ANALYSIS OF ALTERNATIVES

and

SOCIO-ECONOMIC ANALYSIS

Public version

Legal name of applicant(s):	Siemens Healthcare Diagnostics Products GmbH
Submitted by:	Siemens Healthcare Diagnostics Products GmbH
Substance:	Entry #42: 4-(1,1,3,3-tetramethylbutyl)phenol, ethoxylated, covering well-defined substances and UVCB substances, polymers and homologues (Triton™ X-100, Triton™ X-405)
Use title:	1: Use of OPE in isolation of protein from recombinant cell cultures for the production of IVD-kits (protein cell extraction) 2: Use of OPE in formulation of IVD kit reagents 3: Use of OPE in formulation of IVD wash solutions

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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4-tert-OP	4-tert-Octylphenol / 4-(1,1,3,3-tetramethylbutyl)phenol
#D	#D
#D	#D
#D	#D
#D	#D
#D	#D
ADC	Americas Distribution Centre
#D	#D
#D	#D
AfA	Application for Authorisation
#D	#D
#D	#D
#D	#D
#D	#D
AoA	Analysis of Alternatives
#D	#D
#D	#D
#D	#D
#D	#D
#D	#D
#D	#D
B2B	Business to Business
#D	#D
#D	#D
#D	#D
ca	circa
#D	#D
CAI	Chemistry, Automation & Informatics
#D	#D
#D	#D
#D	#D
CFR	Code of federal Regulations (US FDA)
#D	#D

[redacted]	[redacted]
[redacted]	[redacted]
CIA	Change Impact Assessment
[redacted]	[redacted]
CMC	Critical Micelle Concentration
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
CRB	Change Review Board
[redacted]	[redacted]
CSR	Chemical Safety Report
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
DCP	Design Change Process
[redacted]	[redacted]
DfE	Design for the Environment
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
DMR	Device Master Record
DU	Downstream Users
[redacted]	[redacted]
E. Coli	Escherichia coli
ECHA	European Chemicals Agency
EDC	European Distribution Centre
EEA / non-EEA	European Economic Area
[redacted]	[redacted]
EHS	Environment, Health & Safety
ELISA	Enzyme-linked Immunosorbent Assay
EOL	End of Life
EPA	Environmental Protection Agency (US)
[redacted]	[redacted]
EQS	Environmental Quality Standards
[redacted]	[redacted]

EU	European Union
#D	#D
#D	#D
FDA	Food and Drug Administration (US)
#D	#D
#D	#D
#D	#D
FTE	Full-Time Equivalent
#D	#D
#D	#D
#D	#D
#D	#D
#D	#D
GmbH	Gesellschaft mit beschränkter Haftung
GMP	Good Manufacturing Practices
#D	#D
#D	#D
#D	#D
#D	#D
#D	#D
HLB	Hydrophile-lipophile balance
HPV	Human papillomavirus
#D	#D
#D	#D
IFU	Instruction for Use
#D	#D
#D	#D
ISO	International Standards Organisation
IVD	In-Vitro Diagnostic
IVDR	In-vitro diagnostic medical device regulation
IVM	The Institute for Environmental Studies
kg	kilogram
kg/y	kilogrammes per year
#D	#D
#D	#D
LD	Laboratory diagnostics
#D	#D
#D	#D

#D	#D
#D	#D
#D	#D
#D	#D
#D	#D
#D	#D
#D	#D
#D	#D
MAC	Maximum allowable concentrations
#D	#D
#D	#D
#D	#D
#D	#D
#D	#D
#D	#D
#D	#D
#D	#D
#D	#D
#D	#D
#D	#D
#D	#D
#D	#D
NOEC	No Observable Effect Concentration
NPE	Nonylphenol ethoxylate
NPV	Net Present Value
NSB	Non-specific binding
#D	#D
OECD	Organisation for Economic Co-operation and Development
OEM	Original Equipment manufacturer
OP	Octylphenol
OPE, OP/E, OPnEO	Octylphenol ethoxylate
#D	#D
#D	#D
PBT/vPvB	Persistent, Bioaccumulative and Toxic Substances/very Persistent and very Bioaccumulative
#D	#D
#D	#D
PDP	Product Development Process

#D	#D
PEC	Predicted Environmental concentration
#D	#D
PHT	Product Health Team
PMA	Premarket Approval Application
PNEC	Predicted no-effect concentration
POC	Point of Care
P. antipodarum	*Potamopyrgus antipodarum* (New Zealand mud-snail)
#D	#D
ppm	parts per million
#D	#D
#D	#D
#D	#D
#D	#D
#D	#D
PTR	Product Technical Requirements
PV	Present Value
Q&A	Question and Answer
RA	Regulatory Affairs
#D	#D
REACH	Registration, Evaluation, Authorisation and Restriction of Chemicals
R&D	Research and development
RG	Report generation
#I	#I
#D	#D
RTM	Requirements Traceability Matrix
#D	#D
SAP ID	Systems Applications and Products Identification
SCM	Supply Chain Management
SEA	Socio Economic Analysis
SEAC	Committee for socio-economic analysis
#D	#D
#D	#D
#D	#D
STP	Sewage Treatment Plant
SVHC	Substance of Very High Concern
#D	#D
#D	#D

[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
UBA	German Environment Agency
[redacted]	[redacted]
[redacted]	[redacted]
µg/L	Micrograms per litre
UK	United Kingdom
[redacted]	[redacted]
US(A)	United States of America
V&V	Verification & Validation
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
WFD	Water Framework Directive
[redacted]	[redacted]
WTP	Willingness to pay

DECLARATION

The Applicant, Siemens Healthcare Diagnostics Products GmbH, 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 (May 17, 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:  May 17, 2019; Marburg

Michael Heinold (Managing Director Siemens Healthcare Diagnostics GmbH)

Signature:  May 17, 2019; Hoffman Estates

Jörg Berner (Managing Director Siemens Healthcare Diagnostics GmbH)

1 SUMMARY

1.1 Introduction

Siemens Marburg is part of Siemens Healthineers and is a reagent manufacturing facility based at Marburg, Hesse in Germany. 4-(1,1,3,3-tetramethylbutyl)phenol, ethoxylated, purchased by Siemens Marburg under the trade name Triton™ X-100, and (Poly(oxy-1,2-ethanediyl), α-[(1,1,3,3-tetramethylbutyl)phenyl]-ω-hydroxy-, purchased by Siemens Marburg under the trade name Triton™ X-405 are used in three different uses:

1. As a processing aid and component in the isolation of protein from recombinant cell cultures for the production of IVD kits (protein cell extraction) (#C (range: 10-100) IVD products),
2. As a component in the formulation of IVD kit reagents (#C (range: 10-100) IVD products), and
3. As a component in the formulation of IVD wash solutions (#C (range: 1-10) IVD products).

The "Applied for Use" involves the application of Triton™ X-100 as a cell lysis agent (Use #1 only) cleaning agent (detergent) and stabiliser. Triton™ X-405 is also used as a cleaning agent (detergent) and stabiliser in Use #2 only.

Whilst the final kits manufactured under Use #1 do not contain Triton™ X-100 (an exception is one protein extract, #D , which contains Triton™ X-100 and is sent for further processing to another Siemens Healthineers site in the UK), the IVD kit reagents and wash solutions manufactured under Uses #2 and #3 contain OPEs and are used by hospitals, commercial laboratories and research centres on several Siemens Healthineers and third-party analysers to perform vital diagnoses of specific diseases and conditions in patient samples.

Siemens Marburg is requesting an Authorisation for the continued use of OPEs which will allow the continued manufacture and market availability of the aforementioned #C (range: 10-100) IVD products while efforts for phasing out the use of OPEs continue.

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 diagnostic kits function effectively and deliver accurate patient results.

Siemens Healthineers is the manufacturer of over #C (range: 50-500) existing products, across #C (range: 10-25) different analyser platforms, where OPEs are used and which are in the scope of REACH Authorisation; in other words, the present Applied for Uses by Siemens Marburg account for only a small part of the overall use of OPEs in Siemens Healthineers IVD products that are placed on the EEA market. 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. As a result, there is no specific alternative substance or combination thereof which Siemens Marburg could presently switch to for the purposes of any of the three Applied for Uses.

Siemens Healthineers has conducted a full analysis of the impacted product portfolio and launched a 'REACH Response Plan'. The estimated cost of reformulation is over € #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).

With particular regard to the present three Applied for Uses, Siemens Healthineers is planning #D reformulation projects (covering multiple OPE-based formulations) which are estimated to reach completion between end #D, G and end 2032.

1.3 Socio-economic benefits from continued use

The continued use of Triton™ X-100 and Triton™ X-405 over the period 2021-2029 (Use #1) or 2021-2032 (Uses #2 and #3) will confer significant socio-economic benefits within and outside Siemens Marburg's supply chain. These can be summarised as follows:

- Siemens Marburg will be allowed to continue the manufacture of multiple OPE-dependent IVD kit reagents and wash solutions and would avoid potential indirect adverse impacts on the sales of numerous OPE-independent kits that are used on the analysers that use OPE-dependent IVD products. The latter is particularly the case for analysers which use one of the OPE-containing IVD wash solutions; without those wash solutions, the analysers would no longer be possible to operate;

- Siemens Llanberis (a sister company to Siemens Marburg, based in the UK) would avoid disruption to its manufacture and sale of #D IVD kits. Firstly, the #D kit made in the UK is based on the #D that Siemens Marburg formulates in Germany (Use #1), while all #D analysers can only operate if the Marburg-made #D #D (made under Use #3), which must accompany the use of every single #D IVD kit, remains available on the market;

- Siemens Healthineers would be unhindered in their continued sales of several types of analysers within and outside the EEA by virtue of the continued availability of the full range of IVD kits and wash solutions that are manufactured by Siemens Marburg;

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

- Users of #C different analyser models will continue to have access to the full range of IVD kits and wash solutions made in Marburg 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 existing analysers. The cost of replacing a platform is approximately € #E per unit and many hospitals and laboratories run multiple analysers;

- Several jobs in Germany and the UK would be preserved, estimated at #E (range: 10-100) for Use #1, #E (range: 10-100) for Use #2 and #E (range: 100-1,000) for Use #3; and

- Critically, healthcare providers and patients in the EEA (but also outside the EEA) will continue to have access to the #C relevant IVD kit reagents but most importantly the continued use of the #C OPE-containing IVD wash solutions made in Marburg will allow the continued operation of thousands of analysers which each delivers tens of different assays. The number of tests undertaken on the impacted analysers each year in the EEA extend to hundreds of millions. These analysers detect multiple health conditions and can support the early diagnosis of numerous diseases, including life-threatening ones (e.g. several cancers) and other untreatable conditions. 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 of OPEs in the Applied for Uses that can be monetised amounts to € #D (range: €0.1-1 billion) for Use #1 (2021-2029, Present Value, 4% discount), € #D (range: €10-100 million) for Use #2 (2021-2032, Present Value, 4% discount) and € #D (range: €1-10 billion) for Use #3 (2021-2032, Present Value, 4% discount).

1.4 Residual risk to the environment of continued use

It is projected that in 2021 and after the implementation of additional Risk Management Measures, between 0.025% and 5% of the OPEs used by Siemens Marburg in the Applied for Uses will be released into wastewater which is directed to the local municipal STP. Thereafter, 26.5% of total OPE input used by Siemens Marburg is assumed to be emitted to the aquatic environment as 4-tert-OP. No other environmental discharges occur (sludge from the municipal STP is assumed not to be spread to agricultural land). Based on a declining annual usage of OPEs starting in the 100-1,000 kg/y range (#A kg for 2021, a decrease of over #A kg compared to 2018 levels), over the requested review periods, the releases of 4-tert-OP to the aquatic environment account for a total of ca. #A (range: 1-10) kg.

Both the local and regional assessment in the CSR indicate that concentrations in the water are below the latest research values (in some cases by a substantial margin), the releases are not occurring every day since manufacture of the relevant IVD kit reagents and wash solutions 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 CSR. If a half-life of eight days is assumed, then the maximum total 4-tert-OP in the environment resulting from each of the Applied for Uses is #J (range: 0.00001-0.1) kg. If the upper end half-life of 54 days is assumed, then 4-tert-OP stock levels peak at #J (range: 0.0001-1) kg for each of the Applied for Uses.

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:

- **Use #1**: € #E, H (range: €1-10 billion) per kg of 4-tert-OP released, or € #E, H (range: €0.1-1 billion) per kg of 4-tert-OP released when benefits are annualised and the highest annual release of 4-tert-OP (for the year #A, H) is considered;

- **Use #2**: € #E, H (range: €10-100 billion) per kg of 4-tert-OP released, or € #E, H (range: €10-100 billion) per kg of 4-tert-OP released when benefits are annualised and the highest annual release of 4-tert-OP (for the year #A, H) is considered; and

- **Use #3**: € #E, H (range: €0.1-1 billion) per kg of 4-tert-OP released, or € #E, H (range: €10-100 million) per kg of 4-tert-OP released when benefits are annualised and the highest annual release of 4-tert-OP (for the year #A, H) is considered.

