemens Healthineers would be such that customers would likely prefer to seek alternative suppliers anyway.

Overall, the prospect of customers switching to an #D analyser as a replacement for their current #D analyser(s) is highly uncertain.

Scenario 2: Switch to a third-party analyser that can deliver the same assays

OPE-free IVD technology for the same diagnostic tests may be available on the EEA market from the following two possible sources:

- Other EEA manufacturers may theoretically produce OPE-independent kits (and #D) or perhaps will be successful in obtaining a REACH Authorisation for their continued use of OPE in the EEA; or

- Non-EEA manufacturers may (like Siemens Llanberis) produce OPE-free kits but because the production is outside the EEA, the use of OPE in the manufacturing process is not relevant to the Authorisation process.

Siemens Llanberis cannot express an informed view as to whether such replacement of analysers could be successful as it cannot be certain of the current/future dependence of competitors on OPE or their plans for OPE substitution or Authorisation or the prospects of their success.

It is worth noting that several of the affected #D assays (such as #D are considered uncommon and are not widely available on other automated immunoassay systems. Therefore, even if suitable third-party analysers could be identified, Siemens Healthineers #D customers might still be unable to undertake all diagnostic tests that are of relevance and importance to them.

Scenario 3: Outsource diagnostic testing

In theory, Siemens Healthineers #D customers might choose to outsource the testing to another laboratory that has analysers capable of delivering such tests. Such outsourcing might also be considered a stop-gap option when a new analyser is tendered for, brought in and must be validated; this process of validation alone lasts a minimum 6 months and often much longer, as previously described.

There are five key issues with outsourcing diagnostic tests:

- **Availability of relevant OPE-independent technology**: as previously noted, Siemens Llanberis cannot be certain whether there exist third-party analysers that could deliver the assay testing that would become unavailable on the #D platform on the Sunset Date under the "Non-use" Scenario;

- **Capacity**: outsourcing the diagnostic tests could work if capacity in reference laboratories exists. Consultation input from customers of Siemens Marburg suggests that the number of samples that would need to be sent out would be far too high making this an unrealistic option in many cases;

- **Cost**: outsourcing would make operations costlier. If outsourcing was a cheaper option, it would have been already chosen by Siemens #D customers. A 2007 paper by US-based researchers indicated that reference laboratory testing comprised only 1.6% of total testing volume in 2006, while contributing a disproportionate percentage of total laboratory cost (19.5%) (Ardisson, Iafrate and Lewandrowski, 2007). Therefore, costs may increase and for this reason outsourcing may be used only as a temporary solution until a new analyser is purchased and is ready to replace an existing #D analyser;

- **Time**: the logistics of outsourcing would be prohibitive and the turnaround time would be too long as, for some IVD assays at least, very quick results are needed in order to ensure safe acute treatment of patients; and

- **Willingness of the customers**: seeing that the customers have shown a preference for having an in-house analyser (otherwise they would already outsource their tests today), it is reasonable to assume they would still prefer this option especially if outsourcing would need to be undertaken over many years rather than over a short period of time.

It can be concluded that outsourcing might be an option only for (a) customers with small number of affected tests which do not require instant results and have or can establish a business relationship with a larger reference laboratory, and/or (b) a limited period, as a temporary solution to an acute supply problem. The patterns and cost of outsourcing of testing during the period of transitioning to the new analyser are likely to vary between customers and it is not possible to quantify the associated costs.

In the context of this analysis outsourcing is considered as a possibility only if OPE-free technology is available within the EEA. The realism of outsourcing the testing to third party laboratories outside the EEA is questionable, as, arguably, the results of tests would be obtained with considerable delay and at an increased cost to cover collection and transport to the non-EEA diagnostic testing facility. Moreover, it is uncertain whether there would be enough capacity outside of the EEA to deliver the tests required by Siemens Healthineers #D customers based in the EEA.

Scenario 4: Stop the delivery of diagnostic tests

If OPE-free technology is not available on the EEA market, Siemens #D customers would have to stop providing the diagnostic tests connected to the OPE-dependent #D IVD kits.

Discontinuing the diagnostic tests could adversely affect patients' health; as discussed above, some of the affected diagnostic tests are uncommon and inability of Siemens Healthineers #D customers to deliver these tests would have extremely adverse effects on EEA patients. For this reason, users of #D analysers (for example, hospitals) would do their absolute best to identify alternative solutions.

Conclusion

The above analysis presents some important facts:

- Siemens Healthineers #D customers will do their utmost to continue delivering the impacted assays. If this was not possible, patient health impacts would be severe;

- Outsourcing of diagnostic testing is not a realistic or sustainable solution. It might be considered for a few weeks or months and only if OPE-free technology (or authorised OPE-dependent technology) was available within the EEA; and

- Siemens Llanberis cannot be certain as to whether suitable third-party analysers exist and whether these can deliver the required testing. Siemens Healthineers' #D cannot be relied upon to deliver the required tests due to its future being dependent on the outcome of separate AfAs.

For the purposes of the analysis here, we will assume that Siemens #D customers would opt to prematurely invest in a new third-party analyser which can replace their existing #D system. This key assumption hinges upon the assumed existence of OPE-independent or OPE-authorised alternative technologies on the EEA market on the Sunset Date.

In all cases, the practicalities of implementing an alternative technology would have to be considered. Such practicalities include:

- **Availability of same range of tests**: any alternative system would need to cover the full range of tests that the end-user currently utilises within the one system. While the typical assays offered on one immunoassay system are generally offered on another, there can be tests which are unique to certain systems. For example, a customer using an #D system may be utilising the #D range available on that technology. If there is no alternative system which offers (OPE-free) immunoassay tests for the specific disease assays the end-user requires and also has the allergen functionality, the end-user would need to purchase a separate system and run two alongside. Naturally, it is not possible to know or predict what the dependence of competitor platforms on OPE-containing IVD products would be on the Sunset Date;

- **Sufficient space to introduce an additional analyser platform**: any new analyser system or range of systems would need to fit within the current laboratory space. This is often a severe limitation particularly in older buildings. As per the above bullet, this could be a particular problem if additional analyser systems are required to cover the full range of tests; and

- ***Availability of trained staff to perform the alternative technology***: when new analysers are introduced, the existing staff needs to be trained to be able to apply this technology. In the best case, the alternative technology is another analyser that requires similar handling to the existing analyser technology. Then some time is needed to train the staff to operate this analyser. In case the new analyser is being added to an existing one potentially a slightly increased staff number is needed (at least if the old analyser can still be operated and the systems are operated side by side). In case the technology needs far more manual handling, more staff would be needed to perform the same number of diagnostic tests.

Cost of early replacement of #D analysers

If third-party analysers that use IVD kits that are not dependent on OPE (or their associated use of OPE is authorised) and serve the same diagnostic purposes are available on the market, Siemens Healthineers #D customers would invest in new analysers. Customers would have to replace their analysers as soon as possible after the Sunset Date[26] to be able to continue to supply the same range of diagnostic tests.

[26] Assuming the Authorisation decision is clear on the Sunset Date.

Two groups of #D analysers can be distinguished:

- Those belonging to the existing (2017) stock of analysers; and
- Those projected to be sold in the period 2018-2020.

In relation to the existing stock, **Table 2–2** showed that #D analysers were operational in the EEA in 2017. **Table 3–9** further shows that for most of the existing stock, the average age of the analysers in January 2021 will exceed their average lifetime (typically around #D years). As such, it can be assumed that a considerable proportion of the existing stock of EEA-based #D analysers will generally have reached the presumed end of their typical lifetime at or near to the Sunset Date and thus that they would have to be replaced anyway, irrespective of the outcome of this AfA. Therefore, the cost of prematurely replacing this part of the stock of analysers can be disregarded. This approach of course is based on an average life assumption and within the existing stock of analysers some may indeed be reasonably young. Thus, this assumption will underestimate the cost of replacing the existing #D analysers on the Sunset Date.

On the other hand, **Table 3-10** shows that in the period 2018-2020 #D (range: 100-1,000) 27 new #D analysers will be sold in the EEA. In January 2021, these analysers will be between 1 and 3 years old and therefore their premature replacement would translate to a future cost being brought forward by 5-7 years. As such, premature replacement costs are more relevant for #D analysers sold by Siemens Healthineers in the period 2018-2020, i.e. up to the Sunset Date.

While it has been noted that #D analysers may last for longer than #D years (lifetimes of #D years are not uncommon), the assumptions made here generally therefore underestimate the cost to Siemens #D customers in the EEA.