The above estimates are significant underestimates of the actual benefits conferred by the continued use of OPEs in the Applied for Uses as they only encompass benefits that could be readily quantified and monetised. The true benefit-cost ratios must be assumed to also encompass:

- The significant benefits to the health of numerous patients across the EEA who are diagnosed with or monitored for a wider range of diseases through the use of millions of tests that contain OPEs and which are placed on the market by Siemens Marburg;

- The profits that manufacturers of OEM IVD products and analysers (those made on behalf of Siemens Healthineers and other, third-party ones) would preserve;

- The profits for Siemens Healthineers from sales of IVD products and analysers that might potentially be indirectly impacted if the continued use of OPE-containing IVD products within the EEA was not authorised and thus Siemens Healthineers would suffer loss of economies of scale and global reputational damage; and

- The significant cost, impacts on healthcare provision, operational disruption, inconvenience for a period of a minimum 6 months (but potentially as high as 24 months) which the users of Siemens Healthineers analysers would avoid, as they would avert the premature replacement of their units.

In addition, the monetised benefits that have been presented above have been discounted over time, whilst the physical quantities of 4-tert-OP released under the Applied for Uses have not.

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

Siemens Marburg has considered the practicality and cost of implementing a range of different RMMs for the three Applied for Uses with the air of further reducing the releases of OPE/4-tert-OP to the environment. For Use #1 and Use #2 Siemens Marburg has reached the decision to take measures beyond what is currently in place. Therefore, the following measures are planned to be implemented before the Sunset Date:

- Use #1: implementation of a system to collect fraction of OPE-containing buffer, classify as hazardous waste and send for incineration; and
- Use #2: implementation of disposable bulk containers, classification of empty containers as hazardous waste and disposal by incineration.

It is estimated that emission rates for these two Uses will decline by a factor of 95% compared to current (2019) levels.

On the other hand, the most appropriate additional RMM for Use #3 (implementation of a segregation system to collect the fraction of wastewater from OPE-containing buffers, classify as hazardous waste and send for incineration) could not be implemented before the Sunset Date and would have a high cost estimated at ca. € #E (range: €1-10 million) per kg of 4-tert-OP release avoided. This cost is considered disproportionate and as such further measures aimed at reducing releases from that use cannot be justified on either practical or cost-effectiveness grounds.

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

Siemens Marburg'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 Marburg and Llanberis facilities. Siemens Marburg is investing a significant amount of resources and funding towards the phase out of OPEs from a substantial number of IVD products. The cost of Siemens Healthineers' REACH Response Plan exceeds € #F/#G . Siemens Llanberis is also critically dependent on the continued use of Triton™ X-100 under Applied for Use #3. #D, G needs to be able to service the #D analysers that are operated across the globe towards the users of the #D analysers. Without access to the #D #D that is manufactured in Marburg, no #D analyser would be able to operate. Inability of customers to use their Siemens Healthineers analysers with their full functionality would #D, G replacement of these analysers. Apart from the associated wastage and future expenditure brought forward, switching to a new analyser is a lengthy and costly process that impacts the capability of healthcare providers of providing diagnostic services;

- Reformulation of the IVD products that depend on OPEs might include a range of costs, such as (a) Internal R&D (reformulation) cost; (b) Internal re-registration submission preparation cost; (c) Re-registration fees; and (d) Downtime losses. The latter would be the most critical. There is no simple or single drop-in replacement for OPEs in Siemens Marburg's manufacturing processes. As such, reformulation would take several years. In the absence of a REACH Authorisation for the continued use of OPEs, the profit loss that Siemens Healthineers would experience would be very high. Importantly, customers would not be prepared to wait for years for reformulated IVD products to become available. Although switching to a competitor's analyser typically requires 6-24 months preparation and implementation, a long period of downtime would strongly incentivise customers to abandon Siemens Healthineers' products. Once investments into third-party analysers take place, customers would not return back to Siemens Healthineers' products;

- Reformulation of OPE-containing IVD products would also generate additional regulatory activities. The reformulated products would need to be re-registered under the many jurisdictions where they are marketed. There are about 80 countries with re-registration requirements and submission requirements to each country vary. Siemens Healthineers estimates that re-registrations would generally be required in ca. 50 countries. The review time in the different countries vary between a few months to three-and-a-half years, with China taking the longest (42 months). The actual number will vary because it is dependent on the number of countries where each IVD product is placed on the market;

- The continued and declining use of Triton™ X-100/Triton™ X-405 is envisaged to result in modest and declining releases of 4-tert-OP to the environment; in total #A (range: 1-10) kg are estimated to be released to the freshwater environment in Germany across all three Applied for Uses over the period 2021-2032. The socio-economic benefits from the continued use of OPEs are significant resulting in a ratio of **€ #E, H (range: €0.1-100 billion) per kg of 4-tert-OP released per Applied for Use – this figure does not encompass the important benefits to EEA patients' health which have not been possible to express in monetary terms.** Moreover, these figures are certainly underestimates because whilst socio-economic benefits have been discounted, the physical releases of 4-tert-OP have not.

Finally, the business links between the different Siemens Healthineers units should be recognised. A less than optimal outcome for Siemens Marburg's AfA would have a profound impact on the viability of Siemens Llanberis' operations – these depend on the continued availability of the #D #D that is manufactured in Marburg under Use #3. Conversely, 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. 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.

2 AIMS AND SCOPE OF THE ANALYSIS

2.1 Aims of the combined AoA and SEA document

4-(1,1,3,3-tetramethylbutyl)phenol, ethoxylated (Octylphenol ethoxylated - OPE) 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 the 4-(1,1,3,3-tetramethylbutyl)phenol (4-tert-octylphenol = 4-tert-OP). The OPE under discussion in this specific case are two polymeric substances:

- One with an average of 9.5 ethylene oxide units (9 or 10) which is sold under the trade name Triton™ X-100 (4-(1,1,3,3-Tetramethylbutyl)phenylpolyethylene glycol, CAS No. 9002-93-1 and 9036-19-5); and

- Another with an average of 35 ethylene oxide units which is sold under the trade name Triton™ X-405 ((Poly(oxy-1,2-ethanediyl), α-[(1,1,3,3-tetramethylbutyl)phenyl]-ω-hydroxy-, CAS No. 9081-99-6).

OPE 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.

The legal applicant, Siemens Healthcare Diagnostics Products GmbH (hereafter referred to as Siemens Marburg), wishes to continue to use OPEs in the manufacture of In-Vitro Diagnostic (IVD) Kits and associated wash solutions at their manufacturing site in Marburg, Germany beyond the Sunset Date and thus continue to supply Downstream Users (DUs) within the healthcare sector, typically hospitals and commercial laboratories, for diagnosis of certain diseases and conditions in patient samples. There are in total #C (range: 10-100) impacted products, representing #C (range: 10-100) different formulations, as shown in Table 2–2. One formulation in the form of the #D product that is phased out and is used in analyser models (#D which will not be considered further in this AoA-SEA document. These products are used on different analysers/systems and a few third-party ones, as shown in **Table 2–1**.

Table 2–1: Analysers/systems of relevance to the Applied for Uses

#	Analyser/system
#C, Column	#D, Column

Table 2–2: OPE containing products of relevance to this AfA (Uses #1, #2 and #3)				
Applied for Use	Total No. of products	Products		
		Group	Number of products	
			Currently manufactured	Planned to be reformulated (i.e. not end-of-life)
	#C, Column	#D, Column	#C, Column	#C, Column

The aim of this Application for Authorisation (AfA) is to allow the continued use of OPEs in the manufacture of the above Siemens Marburg IVD products beyond the Sunset Date (with the exception of the #D product). The manufacture of this product will cease prior to the Sunset Date (end of 2020) but the use of the product (which contains OPE) is within the scope of Applied for Use #4 which covers the customer use of OPE-containing reagents in the EEA which aims to cover the shelf life of the product in the market. Applied for Use #4 is covered by a separate AfA/AoA-SEA document.

This combined AoA/SEA document aims to discuss and demonstrate the following:

- The technical and economic feasibility, availability, health and safety challenges in identifying an acceptable alternative reagent or technology, which would maintain the functionality and reliability of the affected IVD kits and wash solutions and would be approved by the relevant IVD regulatory authorities (e.g. US FDA) across the globe;

- The R&D that Siemens Marburg and its parent company Siemens Healthineers have undertaken and are planning to undertake towards the identification of feasible and suitable alternatives for OPEs (NB. much of the work undertaken to identify alternatives to OPEs has been conducted at the Siemens Healthineers level. For this reason, there will be references to both entities in this document). The Authorisation of the continued use of OPE is requested while work is underway to re-design or phase out current products and processes where OPEs are used;

- The socio-economic impacts that would arise for Siemens Marburg (and other legal entities under the Siemens Healthineers umbrella), its upstream and downstream supply chains and, crucially, patients and healthcare systems in the EEA and elsewhere, if the applicant was not granted an Authorisation for the continued use of OPEs over an appropriately long review period; and

- The overall balance of benefits of continued use of OPEs and risks to the environment from the endocrine effects of 4-tert-OP into which OPEs may break down in the environment.

This AfA is part of a set of Applications that have been prepared by Siemens Healthineers for a range of different uses of OPEs used by two Siemens legal entities[1]. In addition, one Siemens OEM supplier of Siemens Marburg is also submitting an application that is of relevance. These relationships are shown in **Figure 2–1**.

2.2 Summary of the applicant's substitution strategy

The impacted IVD products are part of a larger total of more than #C (range: 50-500) existing Siemens Healthineers IVD products containing OPE and used by healthcare customers in the EEA and beyond. Therefore, the substitution of OPEs both at a site and global level poses a significant technical and regulatory challenge as discussed in Section 4.1.

Following the inclusion of OPEs on the SVHC list in 2012, Siemens Healthineers implemented a global policy to ensure OPEs were no longer used in new product development, where technically feasible. Where it was not possible to identify a suitable alternative, processes were implemented to keep the concentration in the new design below the 0.1% (w/w) threshold level described for endocrine disruptors in REACH Article 56(6). Later on, in response to the addition of OPEs to the REACH Authorisation list, a global 'Response Plan' was launched to initiate phase out of OPEs from existing products. For customers using OPE-containing products, moving to an alternative IVD technology would cause significant disruption and cost in the healthcare sector, and ultimately impact patient care. In many cases, customers would have to stop patient testing for several (6-24) months while moving to an alternative technology, if there was one available. Moving to an alternative technology not only relies on whether a non-OPE-containing IVD product is available elsewhere but also depends on whether there is sufficient capacity within the existing market. Also, in some cases IVD kit reagents are esoteric and therefore it would not be possible for customers to continue performing these important tests if access to the Siemens Healthineers IVD kits was lost.

Supply disruption is not an option for customers who are performing vital tests and providing potentially life-changing results to patients across the EEA. It is therefore Siemens Healthineers' strategy to prevent any customer impact by phasing OPEs out of its product portfolio as follows:

1. Design or Process Change – OPE will be replaced with an alternative substance in each impacted IVD kit or wash solution (if technically feasible – however this will not be known until each formulation is subject to feasibility testing). Projects have already been initiated with a number of the OPE-containing formulations.

2. Product Phase Out – Some of the IVD kit reagents and wash solutions are used on platforms (analysers) which will come to end of life within the next 10 years and will be replaced with platforms which do not incorporate the use of OPEs.

The above global strategy represents a massive utilisation of resources at a cost of #E (range: €10-100 million) over the phase out period and, as previously noted, presents a significant challenge.

The substitution work initiated at the Marburg site in relation to the specific uses within the scope of this AoA-SEA document can be summarised as follows:

[1] The other is Siemens Healthcare Diagnostics Products Ltd (Siemens Llanberis) located in north-west Wales, UK.

- **Use #1 – Protein Cell Extraction (process used in the production of 3 types of product (#D)**: substitution of OPEs here means a change of process, as OPE is a processing aid in this case and therefore is not present in the final IVD reagents manufactured. Within this process use there are #D product types affected (#D products are manufactured from this process, #D of these are IVD kit reagents, one (#D is a raw material for use in the manufacture of beads at Llanberis and is also the subject of a separate AfA submitted by Siemens Healthcare Diagnostics Products Ltd). Therefore #D, G Process Change Projects (PCP) have been initiated. As with all Process and Design Changes in regard to IVD products, a regulated process must be followed to ensure the continued efficacy and accuracy of the final product in terms of delivering a patient result;

- **Use #2 – Formulation of IVD kit reagents (#C different formulations used in #C commercialised IVD kit reagents)**: substitution of OPEs here means a Design Change of the impacted IVD kit reagents, of which there are #C formulations in total. The Design Change process for IVD kits and accessories is strictly regulated under the In-Vitro Diagnostic EU Regulation 2017/746 and other global IVD regulations. The specific phases and timelines associated with this regulated process are set out later in the AfA (Section 6.3). Once a technical substitute has been identified and fully confirmed, a detailed re-registration process follows to meet the legal requirements in every country where the IVD product is sold; and

- **Use #3 – Formulation of wash solutions (#C different formulations reflected in #C commercialised IVD wash solutions)**: OPEs will be phased out of the #C IVD wash solutions (representing #C commercialised IVD products) in a mixed strategy. A Design Change Project (DCP) is planned for #C products, whereas the #C is planned for the other #C IVD products. An IVD wash solution is manufactured to serve a specific analyser system and it is used with every single IVD kit reagent (#C relevant kits) employed on that analyser. Where such a product is subject to Design Change, any alternative must be proven through extensive testing not to affect the performance of <u>any</u> of the IVD kit reagents used on that analyser, and therefore any change must be tested with all #C reagents. In addition, it needs to be demonstrated that a newly formulated washing solution will avoid carry-over from one assay to the assay run afterwards on the same analyser.

The re-design process leading to full substitution of OPE in <u>one</u> formulation and the commercialisation of all products associated with that one formulation can typically take 8 years; in the IVD sector, it is widely accepted that whilst the duration varies per product, a range of 5-12 years is realistic. In the case of Siemens Marburg's impacted product portfolio, this 5-12-year timeframe applies <u>per re-design of each formulation</u> (except where products are being phased out). To summarise, Siemens Healthineers is working to complete more than #F/#G projects, largely concurrently, within the requested review period timeframe.

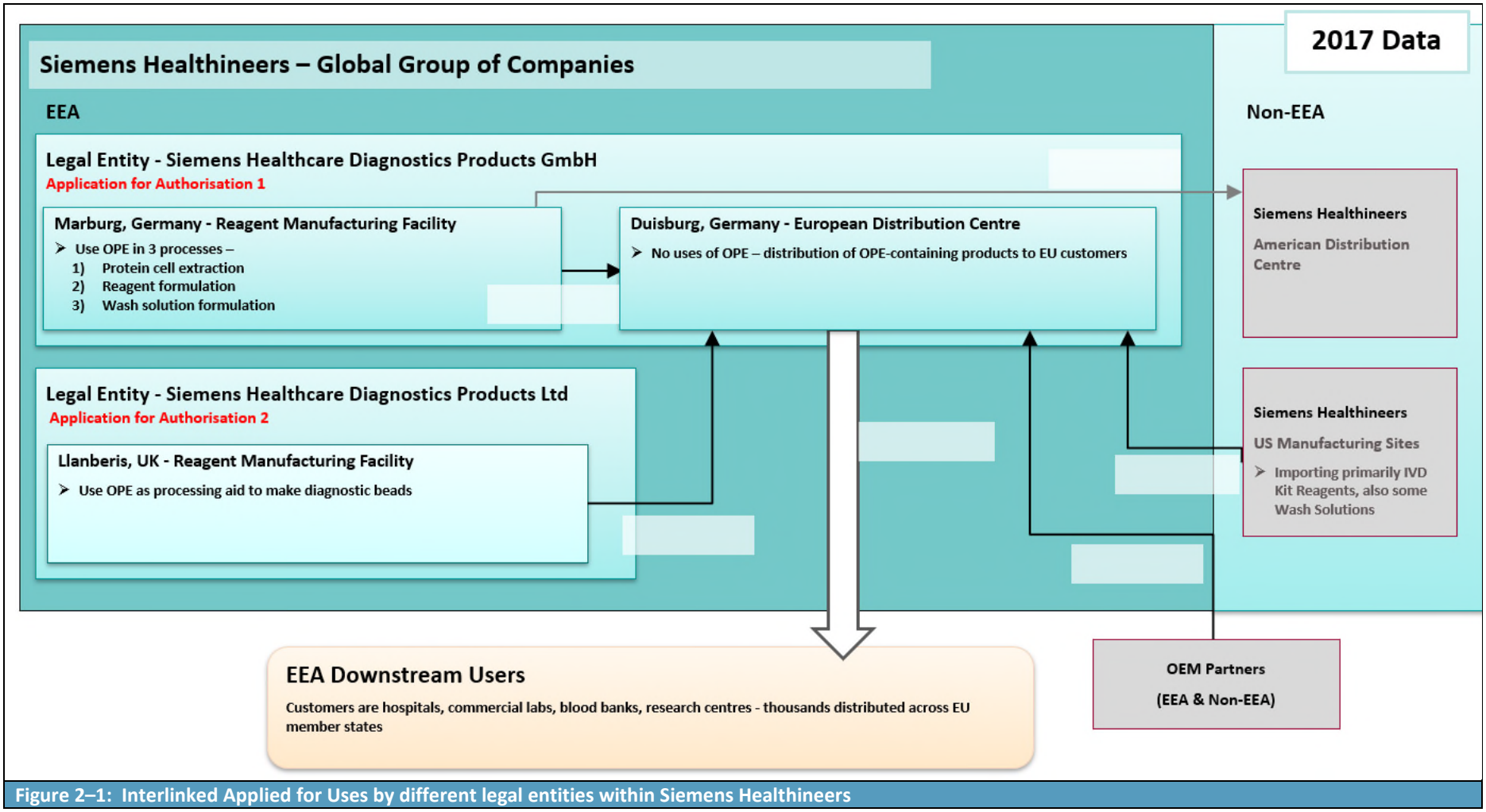

Figure 2–1: Interlinked Applied for Uses by different legal entities within Siemens Healthineers

On the other hand, a Process Change Project where an existing manufacturing process needs to be adapted without the OPE being present in the final product can be quicker to complete; a typical duration of 3 years can be assumed. A project was initiated at the Marburg site to remove OPEs from an existing column purification process in 2018. It is anticipated this Process Change Project will be completed prior to the Sunset Date at a cost of ca. #E, reducing the use of OPE at the site by 10 kg/y.

2.3 Scope of this analysis

2.3.1 Brief overview of uses

This AoA-SEA document concerns OPEs that are used in three manufacturing processes at the Marburg site. The three uses are:

1. Use of OPE in Cell Extraction (to subsequently produce certain IVD kit reagents).
2. Use of OPE in the formulation of IVD kit reagents.
3. Use of OPE in the formulation of IVD wash solutions.

Examples of IVD kits and wash solutions produced from the above three uses are shown in **Figure 2–2** and **Figure 2–3**.

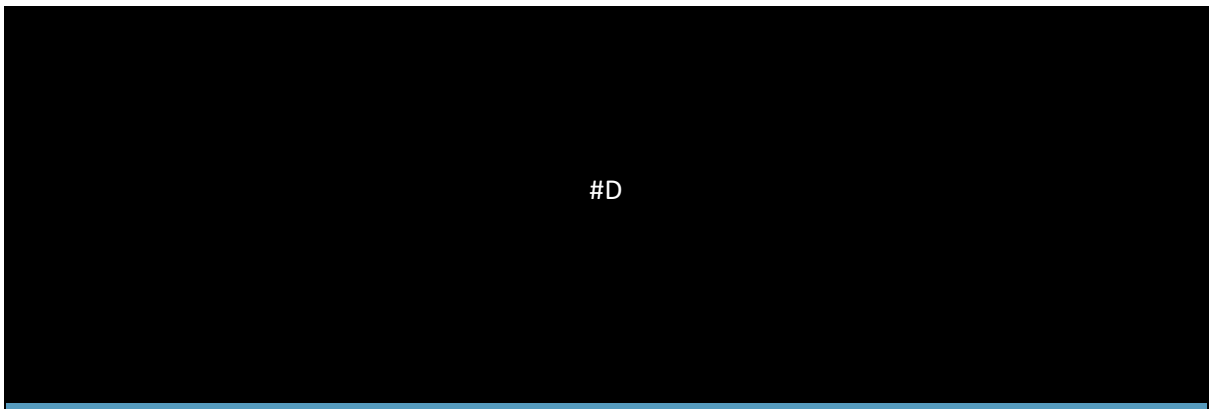

Figure 2–2: Use 1 - IVD Kit example (left) - Use 2 IVD kit example (right)

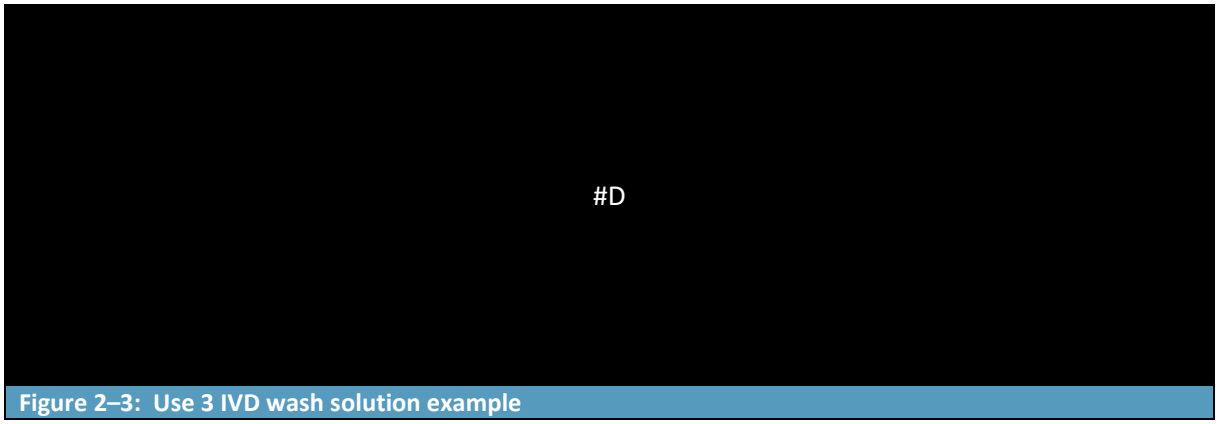

Figure 2–3: Use 3 IVD wash solution example

IVD kit reagents and IVD wash solutions are used by DUs within the healthcare sector, typically hospitals and commercial laboratories, for diagnosis of certain diseases and conditions in patient samples. These DUs are customers of Siemens Marburg.

The IVD kit reagents and IVD wash solutions are used by DUs on Siemens Healthineers (as well as small number of third-party) analyser systems, an example is given in **Figure 2-4**.

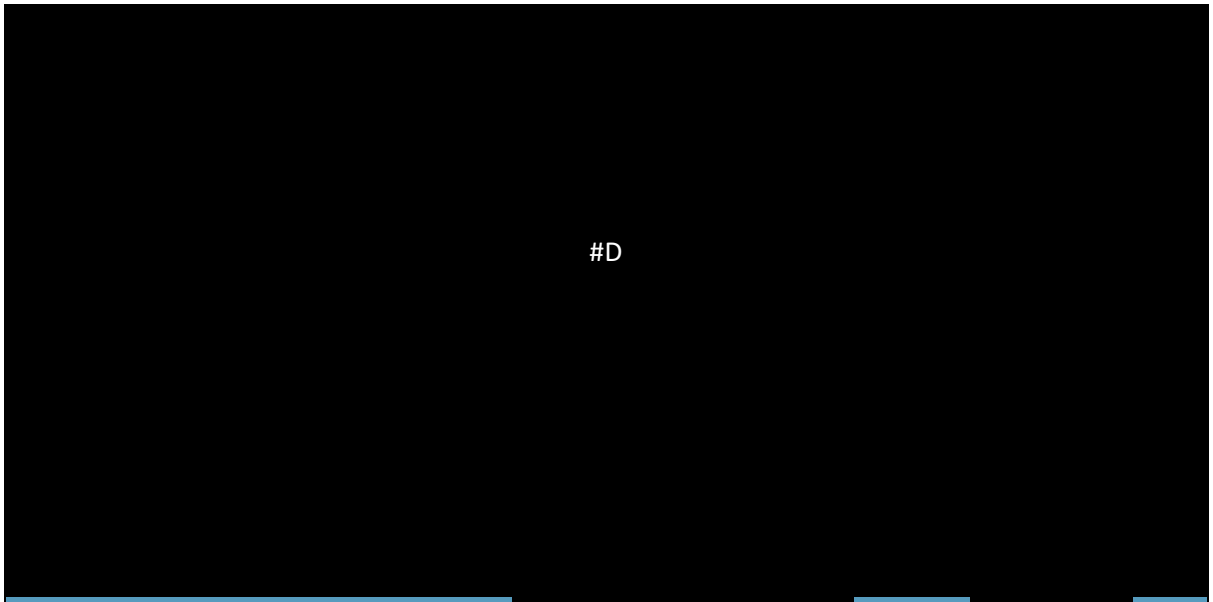

Figure 2-4: Siemens IVD analyser example – #D for use in #D

2.3.2 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 OPEs would be required by Siemens Marburg as a minimum.

The impact assessment periods used in this analysis and the key years are presented in **Table 2-3**.

Table 2-3: Temporal boundaries in the analysis

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	Use #1: 9 years Use #2: 12 years Use #3: 12 years	Based on the length of requested review period
"Non-use"	Loss of profit along the supply chain	Use #1: 9 years Use #2: 12 years Use #3: 12 years	Based on the length of requested review period
	Increased diagnostic costs for healthcare providers	Several months	

Table 2-3: Temporal boundaries in the analysis			
Present value year		2017	
Start of discounting year		2018	
Impact baseline year		2021	
Scenario	**Impact type**	**Impact temporal boundary**	**Notes**
	Disruption to treatment of EEA patients due to loss of range of IVD kits and wash solutions made in Marburg	Use #1: up to 9 years Use #2: up to 12 years Use #3: up to 12 years	Based on the length of requested review period
	Loss of employment	Use #1-3: 1.5 years	Average period of unemployment in Germany (Dubourg, 2016)

2.3.3 Geographic scope

Note: given the uncertainties over the future relationship between the UK and the EU-27 at the time of writing this document, the UK is considered to be part of the EEA.