The Present Value cost to Siemens Healthineers' customers from the premature replacement of #D analysers sold in the EEA in the 3-year period of 2018-2020 is given in **Table 5–1**. Some key assumptions have been made for a basic calculation of costs to be performed[28]:

- Only #D % of the analysers projected to be sold between 2018 and the end of 2020 would be impacted. This is in line with the #D % of impacted Llanberis-manufactured #D products and assumes both that a) use of the analysers with Llanberis-made OPE-independent products would continue, and b) importantly, that Siemens Marburg and the downstream users are granted the authorisations required for the continued use of the #D OPE-containing #D ;

- New analysers, manufactured by Siemens Healthineers and other companies, are assumed to have comparable prices. The analyser prices are also assumed to increase in line with

[27] #D

[28] The sale of analysers is far more complicated than what these simple calculations suggest. For instance, these calculations ignore the commonly used in the EEA business model of seeding instruments (i.e. placement for free and financed through reimbursement for reagents). This business model could exacerbate impacts on Siemens Healthineers' customers under the "Non-use" Scenario. Arguably, the cost for customers in seeding models might be even higher compared to a purchase of instruments or at least at the same level as the reagent prices would include the costs of the provision of the instrument. Given the significant variation in these types of contracts and lack of available data to support this type of analysis, the current calculation is considered the most appropriate approach.

inflation, which means that real prices are assumed to be constant throughout the review period. For the purpose of calculating the avoided capital costs for Siemens Healthineers #D customers, the average price of #D , ca. € #D (range: €10,000-100,000), is used as the indicative future price for all new analysers;

- This premature investment will lead to additional costs for Siemens Healthineers' customers, as they could have alternatively invested the funds in assets that would yield a return. This lost yield is reflected in the discount rate the actor uses when deciding to invest in an asset or not. Siemens Healthineers' customers are diverse, spanning both commercial and not-for-profit actors, so it has not been possible to obtain a common interest rate that reflects the alternative costs in the sector. For the purposes of this analysis, we will instead use the social discount rate of 4%; and;

- Customer expenditure on a new analyser is assumed to take place in 2021 and the additional cost due to premature investment is estimated as *(1+discount rate)^(remaining life time)*.

Table 5–1: Cost to Siemens #D, E (table) customers of premature replacement of analysers bought in the period 2018-2020							
Number of affected analysers in the EEA - % of analysers sold	Average age in the EEA In Jan 2021	Expected lifetime	Remaining lifetime in 2021	Average market price per analyser (€)	Average cost of premature investment per analyser (€)	Total cost of premature investment (Jan 2021)	Total cost of premature investment (PV, 2017)

The additional cost of premature investment is estimated at € #E (range: €0.1-1 million). Essentially, even though the real price of the analysers remains constant, due to discounting, there will be an added cost for Siemens Healthineers #D customers from having to buy a new analyser earlier than planned. Impacts would also arise for non-EEA operators of #D analysers but these are not considered in this analysis.

Note that the avoided capital costs for the customers are not dependent on whether they buy the analysers from Siemens Healthineers or from another company. It is also anticipated that the costs of non-Siemens Healthineers IVD kits would be generally similar to those of #D IVD kits.

Other costs associated with the premature replacement of #D analysers

Validation costs: as briefly mentioned above, there will be a transition period of at least six months when switching from one platform to another. The new analyser would need to be tested, tests results will need to be verified and, in some cases, new benchmark values (values against which test results are measured) would have to be established.

Lost profits: Siemens Healthineers' customers who engage in commercial activities would lose profit for the duration of the validation period. It has not been possible to acquire the information necessary to calculate the lost profits for these actors.

Potential outsourcing costs: if the new analyser is not acquired early enough to complete the necessary validation testing before the Sunset Date, Siemens Healthineers #D customers might need to outsource or cease the testing during the verification period. This cost cannot be quantified

(but see the 2007 article referred to above which shows the increase in testing costs when testing is outsourced).

Impacts on workflow: while the Siemens Healthineers analysers can be placed alongside competitor analysers, laboratories tend to prefer consolidation to one analyser/supplier if possible, to improve workflow efficiency. As such, having to introduce new, potentially non-Siemens Healthineers analysers, or even a range of analysers to encompass the required range of tests, to their operations could be anticipated to affect the workflow of the customers.

Conclusion

This sub-section has outlined the possible scenarios for Siemens Healthineers #D customers in the EEA in the event of no Authorisation being granted. Clearly, for these customers, the benefits of authorisation being granted for the continued use of Triton™ X-100 in the manufacture of OPE-free IVD kits in Llanberis are the retaining of important diagnostic tests on the market and the avoidance of increased costs or time delays for associated diagnostic testing. While the focus here is on EEA customers, the benefits will be similarly relevant globally to all Siemens Healthineers #D customers around the world.

5.1.7 Economic impacts for consumers/patients

Under the "Non-use" Scenario, patients relying on tests provided by Siemens Healthineers' direct customers may experience disruption to the availability of diagnostic testing for a certain period as well as economic losses due to increased costs of testing; in the worst case, some assays might become unavailable, if they cannot be found on third-party analysers. As shown above, any (short-term) outsourcing of diagnostic testing would increase the operating costs of Siemens Healthineers #D customers who would also face the prospect of premature investments into new analysers.

In addition, for an assay design such as #D which is also highly competitive in terms of automatization, ultimately, its non-availability through the #D platform would increase the cost and/or time for patients to obtain results.

However, any price increase would simply be a transfer of the costs from the direct Siemens Healthineers #D customer (hospital, commercial laboratory or other facility) to the patient or health insurance systems. Thus, it is a distributional effect rather than additional cost to society.

5.2 Human Health or Environmental Impact – Costs and benefits of continued use

5.2.1 Environmental costs

Under the "Non-use" Scenario, the environmental impacts described in Section 3.3 would be avoided. The CSR describes an exposure scenario under which only releases to the aquatic environment occur after Triton™ X-100-containing wastewater is successively treated in an industrial and a municipal STP.

Table 3–15 has presented the estimated annual and daily releases of 4-tert-OP over the requested review period. Annual releases in 2021 are projected to be ca. #G (range: 0.1-1) kg in 2018 and will progressively decrease until they reach zero by the end of 2029. Over the requested review period (2021-2029), it is estimated that Siemens Llanberis will be releasing ca. #G (range: 0.1-1) kg of 4-

tert-OP. In terms of environmental stock of 4-tert-OP, it can also be estimated that total 4-tert-OP in the aquatic environment reaches a maximum of #G (range: 0.01-0.1) kg, depending on the half-life assumed (8-54 days). This low amount of releases and the low presence of 4-tert-OP stock build-up would not materialise under the "Non-use" Scenario.

Both the and regional local assessments indicate that concentrations in the water are below the latest research values, the releases are not occurring every day since bead production occurs in batches and the assumptions made in the CSR are generally conservative.

Overall, the benefit to the environment from non-Authorisation would be low.

5.2.2 Health benefits for affected patients

The number of OPE-dependent IVD kits manufactured by Siemens Llanberis and sold in the EEA was approximately #C, D (range: 10,000-100,000) in 2017. It must be understood that each kit may deliver hundreds of different tests; some examples are provided below:

- #C, D : 200 tests;
- : 200 tests;
- : 100 tests;
- : 100 tests;
- : 200 tests;
- : 600 tests; and
- : 600 tests.

Siemens Llanberis can translate the number of IVD kits sold to the equivalent number of diagnostic tests performed with those kits. In 2017 ca. #C, D (range: 10-100 million) tests may have been performed on EEA patients using the OPE-dependent #D IVD kits.

The IVD kits in question provide results used in the diagnosis of:

- #C, D
-

The full range of assays that can be run on the #D platform is shown in **Figure 5–1**. The #D analyte types covered by the #D impacted IVD kits are described in **Table 5–2** where the key characteristics of the relevant diseases diagnosed by means of these kits are presented. A more detailed description is provided in Appendix 2 (Section 10) to this document.

Ultimately Siemens Healthineers #D customers are using the #D impacted IVD kits for delivering to patients test results which can be life-saving or life-changing. These kits can detect severe abnormalities that affect pregnancies, can support the early diagnosis of certain cancers and other untreatable conditions (e.g. #D). The overall number of IVD kits used in the EEA is significant, in the range of #D tests per year (as of 2017). Any disruption to the supply of these kits should be measured not only monetarily from a healthcare provider perspective but also in terms of the impact to patient lives and outcomes. Patients who cannot undergo vital tests within the required timeframe will be significantly adversely affected; this is one of the reasons the IVD industry is so strictly regulated, to ensure healthcare providers can rely on the performance and supply of products, including the delivery of timely results.

Importantly, several of the affected assays are considered uncommon and are not widely available on other automated immunoassay systems #D (paragraph) . Discontinuation of these assays on the platforms would further reduce the diagnostic testing options available to healthcare providers. Customers globally would be forced to switch to an alternative method (in some cases, potentially a manual method) or to outsource to a reference laboratory. This will increase the time to generate patient results, potentially delaying treatment . For certain conditions, early treatment is important, but more generally, delaying the results of testing (if testing can be undertaken at all) would be detrimental to the emotional and physical wellbeing of patients.