Manufacturing locations in the EEA

The focus of this analysis will be on the Siemens Marburg's manufacturing facility located in Marburg, Germany.

The legal applicant, Siemens Healthcare Diagnostics GmbH, manufactures IVD kit reagents and IVD wash solutions at the Marburg site, and then distributes these products from its European Distribution Centre (EDC) in Duisburg, Germany to DUs within the EEA. All impacted products sold to customers in the EEA are sent to the EDC for distribution to customers within the EU. There are some exceptions: the Siemens Marburg entity ships #D customers, however OPE is not in the final products. OPE is present in the final product of the #D, however this is sent to Siemens Llanberis in the UK (see below) for further processing (bead coating – separately applied for a REACH Authorisation by Siemens Llanberis) and is not in the final product sent to customers.

Siemens Healthineers has another manufacturing facility within the EEA, in Llanberis, UK, operated by Siemens Healthcare Diagnostics Products Ltd (hereafter referred to as Siemens Llanberis). Siemens Llanberis is also applying for an Authorisation for the use of OPE in the manufacture of IVD kits in the UK. Those IVD kits are used by DUs in the operation of analysers within the #D portfolio of analysers. Importantly, in the context of the present AoA-SEA, Siemens Llanberis supplies DUs with IVD kits which must be used alongside an IVD wash solution that is made by Siemens Marburg and the manufacture of which is covered by the present AfA. In other words, the outcome of the AfA for Use #3 presented in this AoA-SEA will have a profound impact on the ability of Siemens Llanberis to sell its IVD kits to DUs (without the German-made wash solution, they cannot be used). In addition, parts of the #D IVD kit portfolio has links to the Siemens Marburg Use #1 which is discussed in the present document.

On the other hand, there are also parts of the Siemens Marburg operations that do not involve OPEs, e.g. manufacturing of OPE-free parts of the 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 Marburg's core operation and will suffer the same negative consequences as the OPE-dependent operations under the "Non-use" Scenario, which mean that they will be part of the scope of the AoA-SEA.

Suppliers to manufacturing locations

Siemens Marburg has ten suppliers of relevance to the OPE-dependent activities (supply of OPE, articles and materials), of which the vast majority is are located within the EEA.

Downstream users of IVD products

The DUs affected are located in almost all countries of the EEA #C . Marburg product-line customers are typically hospitals, clinics, commercial laboratories, blood banks and research centres. The highest number of analyser systems can be found in #C . Overall there are #C (range: 10,000-100,000) analyser systems operated across the EEA which use the OPE-containing IVD kit reagents and/or IVD wash solutions manufactured at the Marburg site. #C (range: 10,000-100,000) analyser systems are operated outside the EEA.

The use of OPE-containing IVD kits and IVD wash solutions by DUs is the subject of a separate AfA (for Uses #4 and #5) and thus is described in detail in a separate AoA-SEA document.

Relevant non-EEA operations of Siemens Healthineers

The EDC in Duisburg, which is part of the legal entity of Siemens Marburg, is also the importer of IVD kit reagents and IVD wash solutions containing OPE from US-based manufacturing sites within Siemens Healthineers and also from OEM partners, and which are distributed to DUs within the EEA. With particular regard to Siemens Healthineers' US operations that are of relevance to this AfA, Siemens Healthineers has several operational sites that are interlinked with the OPE-relevant operations in Marburg and which could therefore also be impacted in the event of non-Authorisation:

1. *Siemens Healthineers Flanders, New Jersey, USA* – Laboratory Diagnostics (LD) Systems and IT R&D site with systems manufacturing, distribution and support functions, employing approximately #D personnel. This is the #D platform manufacturing facility and all of the #D analysers are manufactured and distributed from this site and thus is relevant to the Siemens Llanberis AfA which is interlinked to the present Siemens Marburg AfA.

2. *Siemens Healthineers Brookfield, USA* – LD Systems manufacturing, primary manufacturing of the #D instruments, employing approximately #D personnel.

3. *Siemens Healthineers Americas Distribution Centre (ADC)* – All of the IVD kit reagents are distributed via the Americas Distribution Centre (ADC). The EDC is supplied via the ADC. The EDC and ADC are the two main distribution centres for all of Siemens Healthineers.

All of 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 operational sites.

Manufacturers of relevant analysers

As shown above, #C, D analyser models use the IVD kits and wash solutions that Siemens Marburg manufactures with OPEs. Of these only some of the Siemens Healthineers analysers are manufactured within the EEA (more specifically in Germany). These are:


#D

3 APPLIED FOR "USE" SCENARIO

3.1 Analysis of substance function

3.1.1 The substances

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

Table 3–1: OPE substances of relevance to this AfA (Use #1, #2 and #3)			
#	**Common trade name**	**Chemical name**	**Degree of ethoxylation (EO units)**
1	Triton™ X-100	Poly(oxy-1,2-ethanediyl), α-[4-(1,1,3,3-tetramethylbutyl)phenyl]-ω-hydroxy-	9.5 (9 or 10)
2	Triton™ X-405 used on site as a 70% solution	Oxirane, 2-methyl-, polymer with oxirane, bis(2-oxiranylmethyl) ether	35 (average)

3.1.2 Introduction to IVD kit reagents and IVD wash solutions

IVD technology is core to modern medicine, with IVD kit reagents and associated IVD wash solutions used to perform qualitative and quantitative tests to diagnose a broad range of diseases and health conditions.

At Siemens Marburg, IVD kit reagents and wash solutions containing OPEs are manufactured for use within the following diagnostic fields:

- Haemostasis (blood coagulation);
- Plasma Protein Analytics; and
- Immunoassay.

With #C IVD products affected within the above fields, this represents #C different analyser systems (see **Table 2–1**) on which these IVD kit reagents and/or wash solutions are used, as listed in Section 2.1.

An **Immunoassa**y, **Plasma Protein** and **Haemostasis** IVD kit will generally include an IVD reagent, an IVD solid phase (sometimes held in suspension in the reagent solution itself), and an IVD calibrator, control and/or diluent. The reagent will contain a biological element, e.g. an antibody coated onto the surface of the 'solid phase', to provide a binding site and thus facilitating the biochemical reaction. See **Figure 3–1** for an overview of the typical contents of an IVD kit.

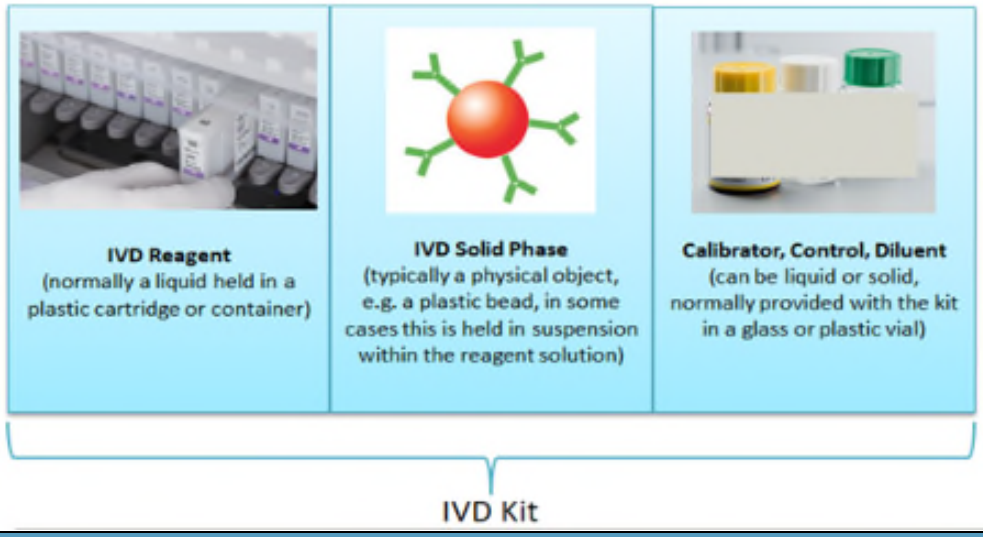

Figure 3–1: IVD kit overview

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 analyser system it is used on. IVD wash solutions are used with every IVD kit on an analyser system 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.

Each of the 3 uses of OPEs in the IVD kit reagent and IVD wash solution manufacturing processes at Marburg are described in detail in the following sub-sections.

3.1.3 Use 1: Isolation of protein from recombinant cell cultures for the production of IVD kits

Triton™ X-100 is used for the extraction of two proteins from cell cultures that are needed in the production of IVD kit components. The proteins in the scope of this AoA-SEA are:

1. [redacted]: for this protein, only an initial isolation step is performed (cell disruption and solubilisation of the protein) and then it is sent to the Siemens production site in Llanberis, UK for further processing[2].
2. [redacted]: this protein is isolated and further purified. During this purification step, all OPE is removed from the product and subsequent steps of the protein use do not need an Authorisation.

These components are needed to formulate IVD kit reagents that are necessary to analyse diagnostic samples in dedicated laboratory instruments (analyser) in the healthcare sector. Reagents are optimised to function according to a protocol specific for one or more individual analyser platforms. These platforms are also part of the Siemens Healthineers product line and are sold as a combination with the IVD kits or as a separate product.

[2] Note: this processing falls within the scope of another AfA submitted by Siemens Llanberis.

The protein purification process at the Marburg site is performed batch-wise on the laboratory scale. The OPE is supplied to Siemens Marburg as pure chemical. This material is diluted to an optimised concentration for the isolation of the target protein in an initial step to the protein isolation procedure. The procedure itself is performed in aqueous solutions close to the physical pH of the cells, so it is important that the detergent used can be dissolved in water, does not interact with other components of the solution (e.g. salts which then can lead to precipitation) and has a physiological pH between 6 - 8.5 when it is applied. The concentration of the OPE is optimised to achieve the following aims:

- The OPEs are present in the solution to ensure a high level of cell membrane permeabilisation during the cell disruption process. This increases the efficiency of the physical cell breaking process which results in an increased protein yield;

- Furthermore, the OPE, as a non-ionic detergent, solubilises lipophilic membrane proteins in the presence of cell membrane fragments and thereby increases accessibility and reactivity of the isolated protein; and

- A third technical function of the presence of OPE is that it stabilises lipophilic membrane proteins in an aqueous solution to avoid aggregation and disintegration. The latter is relevant particularly for #D which, after isolation, it is transported to Siemens Llanberis in solution.

The ingoing concentration in the cell lysis solution for the isolation of the #D and the #D is #B% (>0.1%).

After preparation of the cell lysis solutions, the solution is applied to cells that have been isolated from their growth medium and which are then physically disrupted to make the contained protein assessible. By this, a raw extract is prepared. As already indicated above, the #D is not processed further on site but send to the UK legal entity, Siemens Llanberis, which will cover the subsequent use of the #D raw extract in a separate AfA. On the other hand, the #D raw extract is subjected to a purification column. This column has specific binding sites for the #D to ensure a high efficiency. The OPE containing solution pass through the column and the contained OPE ends up in the wastewater leaving behind an OPE-free protein that can be used in further production processes which do not involve OPE.

All steps are performed by trained personnel in accordance with Good Manufacturing Practice (GMP) and in accordance with the requirements for the manufacture of IVD products: DIN ISO 13485 for the EU and FDA 21 CFR for the USA.

3.1.4 Use 2: Formulation of IVD kit reagents

Triton™ X-100 and Triton™ X-405 are used in the formulation of IVD kit reagents. These reagents are needed to analyse human diagnostic samples in dedicated laboratory analyser systems in the healthcare sector. Reagents are optimised to function according to a protocol specific for one or more individual analyser platforms. These platforms are also part of the Siemens Healthineers product line and are sold as a combination within IVD kits.

The core principle of the IVD kits produced at Siemens Marburg is the interaction of proteins (in most cases antibodies) with proteins present in the blood of humans. The antibodies are coupled to structures that can be detected on the analysers the tests are performed on. The tests are usually not just simple 'yes or no' analytics, but are quantitative as the level of the blood protein can be relevant for the diagnosis of different diseases. A high-content blood protein compared to a standard value in consequence can be an indication for a particular problem whereas a lowered value can be an indication for another. Two core parameters that define the performance level of an IVD kit, its high

specificity and sensitivity. To understand the requirements the OPEs have to fulfil in the test these two parameters are explained a bit more in detail:

- **Specificity** of an IVD kit is the potential of the kit to detect a certain protein with a high accuracy (the antibody only binds to a particular type of target protein); and

- **Sensitivity** of an IVD kit is the degree to which a test does detect a target protein.

To clarify the basic principle and the influence of OPEs on specificity and sensitivity one specific test is explained as an example (others follow the same principle or similar ones but the role of the OPEs remains the same). Further details on these parameters and circumstances that might have an effect on them are demonstrated in the example below.

IVD kit example: #D

Platform – #D
Location of Manufacture – Siemens Healthcare Diagnostics Products GmbH, Marburg, Germany
Applied for Use – Customer use of IVD Kit reagent on analyser systems noted below across EEA
Analyser Systems – #D #D

Function – To diagnose #D .
In this example, the IVD kit is used to detect a #D known as '#D', which is involved in the #D . Deviations in its concentration can be a cause for , and therefore the function of the #D) is to quantify the concentration of #D in a patient sample.

#D

Application of #D kit on an analyser system

There are two IVD kit reagents in the #D kit, these are liquid and contain a 'solid phase' latex bead suspended in the solution. The solution contains OPE. #D are bound to the surface of the latex beads, #D in the first reagent, #D in the second reagent.

During the IVD kit application process on the analyser system, #D

The principle of the #D assay is shown in **Figure 3–2**.

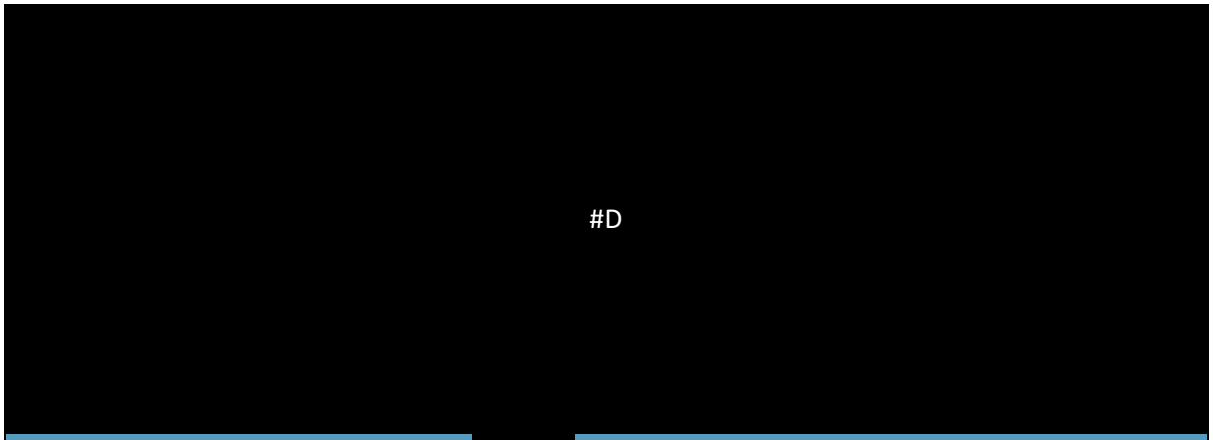

Figure 3–2: Example of a latex bead and from human patient blood plasma

Function of OPE in the #D Kit

The OPE present in the reagent maintains the specificity and sensitivity of the test by ensuring the following:

1. #D are not able to #D or to other molecules/proteins that might be present in the patient sample

   The result of an assay can be influenced by the presence of other molecules that are present, for example other proteins present in the patient sample. Normally, the #D #D follows the lock and key principle. This means, that only the site in such a way that it forms a #D. If another protein in the sample has similar properties (e.g. #D #D etc.) this can lead to non-specific #D complexes. In such cases it is possible that "false positive" signals are detected; this is illustrated in **Figure 3–3**.

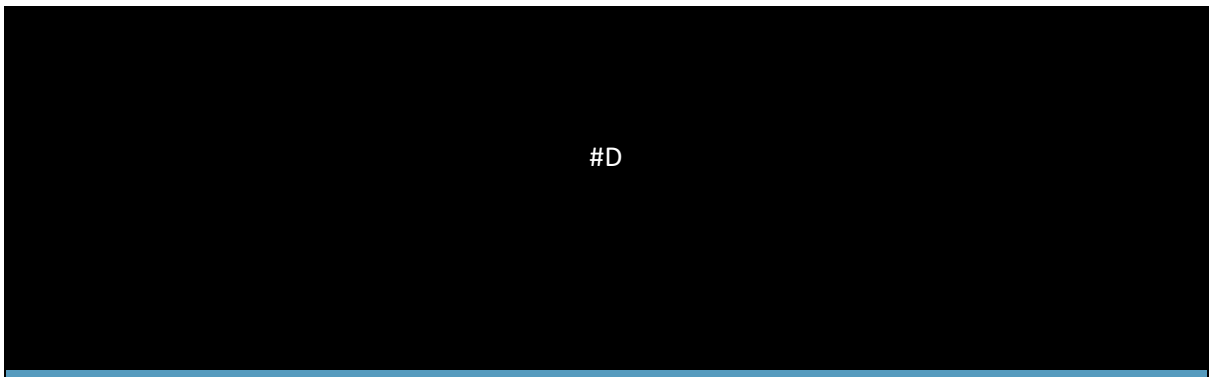

Figure 3–3: Non-specific binding of latex beads to protein, complex formed without presence of target leading to false positive detection of target protein (decrease of specificity)

Another issue can be that a non-target #D to one of the #D in a non-specific way. Then no bead '#D can be formed even #D would be present because #D are already occupied. As a result, the test sensitivity is reduced as the target protein cannot be detected; this is illustrated in **Figure 3–4**.

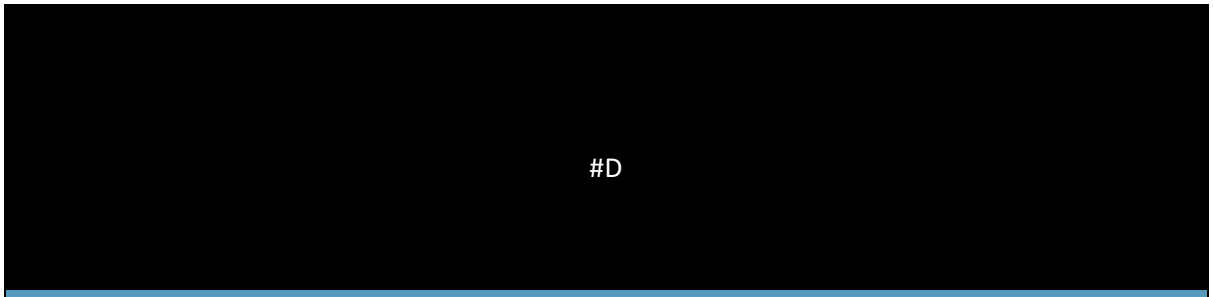

Figure 3–4: Non-target protein occupies binding sites (red square) and thereby avoids specific binding of the target [redacted] even if present in a sample (decreased sensitivity)

2. [redacted]. This effect is known as agglomeration, which can be described as a [redacted] based on [redacted], themselves.

All of the above effects can be summarised under the term "non-specific binding". The presence of OPE inhibits such bindings due to its detergent properties.

It is vital that the role of OPE in preventing 'non-specific binding' is maintained throughout the lifecycle of the IVD kit, from the point of production to its use at the customer site. Thus, OPE ensures the stability of the reactive components over the long shelf-life of the IVD kit.

It also has to be ensured that stability and performance of the reactive components in the IVD kit reagents (the orientation of the antibodies bound to the latex beads but also the suppression of the agglomeration of the beads itself in the kit reagent) is maintained until the IVD kit is used. So, the kit reagent must remain stable for a certain amount of time. Typically, the storage time of the IVD kits are >12 months. A long shelf-life is required for a variety of reasons:

- IVD kit production is performed batch-wise. It can be that a particular product is not produced at all for a certain period of time, which would be the case if there are sufficient amounts of the product still in stock. Nevertheless, these products need to function as if they have just been produced;

- The IVD kits produced at Siemens Marburg are shipped world-wide. The reagent has to be stable during the shipment duration; and

- The IVD kit may not be used directly upon arrival at the customer's site. It can be assumed that hospitals etc. store IVD kits to be able to verify a particular diagnosis when there is an acute suspicion a patient has a certain disease. As it may be unpredictable when this will take place, sufficiently long shelf-life has to be ensured. Shorter times would potentially lead to a situation where DUs would dispose of unused kits due to uncertainties over their accuracy.

So, in the end the overall storage time that has to be achieved is a sum of these three aspects.

It should be noted that the concentration of the OPE in the reagent is specifically optimised to this particular reagent via a long series of tests during product development. Any change of the OPE concentration can have an effect on both the specificity and the sensitivity of the entire test. The concentrations in the products produced by Siemens in Marburg vary from [redacted]% to [redacted]% (range: 0.01-1%) in the final kit reagents (note differences can be in the range of a 10 ppm range – 0.001% between products). For any substitution activity aimed at replacing OPEs by another substance this means:

- The general workability of a substitution has to be verified (i.e., does the alternative work for a particular reagent in principle); and

- The optimisation has to be done per IVD kit reagent to achieve the same performance level of the overall IVD kit (in regard to specificity and sensitivity). It should be noted that even a 'better' performance can be an issue when tests are used to be compared with earlier test results of a patient.

The formulation of the kit reagents is performed batch-wise in a dedicated installation. OPE solutions are prepared from stock solutions directly supplied to Siemens Marburg. During all handling of OPEs no wastewater is generated apart from cleaning water from the cleaning of the devices used for formulation and filling. Measures are implemented to ensure minimisation of residues in all analysers (for more detail, please see the accompanying CSR document).

All steps are performed by trained personnel in accordance with GMP and in accordance with the requirements set out in the production criterial of the relevant authorities for the manufacture of IVD products (DIN ISO 13485 for the EU and FDA 21 CFR for the USA).

3.1.5 Use 3: Formulation of wash solutions

Formulation of the wash solutions

Triton™ X-100 is used in the formulation of wash solutions at Siemens Marburg in Germany. These solutions are needed to remove residues from IVD kit reagents and patient samples from analysers before another round of testing or the next test step can be performed. This cleaning procedure is essential to avoiding cross contamination between patient samples and contamination of IVD kit reagents when different IVD kits are used.

The formulation of the wash solutions is performed batch-wise in a dedicated installation. OPE solutions are prepared from stock solutions directly supplied to Siemens Marburg. During all handling of OPEs, no wastewater is generated apart from cleaning water from the cleaning of the devices used for formulation and filling. Measures are implemented to ensure minimisation of residues in all analysers (for more detail, please see the accompanying CSR document).

All steps are performed by trained personnel in accordance with GMP and in accordance with the requirements set out in the production criterial of the relevant authorities for the manufacture of IVD products (DIN ISO 13485 for the EU and FDA 21 CFR for the USA).

Background to the role of wash solutions at the DU level

By way of background to the role of OPEs, this cleaning procedure involving wash solutions at the DU level is analyser-specific. This means it is performed with the same washing solution for every IVD kit that can be applied to the platform regardless if the IVD kit itself relies on OPEs or not. The solutions are optimised to function according to a protocol specific for one or more individual analyser platforms. They are also optimised for the variety of IVD kits. Sometimes the patient sample solution is pre-diluted, sometimes it is processed by the analyser in concentrated form. In the latter case, the requirements to eliminate residues are far higher. The wash solution nevertheless has to function in all 3 mentioned cases for all kits on the analyser. These platforms are also part of the Siemens Healthineers product line and are sold in combination with the IVD kits. The wash solutions produced at the Marburg production site are used on the #D #D analysers and the #D different #D analyser systems.

The typical set up of an analyser (for example see **Figure 3–5**) that is used in automated IVD testing is that there is one section dedicated for the handling of patient samples. These samples are transferred to the system by a pipettor. The IVD kit reagents, which are responsible to form a complex together with a component from the patient sample that can be detected and quantified, are automatically added by the analyser from a supply. The reaction product is then pumped via a fixed hose through the analyser towards a detection unit. Usually the detection is a photometric method, so the relevant parameter is measured on the analyser as a function of light. Any impurity in the measuring chamber that is present can falsify the test result, which means that the wash solution must remove these impurities very efficiently. In addition, the solution used for the removal of the impurities must not leave behind any impurities itself.