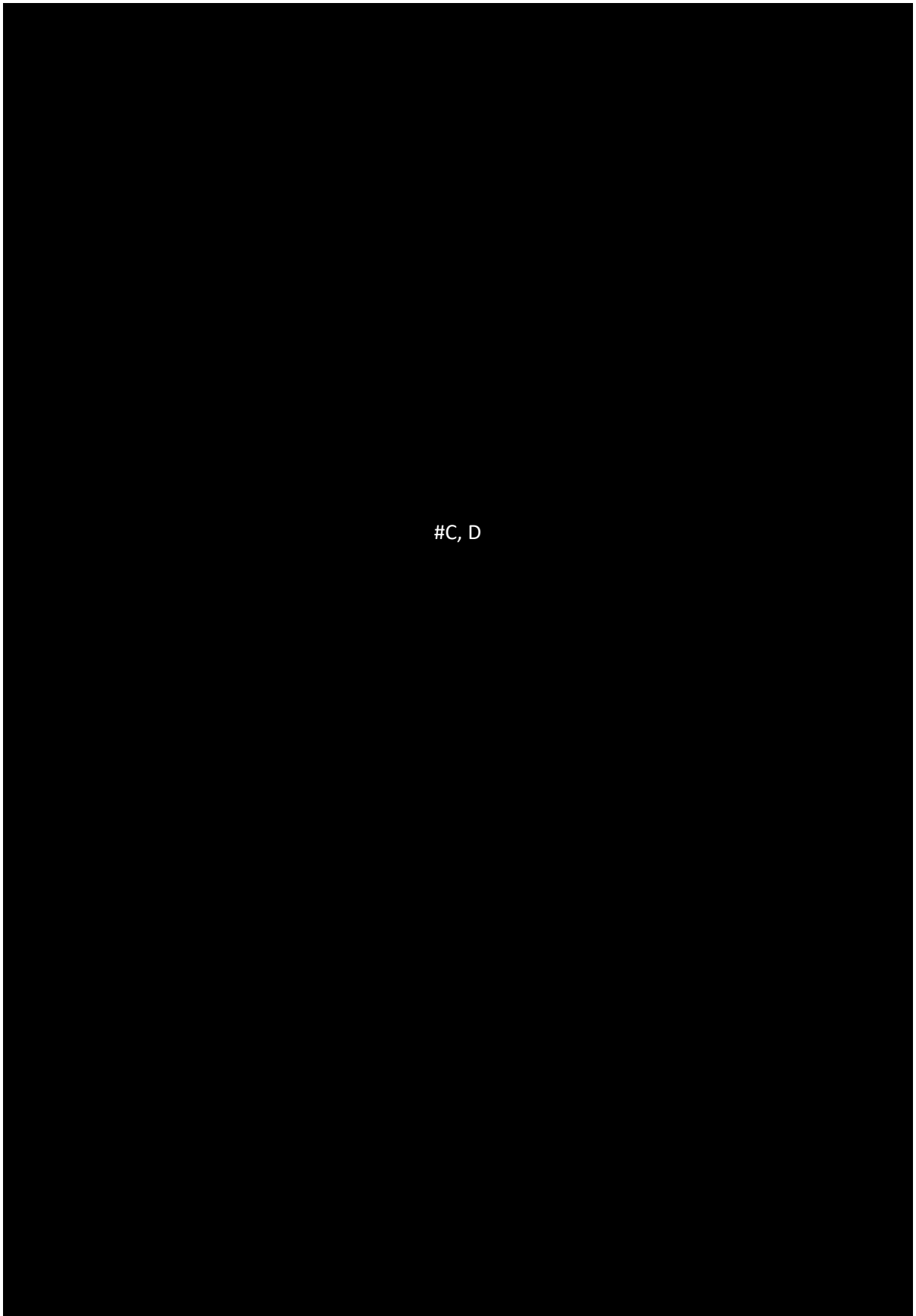

Figure 5–1: Overview of the diseases and conditions detected by the full range of #D platform assays

Table 5–2: Brief overview of the diseases and conditions detected by the OPE-dependent #C, D (table) IVD kits that depend on the use of Triton™ X-100 by Siemens Llanberis					
Impacted IVD kit	**Diseases/conditions tested for/detected**	**Prevalence**	**Severity of disease/ condition**	**Availability of alternate IVD kits within the Siemens Healthineers portfolio**	**Applicant's knowledge of equivalent third-party IVD kits**
[redacted]					

Table 5–2: Brief overview of the diseases and conditions detected by the OPE-dependent #C, D (table) IVD kits that depend on the use of Triton™ X-100 by Siemens Llanberis					
Impacted IVD kit	**Diseases/conditions tested for/detected**	**Prevalence**	**Severity of disease/ condition**	**Availability of alternate IVD kits within the Siemens Healthineers portfolio**	**Applicant's knowledge of equivalent third-party IVD kits**
[redacted]					

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[redacted]					

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[redacted]					

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[redacted]					

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[redacted]					

Table 5–2: Brief overview of the diseases and conditions detected by the OPE-dependent #C, D (table) IVD kits that depend on the use of Triton™ X-100 by Siemens Llanberis					
Impacted IVD kit	**Diseases/conditions tested for/detected**	**Prevalence**	**Severity of disease/ condition**	**Availability of alternate IVD kits within the Siemens Healthineers portfolio**	**Applicant's knowledge of equivalent third-party IVD kits**
[redacted]					

5.3 Social impacts – Benefits of continued use

5.3.1 Avoided job losses at Siemens Healthcare Diagnostics Products Ltd

Under the "Non-use" Scenario the supply of all #D OPE-dependent #D IVD kits manufactured in Llanberis will be discontinued, that is, #D % of the #D product range (in terms of sales) will no longer be produced. Down-scaling the operations at Siemens Llanberis means that the number of employees needed would also decline.

Currently there are #D full-time employees at Siemens Llanberis. #D . If we use the annual growth rates for IVD kits sold/Triton™ X-100 consumed shown in **Table 3-6**, it can be estimated that the headcount could be #D . Although it is certain that several jobs would be lost if OPE-dependent IVD kits could no longer be made and manufacturing operations would be scaled down, the exact magnitude of job losses is difficult to estimate. In the absence of more robust estimates, it is considered that as the OPE-dependent #D IVD kits represent #D % of the profits of Siemens Llanberis from sales of IVD kits, it could be assumed that #D % of all jobs could be lost, or #D (range: 25-75) positions.

As mentioned above, it is likely that the reduction in the production and sales of #D products would extend beyond the OPE-dependent IVD kits. In that case, the number of employees made redundant would be higher than estimated above. In the worst-case scenario, the reduction in sales would be too high to maintain operations at Llanberis, which would lead to all the #D employees estimated to be employed in 2021 losing their jobs.

5.3.2 Avoided job losses among third party contractors

In addition to the staff directly employed by Siemens Llanberis there are #D site-based contractors and more than #D on-site contractors connected to the manufacturing of #D products. The jobs of these #D contractors rely on the continued operations at Llanberis, and would be at risk of losing their jobs if the production of #D IVD kits is downscaled or discontinued.

5.3.3 Avoided job losses among suppliers and customers

Siemens Llanberis has #D suppliers relevant to OPE use, of which #D are located in the EEA. The volumes of materials they sell to Siemens Llanberis are relatively small, therefore, loss of this part of their business would be likely have an insignificant effect on their levels of employment. Many more suppliers are relevant to the manufacture of the full range of IVD kits made in Llanberis.

Siemens Healthineers #D customers are diverse, and the impacts are likely to vary. In a commercial lab or large hospital where staff dedicated to diagnostic testing might work, it might be that a reduction in the #D product portfolio would make some staff redundant for some time, particularly if this is accompanied by a costly and lengthy premature replacement of Siemens Healthineers analysers. However, Siemens Llanberis does not possess sufficient information that would allow the development of estimates of potential job losses among customers.

5.3.4 Monetisation of social impacts

The approach taken to valuing unemployment impacts comprises the following components (ECHA, 2016):

- The value of productivity loss during the period of unemployment;
- The cost of job search, hiring and firing;
- The impact of being made unemployed on future employment and earnings (a typical opportunity cost also referred to as 'scarring' effect); and
- The value of leisure time during the period of unemployment.

The quantification of these components requires assumptions regarding wage rates and labour costs, duration of unemployment, scarring effects, reservation wages and the value of leisure time, and the costs of job search, hiring and firing. Dubourg (2016) gives numerical examples to illustrate how the various pieces of evidence, data sources, and components of cost could be brought together to estimate the value of the impacts of the loss of one job as a direct result of an authorisation decision (ECHA, 2016).

The general conclusion that can be drawn from the approach is that the welfare cost of one job lost is about 2.7 times the annual pre-displacement wages (excluding taxes paid by the employer) of this job, with the variation largely driven by the average duration of unemployment in the individual EU Member States (ECHA, 2016).

Llanberis is located in Gwynedd, North-west Wales, and in this area the median weekly salary for a full-time employee was £421 (StatsWales, 2017) or approximately €470 in 2017. The FTE (full time equivalent) salary at Llanberis is thus assumed to be around €24,400 per year.

In the absence of a ratio of social costs of jobs lost compared to the annual pre-displacement for Wales specifically, the ratio for the UK as a whole is used: this is 2.09 (Dubourg, 2016). Based on the median FTE salary in Gwynedd and a social cost to local salary ratio of 2.09, the social costs of one job lost at the Llanberis site is estimated to €51,000.

Table 5–3 below provides a summary of the expected avoided job losses and the corresponding benefits to society.

Table 5–3: Estimation of social benefits from the continued use of Triton™ X-100 in bead processing in Llanberis

Affected actors	Number of jobs retained		Social costs avoided	
	Base case	Worst case	Base case	Worst case
Siemens Llanberis	#D, E (table)	[redacted]	[redacted]	[redacted]
Suppliers and customers	0	0	0	0
3rd party contractors	0	0	0	[redacted]
Total avoided jobs lost	[redacted]	[redacted]	[redacted]	[redacted]
Source: Siemens Llanberis				

The expected benefits to society from avoided job losses from granting the Authorisation is #E [redacted] (range: €1-10 million), but there are some uncertainties related to the number of workers that would be made redundant in the situation of downscaling the production at the Llanberis site. If the entire Siemens Llanberis workforce were to lose their jobs, then the cost to society would increase to

#E (range: €10-100 million) or ca. € #E (range: €10-100 million) if we exclude the jobs lost among third-party contractors and corresponding societal costs.

5.4 Wider economic impacts

5.4.1 Trade competition

Overview

As is described above, OPEs are not present in the IVD kits manufactured at Siemens Llanberis. However, at this plant, #D OPE-dependent IVD kits are manufactured and these are the subject of this AfA. In addition, Siemens Llanberis is the only Siemens Healthineers plant globally that manufactures these kits, which are then distributed within the EEA and globally to all parts of the world. Four Siemens Healthineers plants in the USA will also be impacted in the event of a non-Authorisation as some of their activities are interlinked with the OPE-dependent activities at Siemens Llanberis. In addition, Siemens Marburg manufactures the #D that is used with every single #D kit and on every test provided by these kits, and therefore the manufacture and sales of this wash solution is dependent on the outcome of the present AfA. See Section 2.3.2 for more details.

As is also described above, there are, in principle, several potential "Non-use" Scenarios for Siemens #D customers depending on whether OPE-free technology can be made available to customers in the EEA on the Sunset Date. As Siemens Llanberis cannot be certain what alternative technologies might be available on the market, a (perhaps optimistic) assumption has been made that such technology would be available to customers on the Sunset Date. In reality, for each of the impacted IVD kits manufactured at Siemens Llanberis there is, at the time of applying for Authorisation, no way of conclusively determining which competitor products which are equivalent to each of the Siemens Llanberis IVD kits relevant to this AfA do or do not contain OPEs, nor which will or will not contain OPEs at the Sunset Date, as this is confidential business information for the manufacturers involved. Moreover, even if such alternative IVD kits were to be found, transitioning to a third-party analysers would be a time-consuming process.

Market effects

Under the main "Non-use" Scenario considered (i.e. customers prematurely replace their analysers), it can be assumed (though not verified) that the manufacturers of OPE-free IVD kits will be able to up their production volumes in order to meet the increased market demand created by the non-Authorisation of these Siemens Llanberis OPE-dependent IVD kits. It is also cautiously assumed, due to the lack of any evidence to the contrary, that competitors would be able to supply the analysers required for these competitor kits. As it is unlikely that any competitor analyser runs precisely the same group of IVD tests that are specific to the Siemens Healthineers #D systems, Siemens Healthineers #D customers are likely to have to acquire multiple analysers (at a unit cost assumed to be € #D each, i.e. the average cost of a new #D analyser). It is also assumed here that Siemens Healthineers #D customers would be able to afford to acquire the analysers required.

Clearly, in the event of non-Authorisation, in this scenario Siemens Healthineers' competitors would be in an advantageous position. As there are a limited number of players in this market, the reduction in number of suppliers will in the short term at least, be reduced with possible consequences for pricing. Note that in this scenario, non-EEA competitors who, like Siemens Llanberis, use OPEs to produce OPE-free kits, are also advantaged.

5.4.2 Changes to international trade and re-location of economic activity

It is not anticipated that there will be significant changes in trade flows internationally. It is not considered likely, given the limited number of players and the limited number of IVD kits relevant to this AfA, that re-location of activities to outside of the EEA will be needed. It is assumed that Siemens Healthineers' competitors who already have OPE-independent IVD kits for these purposes or manufacture of OPE-free IVD kits using OPEs in the production process outside of the EEA would be able to produce more to meet increased market demand.

5.4.3 Changes in EU and MS/regional taxes

Siemens Llanberis is the largest private employer in the county of Gwynedd, North-west Wales. This is not a highly industrialised region. It can be anticipated that there will be a loss of local, regional and national taxes in the event of a cessation of the production of these #D IVD kits.

Impacts in Germany as a result of impacts on the manufacture and sale of #D will be limited, based on the profit made from such sales.

5.4.4 Changes to the local economy

Llanberis is a village, community and electoral ward in Gwynedd, North-west Wales, with a population of 2026 (UK Census Data, no date). In a small village like Llanberis one can assume that the #E jobs that will be directly linked to the Siemens Llanberis manufacturing site in 2021 makes this a cornerstone business in this community. This is not to say that every employee that works for Siemens Llanberis lives in Llanberis, but there will surely be a significant number of people, both the workers and the rest of their households, that rely on the continued production of #D products at this facility.

In Gwynedd, in the year ending 30 June 2018, there was a 4.3% unemployment rate with 2,400 unemployed men and women[29]. If #E employees at Siemens Llanberis were to lose their jobs, this would cause a #E % increase in the total number of unemployed persons; if the entire Siemens Llanberis site was to close, the loss of approximately #E jobs would be a #E % increase to the number of unemployed persons in the area. The workers previously employed by Siemens Llanberis might have to move to find a new job. In some cases, this would mean that the whole household would move, effectively reducing the population in the village and the surrounding area.

[29] Data available at: https://statswales.gov.wales/Catalogue/Business-Economy-and-Labour-Market/People-and-Work/Employment/Persons-Employed/economicactivityrate-by-welshlocalarea-year-gender (accessed on 30 November 2018).

5.5 Distributional impacts

The following table summarises the envisaged distributional impacts from the granting of an Authorisation (table colour key: green = positive impact, red = negative impact).

Table 5–4: Distributional impacts from the continued use of OPE in the Applied for Use		
Affected group	**Economic (and social) impact**	**Human health and environmental impact**
Economic operator		
Applicant: Siemens Llanberis	Continued manufacture and sales of IVD kits that depend on Triton™ X-100 – profits made from OPE-dependent IVD kits: € #D, E (PV, 2021-2029, 4%)	Low local releases of 4-tert-OP to the aquatic environment (#G (range: 0.1-1) kg over the period 2021-2029) after treatment of wastewater at industrial and municipal STPs
EEA suppliers to Siemens Llanberis	Continued sales of raw and other materials to Siemens Llanberis – profits made are uncertain	None
Non-EEA suppliers to Siemens Llanberis		None
Non-EEA Siemens Healthineers operations	Sustained demand for the OPE-containing #D that is manufactured by Siemens Marburg – estimated profits retained: € #D, E (PV, 2021-2029, 4%)	Low local releases of 4-tert-OP to the aquatic environment after treatment of wastewater at a municipal STP
	Full range of #D assays remains available on the market and thus future sales of #D analysers can continue without obstacle in the period 2018- #D (#D (range: 100-1,000) analysers are envisaged to be sold in the EEA and a further #D (range: 1,000-10,000) in non-EEA countries; the respective figures for #D (after the Sunset Date) are #D and #D)	None
Third-party diagnostic test and analyser providers	No access to potential new customers (hospitals, labs) who are currently operating #D analysers and who would be able to make full use of their analysers	No
EEA-based customers of Siemens Llanberis	Continued access to #D IVD kits allowing important assays to be run on #D analysers (#D analysers operating in 2017 plus #D new analysers to be sold in the period 2018-2020); ability to offer full range of assays required by healthcare providers; avoidance of premature replacement of #D analysers, estimated at € #D, E (PV, 4%)	None (NB. OPE is not present in the #D IVD kits)

Table 5–4: Distributional impacts from the continued use of OPE in the Applied for Use		
Affected group	**Economic (and social) impact**	**Human health and environmental impact**
Economic operator		
Non-EEA-based customers of Siemens Llanberis	Continued access to #D IVD kits allowing important assays to be run on multiple #D analysers (#D analysers operating in 2017 plus #D new analysers to be sold in the period 2018-2020); ability to offer full range of assays required by healthcare providers; avoidance of premature replacement of #D analysers (not quantified)	None (NB. OPE is not present in the #D IVD kits and these customers are outside the EEA)
Public (patients) in the EEA	Cost of tests will not increase (if outsourcing of tests is avoided)	Continued access to the full range of testing capabilities of hospitals and labs thus allowing quick test results, diagnoses and treatments for a range of diseases and conditions ranging from cancers to #D). Over #C, D (range: 1-10 million) tests were sold by Siemens Healthineers in 2017
Geographical scope		
North-west Wales, UK	Local economy is supported by retaining #E jobs at Siemens Llanberis, plus protecting tens of associated contractor/service provider jobs	None
Mersey estuary, North-east England, UK	Industrial STP that receives wastewater from Siemens from Siemens Llanberis will continue to earn revenue (ca. #E) from the continued business relationship with the applicant Limited volumes of OPEs will still be released in the period 2021-2029 (albeit gradually declining), thus monitoring of Siemens Llanberis' use and associated releases need to continue*	Low releases of 4-tert-OP to the aquatic environment after treatment of wastewater at industrial and municipal STPs. Overall release of 4-tert-OP in the period 2021-2029 is estimated at #G (range: 0.1-1) kg, while environmental stocks peak at #G kg prior over the requested review period
All EU Member States	Healthcare providers continue to offer full diagnostic services to citizens and avoid an increase to the burden of disease by sustaining current capabilities of swift diagnosis and treatment	None (NB. OPE is not present in the #D IVD kits)
Within the applicant's business		
Employers/Owners	Profit-generating activities continue unhindered (see details above). Business plan for the #D business line can continue as planned	None
Exposed workers Non-exposed employees	Jobs in Llanberis will be retained (see above)	None
* the situation in the UK after Brexit may or not differ to the current one		

5.6 Uncertainty analysis

The following table explains the influence of key uncertainties over the conclusions of the analysis of socio-economic impacts.