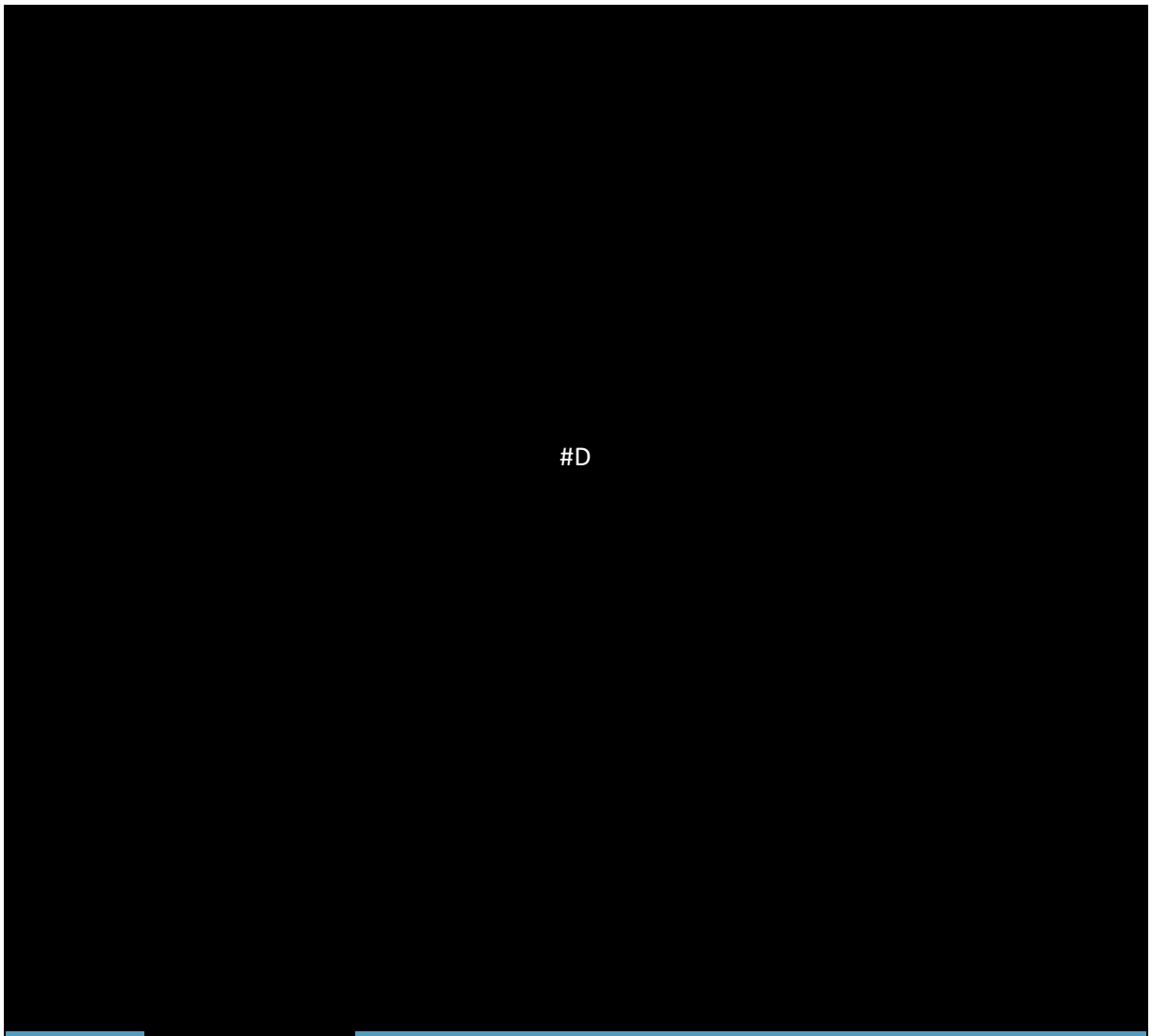

Figure 3–5: #D #D System (Overhead View) Source: © 2014 Siemens Healthcare Diagnostics, Systems Immunoassay System Operator's Guide

Wash solutions are critical for all assays used on the affected analysers, not only the OPE-dependent ones. By way of example, the full number of assays that are 'run' on the affected analyser platforms are shown in the table below.

Table 3-2: Number of assays on relevant Siemens analysers platforms that rely on the use of wash solutions made in Siemens Marburg	
Analyser platform	**Number of unique assays**
[redacted]	[redacted] (range: 50-100)
#D [redacted]	[redacted] #D (range: 50-100)
[redacted]	[redacted] (range: 50-100)
[redacted]	[redacted] (range: 50-100)
Source: Siemens Healthineers	

The OPE is used as a detergent because it reduces unspecific intramolecular interaction between molecules that otherwise might have formed agglomerates that would have the potential to block hoses etc. or interfere with the detection system of the analyser. Substitution of the OPEs will need extensive verification to ensure that the results are not compromised in any way. For any substitution activity of OPEs by another substance this means that:

- The general workability of a substitution has to be verified (i.e., does the alternative work for all IVD kits' particular reagent and patient samples); and

- The optimisation has to be done per platform to achieve the same performance level of each IVD kit (in regard to specificity and sensitivity).

3.1.6 Technical feasibility criteria for the role of OPE in the applied for uses

Technical 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. Scientists recognise a variety of surfactants to choose from in principle, in the development of new products. Nevertheless, some have been used predominantly in the formulation of solutions to be used in biochemistry, among them the OPEs used due to their physico-chemical properties that are compatible with many molecules of biological origin.

Structurally, surfactants consist of a hydrophilic (strongly attracted to water) part and a hydrophobic (very little attraction for 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 beside water (e.g. a protein, a polystyrene 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, with numerous product types within each class. Surfactants are classified by the ionic charge of the hydrophilic group in a water solution.

Anionic surfactants have a negative charge and are considered effective in removing particulates and oily soils. 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 (binding sites can be blocked by detergents that interact with amino acid side

chains, the protein is precipitated from the solution etc.). 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 the anionic and cationic hydrophilic group and are able to form cation or anion according to the ambient conditions. As such, the discussions for cation 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 and Triton™ X-405 belong 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)**: blood and other body liquids are biological, therefore aqueous (water is the solvent). As a consequence of this, the IVD kit reagents are aqueous solutions as well. OPEs possess an ethoxylate group which allows OPEs to be soluble in water.

2. **Hydrophobicity (oil solubility)**: although the specimens are in an aqueous solution, cell membrane proteins are less soluble in water and are associated with less water-soluble components in the specimens (such as e.g. cell membranes, fatty tissue – this may also apply to proteins that are involved in the IVD kits or unspecific non-target protein that is present in a sample). OPEs have a carbon chain that can interact with these components. As such, OPEs can keep these less soluble components in the solution and available for processing. The length of the carbon chain of OPEs varies depending on the degree of ethoxylation grade. The representative chain lengths within the scope of this AfA has an average chain length of 9.5 (Triton™ X-100) or 3.5 (Triton™ X-405) respectively.

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[3]. 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

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

range 0.5 to 19.5[4]. 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 do support removal of hydrophobic particulate (e.g. polystyrene debris) and organic material (e.g. miscellaneous carbon-based pollutants) from surfaces in an aqueous environment. Triton™ X-100 (9.5 EO units) has an HLB of 13.4, Triton™ X-405 (35 EO units) has an HLB of 17.6[5]; potential alternatives should ideally have similar values. For the application of OPEs it is very important that the reagents are clear (or at least translucent), because of the photometric quantification techniques. This is only the case for HLB values of 10 or more.

Not all surfactants having the same HLB value may be acceptable for a specific formulation. The overall chemical structure (branched, linear and aromatic) of surfactants is varied and is an important variable to consider. Therefore, a number of different surfactants with the required HLB need to be examined. Surfactants are very versatile molecules. Depending on what reagent type the formulator is looking for, he can balance his surfactant system so that for any formulation, one could find more than one surfactant type to give at least some of the required functionalities for the specific IVD kit reagent. Moreover, HLB values are additive. Take, for example, a surfactant with an HLB value of 7.8 which is not soluble in water but may have a stabilising effect on a protein in the test (maybe if the protein itself is not very water soluble). The solution is to blend two surfactants of known HLB, one high and one low. Using the following equation:

HLB required = (% surfactant A) x (HLB Surfactant A) + (% surfactant B) x (HLB Surfactant B).

A blend of surfactant A with an HLB of 7.8, and surfactant B with an HLB of 13.4 produces a combination that is water soluble and contributes other required functionalities.

Technical feasibility criterion 3: Critical micelle concentration

A micelle is an aggregated unit composed of a number of 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 remove particles.

Critical micelle concentration (CMC) is a measure of surfactant efficiency. A lower CMC indicates 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 and Triton™ X-405 has a CMC of 2,442 ppm). CMC values provide a valuable guideline for comparing surfactant detergency. Other formulation components and temperature may affect micelle formation.

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

[5] Information from the substances manufacturer's (Dow) technical data sheets (retrieved 0n 5 September 2018).TRITON™ X-100 Surfactant, http://msdssearch.dow.com/PublishedLiteratureDOWCOM/dh_0971/0901b80380971362.pdf?filepath=surfactants/pdfs/noreg/119-01882.pdf&fromPage=GetDoc

TRITON™ X-405 (70%) Surfactant, http://msdssearch.dow.com/PublishedLiteratureDOWCOM/dh_097b/0901b8038097b300.pdf?filepath=surfactants/pdfs/noreg/119-01889.pdf&fromPage=GetDoc

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. 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 whilst that of Triton™ X-405 is >100 °C. A cloud point should, as a consequence, be well above ambient temperatures in the countries the IVD kits are shipped to. Under extreme conditions like intense sun and road transport temperatures could rise up to 50 °C.

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	Relevant applied for uses		
				Use 1	Use 2	Use 3
1	Nonionic surfactants	OPEs are such surfactants	Alternative substances need to be nonionic	✓	✓	✓
2	Hydrophile-lipophile balance	Triton™ X-100: 13.4 Triton™ X-405: 17.6	> 13 >15	✓	✓	✓
3	Critical micelle concentration	Triton™ X-100: 189 ppm Triton™ X-405: 2,442 ppm	Similar range to respective Triton	✓	✓	✓
4	Cloud point	Triton™ X-100: 66 °C Triton™ X-405: >100 °C	#B °C	✓	✓	✓

The table on the next page provides a wider overview of the key parameters of the use of OPEs in the applied for uses.

Table 3–4: Overview of the key parameters of the applied for uses of OPEs by Siemens Marburg			
#	Parameter of use	Description	
1	Task(s) performed by the substance	Suppression of unspecific binding between molecules, e.g. protein – protein interaction, protein interaction with artificial surfaces (e.g. with analyser probe or hoses)	
2	Physical form of the product	Liquid, clear solution, sometimes containing particulate matter at a microscopic level (e.g. antibody beads)	
3	Concentration of the substance in the product	The concentration may vary from concentrations at 0.1% up to 1%. Some products are shipped as concentrates at higher concentrations which have to be diluted down to the working concentration at the downstream user's site (e.g. one solution is shipped at a concentration of #D % Triton™ X-100, whereby the working concentration in the test is below 0.1% - 0.0168%, therefore only the dilution step would be in scope of Authorisation at the DU site).	
4	Critical properties and quality criteria OPEs fulfil	All reagents used for IVD testing, and their individual components must remain functional throughout production, storage, shipping, on-board the analyser and finally for the final testing. As such, the chemical properties of OPEs (as described above) provide a wide range of required functionalities throughout this entire process. This is true both generically and technology-specific. All aspects of the product, from raw material generation through final use, are therefore considered and need to be evaluated when identifying specific alternatives. Some considerations are	
		Mild detergent action, non-specific binding	OPEs do not interact strongly with proteins or other constituents, which would negatively affect structure and function. The necessary reaction components, such as antibodies and other proteins, remain functional. Furthermore, this property inhibits non-specific binding, a common problem in all aspects of the production of IVD-kit reagents, in this case protein isolation and upon storage for further processing. Unwanted compounds adhering to the target molecules or in case of membrane proteins also tend to agglomerate (to stick to each other). The causes of unwanted, non-specific binding are varied, but the properties of the OPEs inhibits many of these without denaturing the primary, necessary components. One property that is the cause of the variation of the effect of a detergent on a protein is the protein itself, as it is interacting with the detergent in the solution. Given the high number of different proteins there is no clear property that can be used to identify if a detergent is suited for a protein purification process or not. Furthermore, to find the optimal concentration extensive laboratory testing would be needed
		Easily dissolved/dispersed in aqueous solution	Since the component purification is performed in water-based solutions, the surfactant must be able to be completely mixed. In addition, due to the varied needs, a range of OPE concentrations are needed. OPEs can be mixed into water from very low (<<0.01%) to very high (>2%) concentrations
		Non-foaming	Bubbles interfere with the manufacturing process and will interfere with fluidics and measurements on-board the analyser. In the given example, detection is performed via light scattering which can also be caused if bubbles are present in the measuring chamber of an analyser. The latter causes incorrect test results
		Stability	OPEs, both in concentrated and diluted form, are stable for at least 2 years, remaining in solution. This is needed for sufficient shelf-life in inventory and within the final product that is placed on the market

Table 3–4: Overview of the key parameters of the applied for uses of OPEs by Siemens Marburg			
#	Parameter of use	Description	
		Heat (>37 °C) and cold (<-15 °C) stable	This is the typical temperature extremes during IVD kit shipment and storage
		Able to disrupt cell membranes	The initial step of protein purification does involve cell disruption to make the necessary protein available for further preparation. The OPE 8-carbon chain is very effective in interacting with the cell membrane of eukaryotic (e.g. human cells) and prokaryotic (bacteria like e.g. E. Coli) cells. This is relevant e.g. for IVD kit reagents that are used to release cell-bound target molecules (attached or in the cell) to make them assessable for subsequent detection
5	Function conditions (frequency of use and quantity used)	Reagent Formulation production	For each of the affected reagents a maximum for #C lots/year are planned. With #C affected products this brings us to #C manufacturing slots
		Wash buffer formulation	Formulation of the wash will happen max. #B a day
6	Process and performance constraints	Does not interact with salts within aqueous solutions	Salts are needed in biological-based solutions to keep reagents active and stable. A reaction with salts would cause precipitation which could lead to incorrect test results
		Soluble and functional within the pH range of typical biological reactions	Specimens are available between pH 6.0 – 8.5 which is the typical pH range of process solutions and final products
		Leaves no residue	To ensure complete removal of the detergent, no residues may remain on parts of the analysers
		Clear and colourless in solution	Cloudiness (precipitation) and colour can interfere in photometric measurements
		Does not interact with films or plastics	Films and plastic are used in multiple aspects of the entire process (e.g. on-board analyser hoses, reaction tubes). Surfactant interactions with final packaging, for example, have shown to negatively impact shelf-life
		No interference with assay technology-specific components	For example, #D is used as the detection method for #D and #D technologies. OPEs do not interfere with this enzyme
7	Can the use of OPEs be eliminated and the	In the short term the OPEs cannot be eliminated and the uses cannot be continued. Phase out of the substance or the kit reagents to retain the functionality is dependent on:	