Table 5–5: Uncertainty analysis		
Area of uncertainty	**Basic assumption**	**Alternative assumptions – Sensitivity analysis**
Reliability of projections of future sales of IVD kits/analysers	The projections used are based on a strategic (#D) business plan developed by Siemens Healthineers' Finance Department #D [redacted]	More reliable estimates are not available
Number of jobs to be lost	The assumed number of jobs to be lost is based on the share (#D) of the #D IVD kits within the sales of all IVD kits made in Llanberis	It cannot be certain what the actual number of job losses might be. However, the loss of the sales of the OPE-dependent IVD kits could have a strongly undermining impact on the marketability of OPE-independent IVD kits made in Llanberis and thus the losses incurred by Siemens Llanberis could be far greater than this factor (#D %) would imply
Availability of OPE-independent kits/analysers on the market	Siemens Llanberis cannot be certain whether competitors in the field of immunoassay IVD kits are similarly or more or less dependent on the use of OPEs. Several scenarios have been developed to address this uncertainty in terms of the reaction of Siemens Llanberis' customers in the event of non-Authorisation and for the purposes of the present analysis it is assumed that customers would switch to an alternative analyser, ignoring the time constraints this would entail in reality	No further analysis can be provided, in the face of lack of information on the use of OPE by competitors (which is confidential business information)
Ability of Siemens Llanberis' customers to outsourcing their diagnostic activities	Siemens Llanberis cannot be certain whether the outsourcing of the affected tests would be possible. Due to the volume of tests that would be impacted and the need for quick turnaround of rest results in many cases, outsourcing is considered infeasible and unrealistic, unless it is assumed to happen for smaller customers over a short period of time as a stop-gap solution. Literature suggests that this could increase testing costs for patients/healthcare authorities	In light of contributions from the supply chain (see Appendix 1 in the Siemens Marburg AoA-SEA for Uses #4-5), no alternative scenario can be developed. Any increased costs arising from outsourcing diagnostic tests are not taken into account in quantifying the benefits of continued use of OPE

6 Conclusions

6.1 Comparison of the benefits and risk

Table 6–1 summarises the socio-economic benefits of continued use of Triton™ X-100 in Llanberis that were presented in Section 5. Overall, a benefit of € #E (range: €10-100 million, Present Value, 4% discount, 2021-2029) can be estimated.

Table 6–1: Summary of socio-economic benefits from the continued use of OPE under the "Applied for Use" Scenario (2021-2029)

Stakeholder affected/impacted	Description of impact	Quantification of impact	Considered in the total monetised benefit calculated below
Benefits to the applicant and/or their supply chain			
Siemens Llanberis	Continued manufacture and sale of #D, E (table) IVD kits that contain beads manufactured with OPE-based formulations – Gross profit projected to be made	€ (2021-2029, PV, 4%)	Yes
	Uninterrupted/unaffected manufacture and sale of OPE-independent IVD kits – Gross profit projected to be made	€ (2021-2029, PV, 4%)	No – profits might not be lost without an Authorisation (an optimistic assumption)
Siemens Marburg	Uninterrupted/unaffected manufacture and sale of OPE-containing – Gross profit projected to be made from sales of 14% of global sales of	€ (2021-2029, PV, 4%)	Yes
Siemens Healthineers non-EEA operations	Uninterrupted/unaffected manufacture and sale of analysers to global customers – Gross profit projected to be made from sales of % of new analysers in period 2018-	€ of which ca. € is from sales to EEA-based customers (2021- , PV, 4%)	Yes – only profits from sales in the EEA are taken into account
Customers of Siemens Healthineers users of analysers	Continued operation of existing (and future) analysers that use the IVD kits – Avoidance of: - Operating costs increase from outsourcing of diagnostic testing - Cost of validation of third-party analysers/kits - Cost of premature replacement of analysers	Cost of premature replacement of analysers: € (PV, 4%)	Yes

Table 6–1: Summary of socio-economic benefits from the continued use of OPE under the "Applied for Use" Scenario (2021-2029)			
Stakeholder affected/impacted	**Description of impact**	**Quantification of impact**	**Considered in the total monetised benefit calculated below**
Benefits to other actors			
Healthcare providers/patients	Continued access to quick tests for the quick diagnosis and treatment of a range of diseases/conditions – Avoidance of: - Cost increases for healthcare systems to be avoided: unknown; - Delays in treatment/health outcome impacts from delayed testing or loss of diagnostic capability	Not possible	No – no quantified data (NB. over [redacted] tests in the EEA in 2017)
Workers at Llanberis	Preservation of an estimated [redacted] jobs in North-west Wales (if not more, up to [redacted])	€[redacted] (PV, 4%)	Yes
Village of Llanberis/ North-west Wales	Prevention of increased unemployment around Llanberis	Included above	Yes
Aggregated socio-economic benefit of continued use of OPE		[redacted] **(range: €10-100 million)**	

On the other hand, the total emissions of OPE to the environment under the "Applied for Use" Scenario were shown in **Table 3–15**. As sludge is not applied to agricultural soil, only releases to the aquatic environment are of relevance to the present analysis. These releases represent a total of ca. #G kg (range: 0.1-1 kg) over 9 years. In addition, **Figure 3-11** and **Figure 3-12** showed the build-up of 4-tert-OP stock in the aquatic at its peak ranges between #G kg (depending on the half-life assumed).

The ratio of the total cost of non-Authorisation (i.e. the benefit of continued use) and the total emission of 4-tert-OP to the environment is **€ #E (range: €100-500 million) per kg of 4-tert-OP released**. A more conservative calculation can be performed if the total benefit (cost of non-use) is annualised and the highest annual release of 4-tert-OP (for the year 2021) is considered. Then the ratio becomes **€ #E (range: €10-100 million) per kg of 4-tert-OP released**.

Table 6-2: Cost of non-use per kg and year		
Parameter	**Present Value, 2021-2029**	**Annualised value (worst-case release)**
Total cost of non-use	€ #E	€ #E
Total emissions	#G kg	#G kg (max. value for 2021)
Ratio	**€ #E per kg (range: €100-500 million per kg)**	**€ #E per kg (range: €10-100 million per kg)**

These benefit:cost ratios are certainly underestimated for a number of reasons:

- The assumptions made in the CSR are likely to be overly conservative;
- The emission reduction that is likely to be achieved through the implementation of additional RMMs (segregation and incineration of wastewater) would probably well exceed 99%;

- The important health benefits to the patients from the continued availability of the impacted assays has not been possible to express in monetary terms; and
- Whilst benefits have been discounted, physical amounts of 4-tert-OP released over time have not been discounted.

6.2 Information for the length of the review period

6.2.1 Introduction

In a 2013 document, the ECHA Committees outlined the criteria and considerations which could lead to a recommendation of a long review period (12 years) (ECHA, 2013):

1. *The applicant's investment cycle is demonstrably very long (i.e. the production is capital intensive) making it technically and economically meaningful to substitute only when a major investment or refurbishment takes place.*

2. *The costs of using the alternatives are very high and very unlikely to change in the next decade as technical progress (as demonstrated in the application) is unlikely to bring any change. For example, this could be the case where a substance is used in very low tonnages for an essential use and the costs for developing an alternative are not justified by the commercial value.*

3. *The applicant can demonstrate that research and development efforts already made, or just started, did not lead to the development of an alternative that could be available within the normal review period.*

4. *The possible alternatives would require specific legislative measures under the relevant legislative area in order to ensure safety of use (including acquiring the necessary certificates for using the alternative).*

5. *The remaining risks are low and the socio-economic benefits are high, and there is clear evidence that this situation is not likely to change in the next decade.*

The requested review period for OPE use at Siemens Llanberis is 9 years. Under the "Applied for Use" Scenario, OPE use continues to the end of 2029 with a decline in OPE use forecast year on year from 2018 from an initially low level of ca. #G kilograms per year used in bead manufacture.

6.2.2 Criterion 1: Siemens Llanberis' investment cycle

At present, under the "Applied for Use" Scenario #C, D [30].

[30] It should be noted that there are several #D reagents #D which contain OPE (and are used by EEA-based customers); however, these are subject to a significant

#C, D

. Therefore, Siemens Healthineers will need to continue to supply OPE-dependent kits to its customers at least until the end of 2029 (9 years from the Sunset Date).

The full Siemens Healthineers product portfolio is heavily impacted by the inclusion of OPEs on the REACH Authorisation list, with over #D individual IVD products falling within the scope of REACH Authorisation. This requires significant investment in resources and funds #C . It is important to note that the successful substitution of Triton™ X-100 in one product by an unrestricted alternative substance will not necessarily mean that this alternative will be appropriate as a substitute for the next IVD product, even within the same product line. The properties which make Triton™ X-100 effective in one product may be completely different to what makes it effective in another, and the suitability of alternatives can only be proven through 'trial and error' feasibility testing.

As a result, Siemens Healthineers has conducted a full analysis of the impacted product portfolio and launched a 'REACH Response Plan'. As part of this plan, certain priorities have been set for allocating relatively scarce resources to the vast reformulation task that Siemens Healthineers is facing:

- Priority is given to products that have a long lifetime ahead of them, both in terms of future profitability (and return on investment) and length of time over which potential releases of 4-tert-OP may occur; and
- Priority is given to products that contain the largest volumes of OPEs and may result in the largest theoretical releases of 4-tert-OP (i.e. wash solution products).

Hence, products which are connected to the #D are being given the highest priority in terms of design change, and plans to reformulate these products are underway on a per product basis. Products which are predicted to have a shorter life-cycle (e.g. #D) and thus their associated releases of 4-tert-OP are low will not be subject to Design Change so that the company can focus its re-design efforts on products which will continue to be used well into the future.

6.2.3 Criterion 2: Cost of using alternatives

For the business and economic reasons explained above, Siemens Llanberis will not be looking into reformulating the OPE-dependent #D IVD kits in order to best allocate its R&D resources. It has also been explained that the identities of alternative substances that could substitute Triton™ X-100 in the OPE-dependent #D IVD kits are unknown; feasible alternatives need to be identified through research and trial testing and it cannot be assumed that a single substance would adequately serve the needs of all impacted IVD kits.

reformulation effort by Siemens Healthineers and their use by customers is the subject of a separate Siemens Marburg AfA.

The calculations made in Section 4.3.1 suggest that reformulating the #D impacted IVD kits would take several years and could cost #D . Most importantly, implementation of an alternative substance (or combination thereof) would mean that the OPE-dependent #D IVD kits would be removed from the market for several years. Those customers who currently rely on their use on their #D analysers would be obliged to seek alternative solutions, of which the most likely in the longer term is to invest in new analysers supplied by a third-party (assuming that technology that does not depend on OPE exists). Siemens Llanberis' inability to supply the affected kits over a long period of time would in practice mean that this part of #D IVD kit market would be irrevocably lost. The gross profit associated with global sales of these IVD kits is estimated at € #D (range: €10-100 million) for the period 2021-2029 (Present Value, 4% discount).

It is also useful context to point out that Siemens Healthineers is planning to reformulate numerous OPE-dependent IVD kits across all of its affected product lines and the estimated cost of reformulation is #F (range: €10-100 million) for the Design Change effort alone associated with the #D that Siemens is planning to reformulate to address the inclusion of OPEs on the Annex XIV list.

Overall, the combination of the economic cost of reformulating the #D IVD kits and the downtime in the manufacture of these kits would eliminate the projected profits from the sales of these kits and would undermine the viability of the ongoing manufacture of all #D kits and impact upon the future sales of #D analysers.

6.2.4 Criterion 3: Results of R&D on alternatives

As explained, the implementation of alternative substances or technologies is not a realistic course of action in the event of non-Authorisation. Nevertheless, Siemens Healthineers has been undertaking R&D on potential alternatives to its use of OPEs and Section 4.1.1 describes relevant experiments that have been conducted.

Section 4.1.1 explains that each immunoassay IVD kit design is unique and each one must be fully tested, with product validation usually involving lengthy real-time stability testing, to confirm that any one alternative is acceptable. There are no guarantees of success at the outset of this process, even if an alternative substance has previously been successfully (or unsuccessfully) proven for a similar assay.

To establish the most appropriate alternative substances for each of the #D impacted #D IVD kits #C, D , it would require resources and effort which, in the light of #C, D the small and decreasing use of OPE, could not be justified as they are better spent on higher volume, longer-life OPE-dependent products where substitution will have the higher impact on reduced OPE emissions.

6.2.5 Criterion 4: Legislative measures for alternatives

As noted in Section 4.3.1, after the reformulation of the IVD kits to substitute away from Triton™ X-100, the performance of the products would have to be verified and any performance changes will require a re-registration in most countries. There are about 80 countries with registration requirements, with varying submission requirements. In the case of reformulation of the OPE-dependent kits, approximately #C, D country re-registrations would be envisaged. For each submission of a re-registration application, around #C months of preparation time is needed, in addition to the time necessary for the regulatory authorities to complete the reviews. The review time

in the different countries varies between a few months to three-and-a-half years, so the entire re-registration process can be expected to take 5-12 years, with 8 years being a typical duration.

This analysis is, of course, theoretical only, as Siemens will focus on reformulation and re-registration of those affected IVD kits in their portfolio that have the highest volume and the longest life, and which will contribute more to the reduction in OPE emissions.

6.2.6 Criterion 5: Comparison of socio-economic benefits and risks to the environment and effective control of the remaining risks

It has been shown above that under the "Non-use Scenario", Siemens Llanberis would suffer a loss of profit of € #E (range: €10-100 million) and job losses would be translated into an additional loss of society of € #E (range: €1-10 million). In addition, access of EEA patients to certain key immunoassay diagnostic tests would be impacted, thus affecting the EEA's diagnostic capabilities and the timeline of diagnosis and treatment of several diseases. In 2017, over #C, D (range: 10-100 million) tests were performed in the EEA using the #D IVD kits manufactured by Siemens Llanberis. It cannot be certain if will be possible, and if possible, if there would be capacity, for such tests to be undertaken in the EEA in the event of a non-Authorisation for Siemens Llanberis, as IVD kits of other manufacturers which may perform these tests might also rely on OPEs. Premature replacement of #D analysers would be a costly and lengthy process.

The volume of OPEs used by Siemens Llanberis will be ca. #A kg by 2021 range and it will gradually reduce #A, C by the end of 2029. The residual emissions from the wastewater treatment process will reduce year on year as the #C, D. As shown above, the continued (but importantly, declining) use of Triton™ X-100 in Llanberis would result in the release of #G kg of 4-tert-OP to the aquatic environment over a period 2021-2029. Thereafter, use of OPE will cease. It is calculated that the benefit to society from the continued use of OPE is equivalent to a very substantial € #E (range: €100-500 million) per kg of 4-tert-OP released to the aquatic environment. The worst-case ratio obtained when annualised benefits from continued use are considered is € #E (range: €10-100 million) per kg of 4-tert-OP released (for the year 2021). As discussed above, these figures are certainly underestimates of the actual benefit:cost ratios.

In 2015, the Institute for Environmental Studies (IVM) conducted a study (Oosterhuis and Brouwer, 2015) to provide SEAC with information that could be used in the development of such a benchmark. The study gathered information on the past (and current) cost of PBT (Persistent, Bioaccumulative and Toxic substance) emission reduction or on reductions in the use of, or exposure to PBTs/vPvBs. In turn, the study identifies that this information provides an indication of "public willingness to pay (WTP)" for such reductions through a revealed preference.

Taking all the available evidence into account and also differences between PBTs/vPvBs and their effects, the study identifies a very wide 'grey zone' of somewhere between €1,000 and €50,000 per kg PBT substituted, remediated or emission reduced. Within this 'grey' zone, measures may be either proportionate or disproportionate from a cost-effectiveness perspective (depending on factors including the nature of the PBT/vPvB).

Whilst it is acknowledged that that 4-tert-OP is an endocrine disruptor rather than a PBT/vPvB substance, the above WTP values provide some guidance as to what benefit-cost ratio might be considered acceptable from society's perspective. The estimates provided for the Applied for Use above (at least € #E per kg 4-tert-OP released) in the aquatic environment are significantly higher than the higher end of the WTP values established by the IVM researchers.

6.2.7 Implications of a granted Authorisation review period that is shorter than the one requested

If a review period shorter than 9 years were granted, Siemens Llanberis would probably continue the use of OPEs and anticipate the submission of a review report to ensure customers using #D analysers could continue to perform diagnostic tests for the impacted products. However, a shorter review period would increase the uncertainties over the future of the #D business line and would make #C, D . This could potentially leave several customers unable to operate their #D analysers with the full functionality and thus hasten the premature replacement of these analysers.

The business links between the different Siemens Healthineers units should be recognised. A less than optimal outcome for Siemens Llanberis' AfA would increase the business uncertainty for the manufacture of the #D #D in Marburg. If that manufacturing activity was to be impacted, no #D IVD kits (whether OPE-dependent or not) could be used anywhere across the world and all #D analysers would become unusable.

6.3 Substitution effort taken by the applicant if an authorisation is granted

For the reasons described elsewhere in this document, Siemens Llanberis will not actively aim to substitute OPE in the preparation of #B beads. Instead, the applicant will aim to further minimise releases of OPEs from the use of Triton™ X-100 as a process chemical in Llanberis #A, C at the end of the requested 9-year review period.

6.4 Links to other Authorisation activities under REACH

The discussion and analysis presented above should be seen in the context of other AfAs applied for by Siemens Healthineers legal entities:

- Siemens Marburg is separately applying for its own continued use of OPE in the manufacture of OPE-free IVD kits, OPE-containing IVD kit reagents and OPE-containing IVD wash solutions. Under its Applied for Use 1, Siemens Marburg manufactures the #D that contains OPE and is then shipped to Llanberis for the coating of beads used in the #D kit. Also, Siemens Marburg manufactures the #D #D (Applied for Use 3) which must be used alongside all #D IVD kits manufactured in Llanberis whether these depend on the use of OPE in Llanberis of not. The following dependencies are therefore noted:

  - Siemens Llanberis relies on Siemens Marburg being granted an Authorisation in order for (a) the #D to remain available and thus sales of the OPE-free #D IVD kit to #D analyser users across the globe to be maintained after the Sunset Date, and (b) the #D to remain available or else the entire #D business line would collapse after the Sunset Date as no #D analyser could operate without the ; and

  - Siemens Marburg relies on Siemens Llanberis being granted an Authorisation in order for (a) demand for the #D (Marburg Use 1) to be maintained after the

Sunset Date, (b) demand for the #D (Marburg Use 3) by those analyser operators that use Llanberis-made OPE-dependent IVD kits to be maintained after the Sunset Date.