Table 3–4: Overview of the key parameters of the applied for uses of OPEs by Siemens Marburg		
#	**Parameter of use**	**Description**
	process/use of IVD kits continued?	• Time needed to identify an alternative substance, kit reagent to remain the test functionality • Time needed to fulfil the requalification of the adapted test according to European rules for the introduction of an IVD Kit • Time needed to find alternative products or analyser platform that do not rely on the use of OPEs • Time needed to identify service providers that can provide diagnostics without using OPEs
8	Customer requirements associated with the use of the substance	Customers need IVD kits that can be handled with a justifiable effort for the trained staff in the healthcare system (not scientists but well-trained professionals). Time needed for a diagnostic analysis must be sufficiently fast to provide good treatment to patients at a reasonable time (or to make quality checks on products e.g. in case of blood banks that test blood from donors). Diagnosis must have a guaranteed specificity and sensitivity and also a good reproducibility (e.g. to follow the development of a diagnostic parameter over time to check if a medication works)
9	Industry sector and legal requirements for technical acceptability that must be met	Healthcare sector. Products must fulfil the requirements of the regulatory framework in the EU (Regulation (EU) 2017/746 of the European Parliament and of the Council of 5 April 2017 on in vitro diagnostic medical devices and repealing Directive 98/79/EC and Commission Decision 2010/227/EU) as well as the specific legal requirements in any country worldwide where the product is envisaged to be sold

3.2 Market and business trends including the use of the substance

3.2.1 Brief overview of interlinkages between Siemens Healthineers REACH Authorisation activities

Figure 2–1 summarises the REACH Authorisation activities that are co-ordinated by Siemens Healthineers and which are linked to the present AfA. As can be seen, the following linkages exist:

- Siemens Marburg Use #2 links to DU Use #4;
- Siemens Marburg Use #3 links to DU Use #5; and
- Siemens Marburg Uses #1 and #3 link to Siemens Llanberis Use #1.

It should be noted that the DU AfA has a scope greater than the present AfA for Siemens Marburg as it encompasses IVD products that are manufactured not only in Marburg but also in the USA as well as OEM-made IVD products.

3.2.2 Annual tonnage of OPE used per Applied for Use

Use #1: Isolation of protein from recombinant cell cultures for the production of IVD kits

Description of current (2017) situation

The annual tonnage of Triton™ X-100 used for protein cell extraction was #A (range: 1-10) kg in 2017. The two isolated proteins end up in #C IVD products. This comprises the production of #C products of the #D® product line from which one product is basically the pure protein that is sold to a third party IVD kit producer on a B2B level. The last affected product #D #D, is an IVD kit part of the #D product line. The downstream processing of that protein is not performed at the Marburg site but sent to Siemens Llanberis in the UK.

The ingoing buffer that is used for cell disruption to produce the #D has a Triton™ X-100 concentration of #B %. Since the dilution during cell disruption is not very high, it can be assumed the shipped raw protein extract has a resulting concentration of nearly #B%, and is therefore in the scope of REACH Authorisation activities of the UK legal entity. An amount of #A (range: 0.1-1) kg was needed for the #D in 2017. The remaining #A (range: 1-10) kg was used for the isolation of the – #D (see **Table 3–5**). The following figure presents an overview of the flow of OPE through the Marburg site in relation to the applied for Use #1.

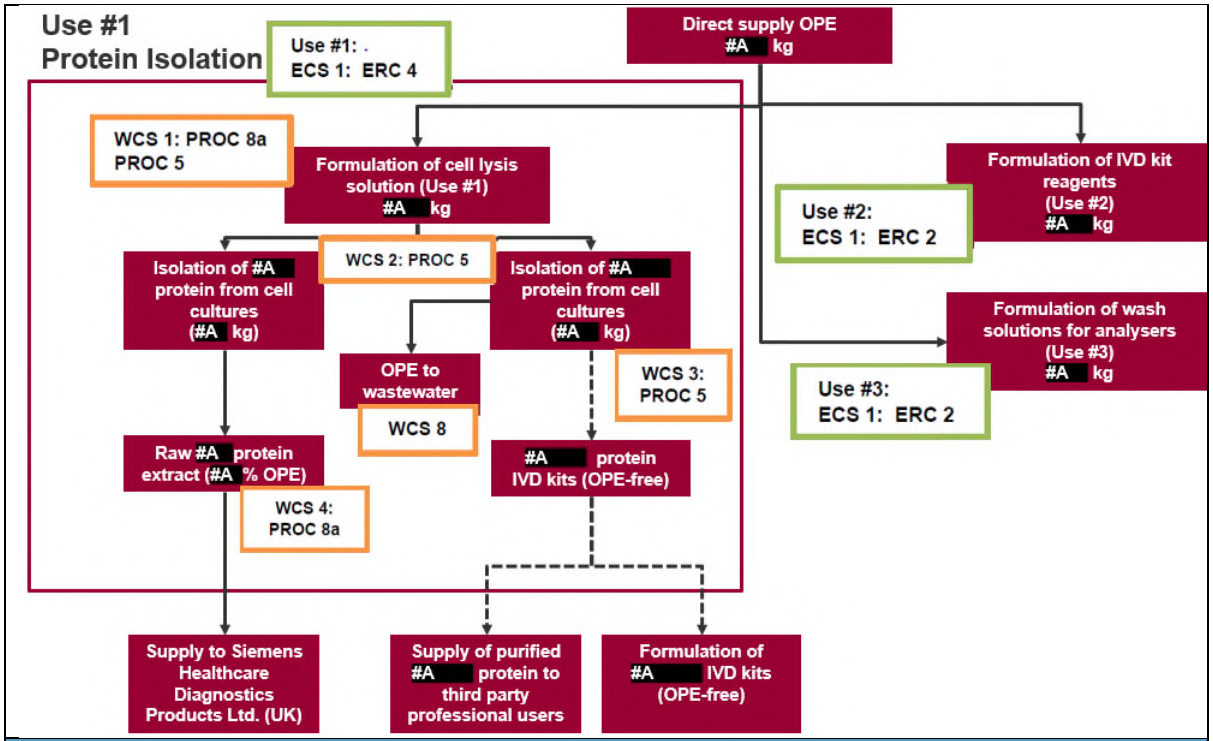


Figure 3–6: OPE substance flow scheme for the Marburg production site - Use #1 Protein isolation (based on data for 2017)

Table 3–5: Products produced with protein that relies on the use of OPE at Siemens Marburg site (Use #1) – All volumes are Triton™ X-100

Product	Product Name (DOC/Label)	Analyser	Volume used per annum (kg) /2017
#D, Column	#D, Column	#D, Column	#A, Column
[redacted]			
Total			[redacted] **(range: 1-10 kg)**

Planned phase out of OPE and projected consumption of Triton™ X-100 over the requested review period

Figure 3–7 presents Siemens Healthineers' REACH Response Plan with particular reference to the use of Triton™ X-100 in IVD products that fall under Uses #1-3 of Siemens Marburg. With reference to Use #1, the figure shows:

- One Process Change Projects aimed at finding and registering alternative surfactants; and

- One product #D for which activities will involve both a process change and a phase out of Triton™ X-100. The REACH Response Plan makes provision for the re-formulation of the #D product to cover the needs of Siemens Healthineers' #D system. This re-formulation work is expected to finish at the end of #D, G. However, the use of OPE in the manufacture of #D in Marburg needs to continue until 2029 because this product is required for the operation of the #D. It should be clear that the reformulation of #D for the #D analysers does not mean that the reformulated product would be 'ready for use' for the coating of beads in Llanberis. If #D were to change for the use in Llanberis, its compatibility with related #D IVD kits would have to be tested, the reformulated #D be re-registered, etc. This process would take years #D.

Taking into account the timing of the Process Change Projects for the phase out of Triton™ X-100 in Use #1, a time series showing the future consumption of Triton™ X-100 over the requested review period can be generated – see **Figure 3–8**. Consumption will marginally decline in the period 2021-#E as R&D work will be ongoing. However, as R&D projects deliver results (i.e. substitutes for Triton™ X-100 are identified), consumption of Triton™ X-100 will dramatically decrease after #E as kits become independent of the use of Triton™ X-100. At the end of 2029, consumption of Triton™ X-100 is envisaged to cease.

Figure 3–7: REACH Response Plan – Substitution of OPEs in Uses #1-3 of Siemens Marburg

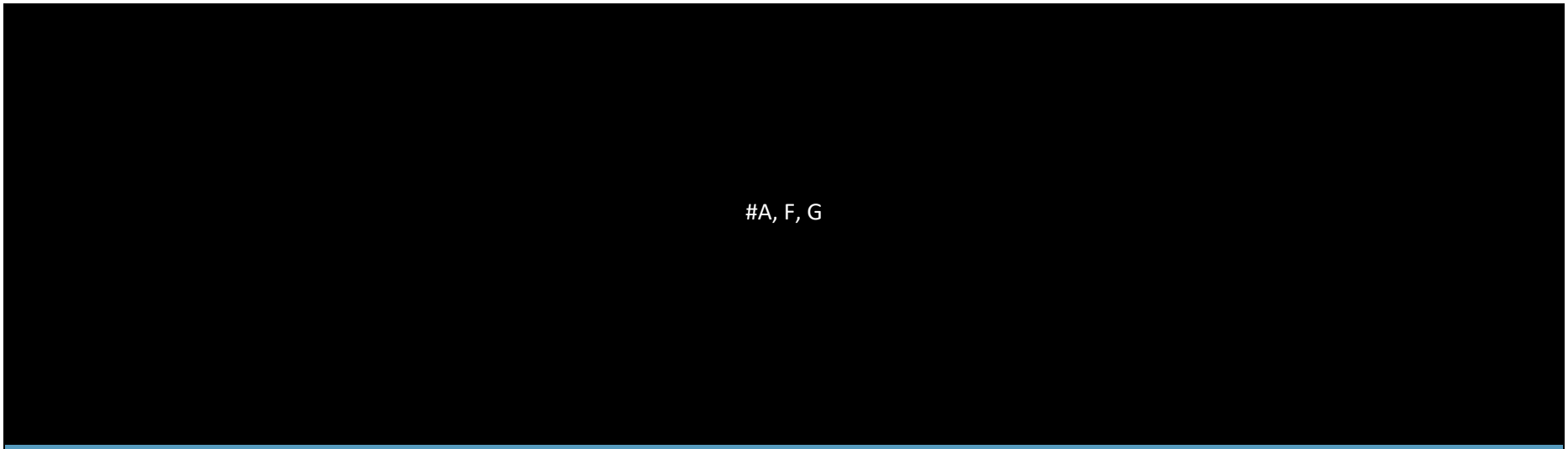


Figure 3–8: Time series of OPE consumption by Siemens Marburg for the manufacture of kits within the scope of Use #1

Use #2: Formulation of IVD kit reagents

Description of current (2017) situation

Two OPE substances are of relevance here, Triton™ X-100 and Triton™ X-405. In 2017, in Use #2, #A (range: 1-10) kg OPEs were used. This included #A (range: 0.1-1) kg Triton™ X-405 (see **Table 3-6**) and #A (range: 1-10) kg Triton™ X-100 (see **Table 3-7**). An overview on the mass flow of Triton™ X-100 and Triton™ X-405 through the uses at the Marburg site is given in **Figure 3-9**.