- Siemens Marburg is separately applying for the continued use of OPE-containing IVD kits (Use 4) and wash solutions (Use 5) by its EEA-based customers. These IVD kits and wash solutions are made either in Marburg or by Siemens Healthineers outside the EEA (the USA) or by OEMs. The following dependencies are therefore are noted:

  - **Siemens Llanberis** relies on Use 5 being granted an Authorisation in order for EEA use of the #D #D to continue thus sustaining demand for #D IVD kits after the Sunset Date. Without the #D, no #D IVD kit can be used;

  - **Siemens Marburg** relies on Uses 4 and 5 being granted an Authorisation in order for (a) EEA demand for the OPE-containing IVD kits manufactured under Applied for Use 2 to be maintained after the Sunset Date, (b) EEA demand for the OPE-containing IVD wash solutions manufactured under Applied for Use 3 to be maintained after the Sunset Date; and

  - **EEA-based customers** of Siemens Marburg rely on Siemens Marburg being granted an Authorisation for Applied for Uses 1, 2 and 3 in order for supply of OPE-containing IVD kits and wash solutions made in Marburg to be maintained after the Sunset Date. They also rely on Siemens Llanberis being granted an Authorisation for its own use of OPE in order for supply of the #D OPE-dependent #D kits to be maintained after the Sunset Date.

7 References

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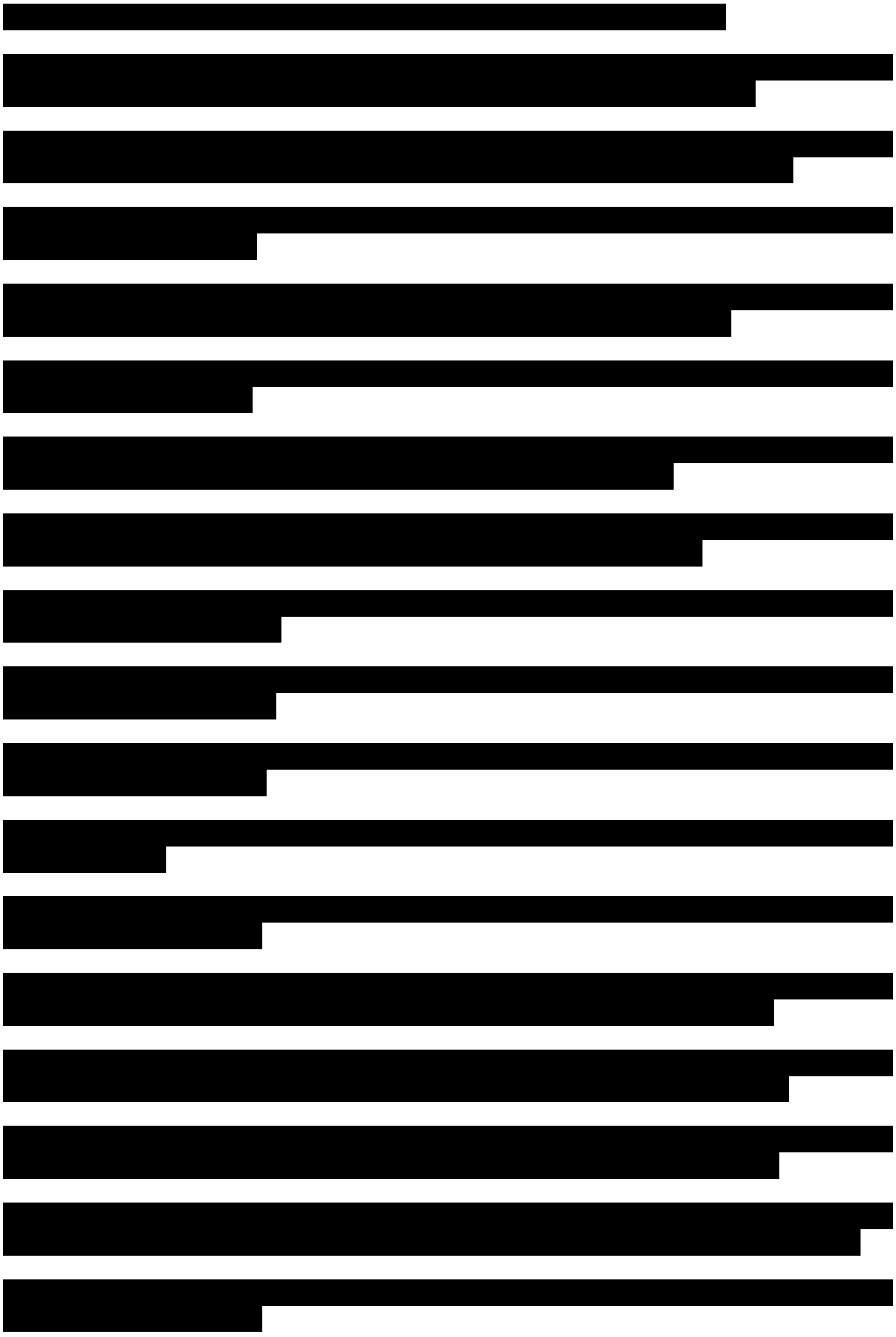

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8 Justifications for Confidentiality Claims

[redacted]

Table 8-1: Justifications for confidentiality claims			
Reference type	**Commercial Interest**	**Potential Harm**	**Limitation to Validity of Claim**
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

Table 8-1: Justifications for confidentiality claims			
Reference type	Commercial Interest	Potential Harm	Limitation to Validity of Claim
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

Table 8-1: Justifications for confidentiality claims			
Reference type	**Commercial Interest**	**Potential Harm**	**Limitation to Validity of Claim**
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

Table 8-1: Justifications for confidentiality claims			
Reference type	**Commercial Interest**	**Potential Harm**	**Limitation to Validity of Claim**
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

9 Appendix 1: Consultations

No specific consultation outside the relevant Siemens Healthineers units has been conducted for the purposes of this specific Application for Authorisation. The #D impacted #D IVD kits do not contain OPE. They only contain beads that were previously processed with Triton™ X-100.

However, it its noted that Siemens Healthineers co-ordinated extensive consultation with Downstream Users of Siemens Marburg. The reader is referred to Appendix 1 to the Siemens Marburg AoA-SEA document for downstream uses #4 and #5 for the results of interviews and a survey.

10 Appendix 2: Disease information for relevant IVD kits

Table 10–1: Disease information relating to diagnostics carried out by OPE-dependent #D (table) IVD kits	
Parameter	**Description**
[redacted]	

Table 10–1: Disease information relating to diagnostics carried out by OPE-dependent #D (table) IVD kits	
Parameter	**Description**
[redacted]	

Table 10–1: Disease information relating to diagnostics carried out by OPE-dependent #D (table) IVD kits	
Parameter	**Description**
[redacted]	

Table 10–1: Disease information relating to diagnostics carried out by OPE-dependent #D (table) IVD kits	
Parameter	**Description**
[redacted]	

Table 10–1: Disease information relating to diagnostics carried out by OPE-dependent #D (table) IVD kits	
Parameter	**Description**
[redacted]	

Table 10–1: Disease information relating to diagnostics carried out by OPE-dependent #D (table) IVD kits	
Parameter	**Description**
[redacted]	

Table 10–1: Disease information relating to diagnostics carried out by OPE-dependent #D (table) IVD kits	
Parameter	**Description**
[redacted]	

Table 10–1: Disease information relating to diagnostics carried out by OPE-dependent #D (table) IVD kits	
Parameter	**Description**
[redacted]	

Table 10–1: Disease information relating to diagnostics carried out by OPE-dependent #D (table) IVD kits	
Parameter	**Description**
[redacted]	

Table 10–1: Disease information relating to diagnostics carried out by OPE-dependent #D (table) IVD kits	
Parameter	**Description**
[redacted]	

11 Appendix 3: Proportionality of additional Risk Management Measures

11.1 Introduction

This Appendix provides an analysis of the potential alternative scenarios for dealing with OPE-containing waste-water from the Bead Manufacturing process, with the aim of analysing the feasibility of implementing additional risk management measures (RMMs) to minimise releases of OPE to the environment.

Some important parameters to the use of Triton™ X-100 in Llanberis are:

- **Amount of Triton™ X-100 consumed**: #A (range: 10-100) kg in 2021, declining thereafter;

- **Volume of wastewater generated at Llanberis**: ca. 3,500 t/y – wastewater is generated from discharge of buffers containing Triton™ X-100, but also numerous bead washing and coating buffers which do not contain OPE, and wash-waters; and

- **Current wastewater disposal arrangements**: wastewater is captured in a dedicated closed drainage system, collected in the 'Phosphate Waste-Water Plant' tank system installed on-site. Wastewater is vacuum-piped from tank into a road tanker 2-3 times/week (max) and transported to an industrial STP in Liverpool. Processed wastewater is then discharged to a municipal STP also in Liverpool, with treated effluent from that process discharged to the Mersey Estuary.

11.2 Possible scenarios for further reduction of 4-tert-OP releases

Four alternative scenarios have been developed for the theoretical implementation of additional RMMs beyond what is currently in place. These are set out in **Table 11-1** and assessed for feasibility.

On the basis of the analysis presented in the table, Alternative Scenario 2 has been concluded to be the most feasible for the following reasons:

- It can theoretically result in the elimination of 4-tert-OP releases to the environment;
- It is in principle technically feasible;
- Its costs can be estimated with a minimum degree of confidence; and
- It can theoretically achieve elimination of 4-tert-OP releases to the environment at a cost lower than other Scenarios

Alternative Scenario 2 has thus been taken forward for further analysis.

Table 11-1: Alternative scenarios for the implementation of additional Risk Management Measures for the minimisation of 4-tert-OP releases to the environment				
	Alternative Scenario 1	**Alternative Scenario 2**	**Alternative Scenario 3**	**Alternative Scenario 4**
Technical and cost considerations				
Description	Classify as hazardous waste (despite the required Waste Framework thresholds not being met) and send all wastewater from Bead Washing & Coating operations for incineration, i.e. the waste-water currently collected and which is sent to Liverpool is diverted to an incineration plant	Implement segregation system to collect fraction of wastewater from OPE-containing buffers, classify as hazardous waste (despite the required Waste Framework thresholds not being met) and send for incineration	All wastewater from Bead Coating passes through a filter, which captures the majority of the OPE and the filters are then sent for incineration	Install wastewater treatment facility on site which could deal specifically with OPE's wastewater fraction, e.g. Vacuum Evaporator or Incinerator
Key technical parameters	- The volume of wastewater would be ca. 3,500 t/year - The closest incinerator is at Ellesmere Port (115 km from Llanberis) - No alterations foreseen for wastewater collection system or transport	- The volume of wastewater would be ca. 150 t/year - Certain V-Mixers (see **Figure 3–6**) would need to be restricted so OPE-containing buffers were used on this production equipment only - Internal tank system would need to be installed for draining of those V-Mixers and pipework installed to feed an external collection point. Could potentially utilise existing pipework to Phosphate Waste-Water Plant and look at existing sump/tank facility or IBC collection system	- At present no known filter technology on the market designed for OPEs - The volume of wastewater would be ca. 70 t/week (i.e. ca. 3,500 t/y) , but assume OPE wastewater fraction could be segregated in this scenario	- The volume of wastewater would be ca. 70 t/week (i.e. ca. 3,500 t/y), but assume OPE wastewater fraction could be segregated in this scenario - Area on site would need to be identified for installation

Table 11-1: Alternative scenarios for the implementation of additional Risk Management Measures for the minimisation of 4-tert-OP releases to the environment				
	Alternative Scenario 1	**Alternative Scenario 2**	**Alternative Scenario 3**	**Alternative Scenario 4**
Key cost parameters	- **Investment cost**: assumed nil - **Ongoing cost - incineration cost**: €430/t (comprising a €332/t incineration cost plus transportation cost), or €1.5 million/y - Treatment of the waste-water currently costs €80,000-110,000/y, incineration of the wastewater would represent a ca. 1500% increase	- **Investment cost - Initial set-up**: €20,000-40,000 - **Ongoing cost – incineration cost**: €40,000-80,000/y - Treatment of this wastewater fraction currently costs ca. €5,000-8,000/y, incineration of the wastewater would represent a ca. €900% increase	Not possible to calculate at present	- **Investment cost - Costs for on-site incinerator**: unknown - **Investment cost - Costs for Vacuum Evaporator installation**: ca. €250,000 plus civil works - **Ongoing cost – Disposal**: €400-800/t for incineration of filtered material (unknown how much would be generated) - Treatment of this wastewater fraction currently costs ca. €5,000-8,000/y, vacuum evaporation of the wastewater would represent a ca. €3800% increase
Anticipated reduction in 4-tert-OP emissions	Assumed 100% (>99%)	Assumed 100% (>99%)	Unknown until filter was designed and efficacy tested	Incinerator: assumed 100% (>99%) Vacuum Evaporator: unknown until desktop sample testing conducted

Table 11-1: Alternative scenarios for the implementation of additional Risk Management Measures for the minimisation of 4-tert-OP releases to the environment				
	Alternative Scenario 1	**Alternative Scenario 2**	**Alternative Scenario 3**	**Alternative Scenario 4**
Envisaged business benefits and risks				
Benefits	- Complete elimination of 4-tert-OP emissions - Current wastewater collection arrangements would not need to be altered except for diversion to incinerator plant (i.e. existing drainage network used, collection by tanker, etc.) - Work required in terms of setting up contractual agreement with incinerator instead of industrial STP would be minimal - As the site has one waste contractor managing all waste streams expectation that best 'per tonne' costs could be achieved	- >99% elimination of 4-tert-OP emissions	- If filter was available, volume of hazardous waste generated would be low	- Potentially complete elimination of 4-tert-OP emissions - Wastewater does not need to be transported off-site, once treated assume wastewater could go to public sewer system
Risks/Drawbacks	- Significant overall costs due to low calorific value of wastewater - Environmental impact of transporting and incinerating high volumes of wastewater	- Change in practices for Bead Manufacture Team to ensure correct disposal (update of procedures, training etc) - Initial investment and ongoing costs due to low calorific value of wastewater - Environmental impact of transporting and incinerating relatively high volumes of wastewater	- At present no known filter on the market designed to deal with OPEs, developing one (if technically feasible) could take significant time - The volume of wastewater to pass through the filter media would be significant (particularly if at 70 t/week), likely the number of changes for filters would be high	- Incinerator: community concern over installation of an incinerator very likely (based on similar initiatives in region). Likelihood of receiving planning permission considered low. - Vacuum Evaporator: initial set-up costs high (however ongoing costs low)

11.3 Proportionality of the additional RMMs (wastewater segregation and incineration)

11.3.1 Practical implementation of the additional RMMs

The below method for segregation was developed by the Facilities Team at Siemens Llanberis and supported by quotations from third-party plumbing and waste management contractors. Additional work was done in collaboration with the Bead Manufacture Team to identify the most viable method in terms of maintaining the validated production process.

Implementation steps would include:

- Installation of a stainless steel tank within the V-Mixer enclosure for 2 V-mixers (00783 &1473). In this scenario only these 2 V-Mixers are used for bead washing & coating with Triton™ X-100 buffers;

- Wastewater would be pumped to pipework traversing the building within ceiling void to original drain for the now redundant production process waste, leading to the Phosphate Waste-Water Plant (tank system is already in place to capture all Bead Coating wastewater);

- At the Phosphate Waste-Water Plant, the existing sump would be extended (6m x 2m x 1200H) and section segregated, with environmental controls to prevent spillage. This would allow a maximum capacity 12 tonnes of wastewater before it must be emptied; and

- Tankers would vacuum the wastewater from sump with an expected 1 visit/month to empty 12 tonnes of waste.

11.3.2 Implementation cost

Set-up costs

Siemens Llanberis estimates that the initial set-up costs would be ca. €34,000.

Ongoing costs

The cost of one tanker transport per load (12 tonnes) is £578. The anticipated wastewater volume would be a maximum 153 t/y. On the other hand, the wastewater incineration costs are £332/tonne. Thus, the annual costs would be:

- Transportation costs: £578 × 12 = £6,926 or ca. €7,800 per year; and
- Incineration costs: 153 × £332 = £50,796 or ca. €57,400 per year.

Thus, the overall ongoing costs per year would be ca. €65,200. By way of comparison, the current costs for the treatment of the Triton™ X-100-contaning wastewater fraction are ca. €5,000 per year, i.e. this would be a cost increase of ca. 1,200%. However, wastewater treatment costs would generally decline as consumption of Triton™ X-100 decreases over the review period.

The overall cost of implementing this additional RMM expressed in 2017 prices is calculated in **Table 11-2**. The table also shows the quantity of 4-tert-OP release that would be avoided (conservatively assumed to be 99% of the current emission factor).

Table 11-2: Calculation of the present value implementation cost of additional Risk Management Measures for the minimisation of 4-tert-OP releases to the environment						
Year	**Triton™ X-100 amount used (kg)**	**% of previous year**	**4-tert-OP releases to water prevented (kg/y)**	**Discount factor (4%)**	**Set-up cost (PV)**	**Ongoing cost (PV)**
2018	#A	#D		*104%*		
2019	[redacted]	[redacted]		*108%*		
2020	[redacted]	[redacted]		*112%*		
2021	[redacted]	[redacted]	#G, H	117%	€29,063	€55,733
2022	[redacted]	[redacted]	[redacted]	122%		€46,087
2023	[redacted]	[redacted]	[redacted]	127%		€42,253
2024	[redacted]	[redacted]	[redacted]	132%		€39,637
2025	[redacted]	[redacted]	[redacted]	137%		€37,160
2026	[redacted]	[redacted]	[redacted]	142%		€36,189
2027	[redacted]	[redacted]	[redacted]	148%		€36,118
2028	[redacted]	[redacted]	[redacted]	154%		€33,882
2029	[redacted]	[redacted]	[redacted]	160%		€20,362
			[redacted]		**€376,486**	

11.4 Comparison of costs and benefits

Table 11-2 indicates that implementing the selected RMM would be accompanied by a Present value cost of ca. €0.38 million but would also be theoretically possible to achieve elimination of 4-tert-OP releases, i.e. an emission reduction of #A, G kg over the 9 years of the requested review period. These figures would imply a ratio of €0.38 million ÷ #A, G = ca. #A, G, H (range: €5,000-10,000) per kg of 4-tert-OP release avoided.

Although this cost is not insignificant, Siemens Llanberis is prepared to accept it in order for the releases of Triton™ X-100/4-tert-OP to the aquatic environment associated with the continued use of Triton™ X-100 to be minimised. As such, the management of the company has approved the adoption of Alternative RMM 2 with implementation planned to be executed and completed before the Sunset Date.

12 Appendix 4: Past research on alternative for OPEs