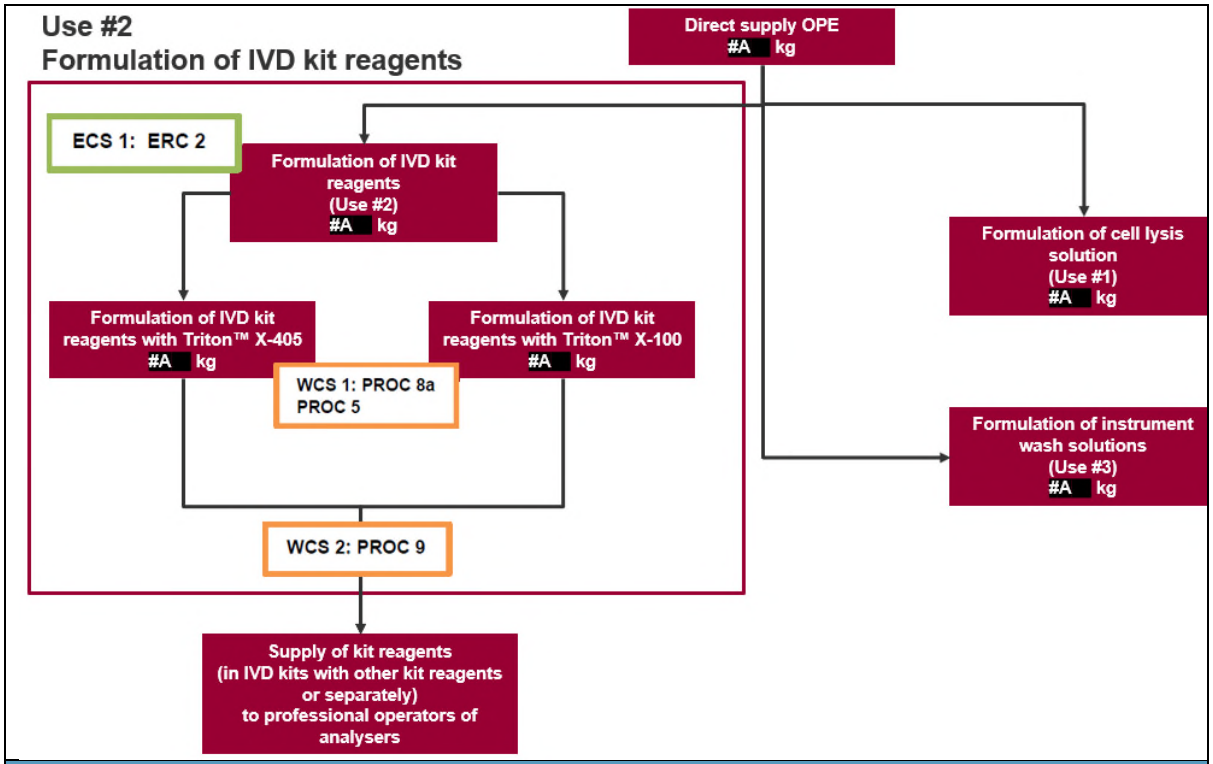


Figure 3-9: OPE substance flow scheme for the Marburg production site – Use 2 (Formulation of IVD kit reagents), based on data for 2017

Table 3-6: IVD kit reagents formulated at Siemens Marburg site on the basis of Triton™ X 405 (for reduction in non-specific binding in Use #2)

Product	Product Name (DOC/Label)	Relevant analysers	Volume of 70% solution used per annum (kg) /2017
#D, Column	#D, Column	#D, Column	#A, Column
		Total	**(range: 0.1-1 kg) as substance**

Table 3-7: IVD kit reagents formulated at Siemens Marburg site on the basis of Triton™ X 100 for Use #2			
Product	**Product Name (DOC/Label)**	**Analyser**	**Volume used per annum (kg) /2017**
#D, Column	#D, Column	#D, Column	#A, Column
		Total	**(range: 1-10 kg)**

Important note: **Table 3-7** excludes the tonnages of #D products: #D and #D. Details of the use of OPE in these products are provided in a separate AfA that is submitted by a separate legal entity #I. #I is an #I supplier to Siemens Marburg, who label these #D products and which are then #D through the #D

Planned phase out of OPE and projected consumption of Triton™ X-100 and Triton™ X-405 over the requested review period

Figure 3–7 presented Siemens Healthineers' REACH Response Plan with particular reference to the use of Triton™ X-100 in IVD products that fall under Uses #1-3 of Siemens Marburg. With reference to Use #2, the figure shows #D Design Change Projects aimed at finding and registering alternative surfactants: #I and is expected to be completed in late #I, another is envisaged to be completed by early , while the third one requires at least until the end

of [redacted]. Finally, a #D project is an End-of Life project that is relevant to both Use #2 and Use#3 and has a timeframe to end of #D, G.

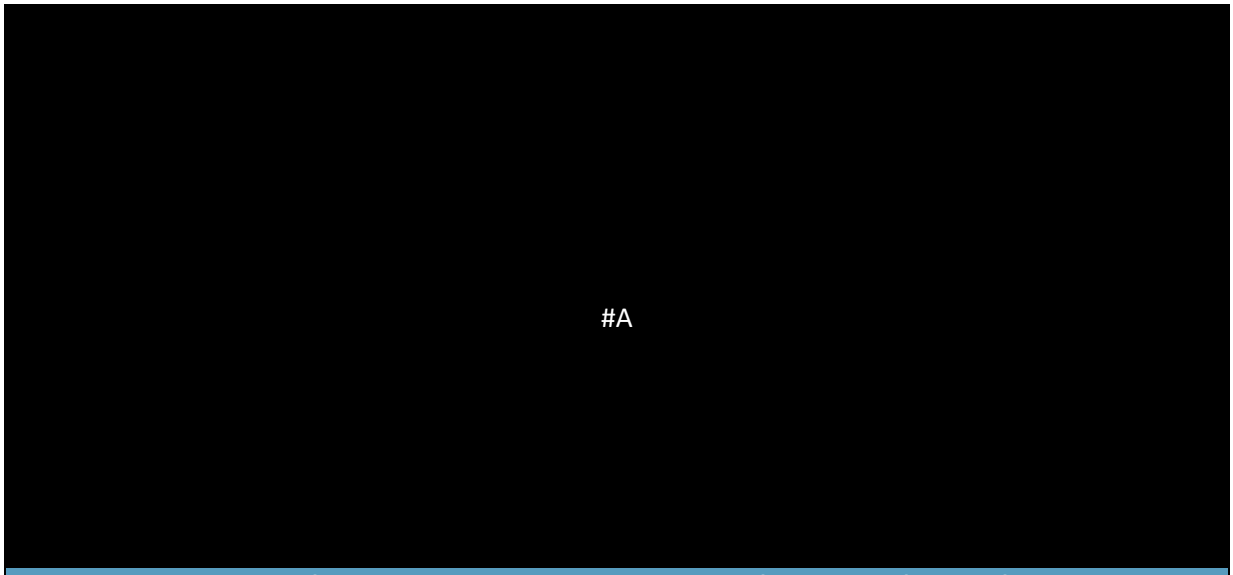


Figure 3–10: Time series of OPE consumption by Siemens Marburg for the manufacture of IVD kits within the scope of Use #2

Use #3: Formulation of wash solutions

Description of current (2017) situation

Only Triton™ X-100 is relevant for this Applied for Use. The annual tonnage of Triton™ X-100 used in the formulation of wash solution was #A (range: 100-1,000) kg in 2017. Two different wash solution formulations were produced in a single operation (see **Table 3-8**).

Table 3-8: Wash solutions formulated at Siemens Marburg site on the basis of Triton™ X 100

Product	Product Name (DOC/Label)	Analyser	Volume Used per annum (kg) /2017
#D, Column	#D, Column	#D, Column	#A, Column
		Total	[redacted] **(range: 100-1,000)**

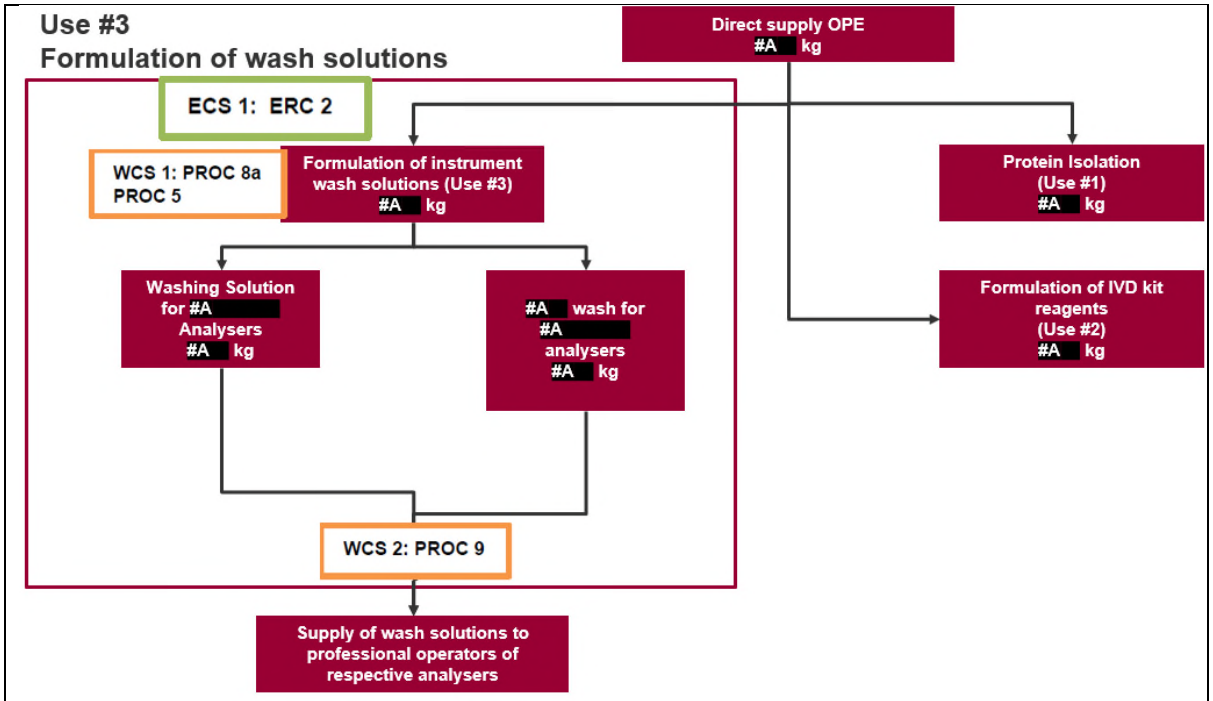


Figure 3-11: OPE substance flow scheme for the Marburg production site - Use #3 Formulation of Wash solutions for Analysers (based on data for 2017)

Planned phase out of OPE and projected consumption of Triton™ X-100 over the requested review period

Siemens Healthineers' REACH Response includes #G that is relevant to Use #3; this is relevant to the #D wash solution for the #D analyser and was shown in **Figure 3–7**. this is expected to take 12 years to complete this work due to the Design Change process and resources required at Marburg. The reformulation of the #D wash solution must be done sequentially (as indicated in the REACH Response Plan) following the reformulation of the ***#D*** IVD kit reagents. The reason for this is because the reformulated wash will need to be tested with all ***#D*** assays used on the same platform (at the feasibility stage).

On the other hand, no R&D on alternatives for Triton™ X-100 in the #D wash solution is planned. #D . As is explained in more detail in the separate AfA #D the investment of resources towards the reformulation of this wash solution cannot be justified. Still, as long as analysers are operated by DUs, there is the need to continue the production and the supply of customers with the wash solution.

Since the wash solutions have to be applied in each test cycle of the analyser it can be assumed that the consumption per analyser is more or less stable. It can be assumed that the demand for wash solution will depend on the increase or decrease in the number of analysers installed plus the number of analysers that will be reaching the end of their useful lifetime. Consequently, #D , whilst demand for #D wash solution by an increasing number of #D analysers will increase. Taking these as well as the planned R&D work into account a time series showing the future consumption of Triton™ X-100 over the requested review period has been generated – see **Figure 3–12**. Consumption can be shown to halve (compared to 2017) by #E and will be below #A kg/y by #E before it ceases soon after 2032.

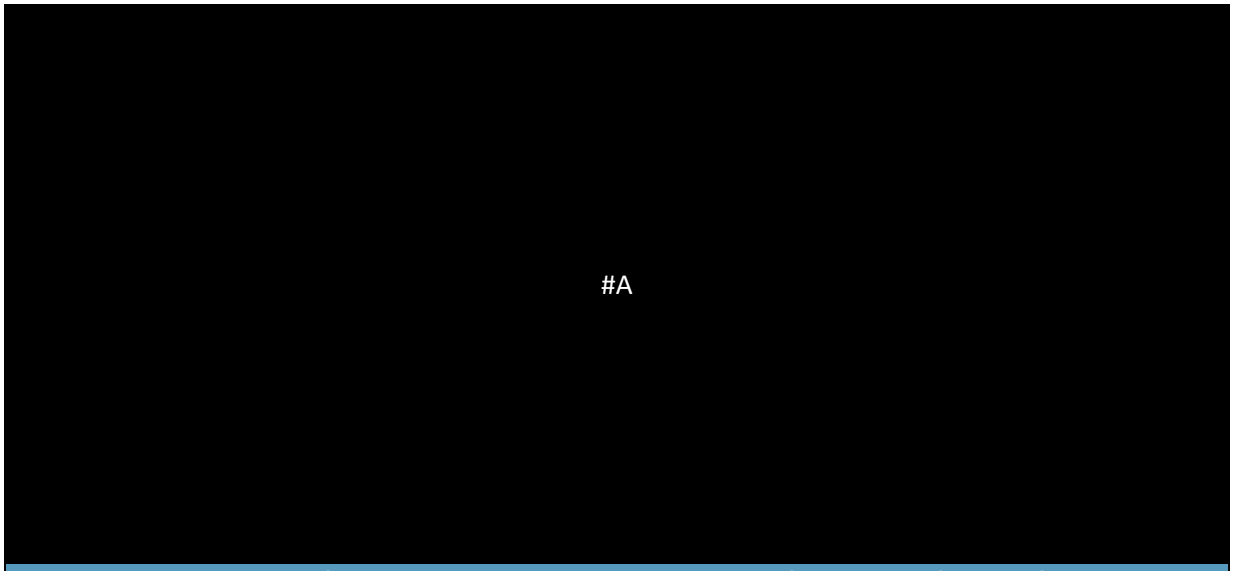


Figure 3–12: Time series of OPE consumption by Siemens Marburg for the manufacture of kits within the scope of Use #3

3.2.3 Market for Siemens Marburg IVD kits and wash solutions

Sales of IVD kits products relying on protein isolation (Use #1)

The sales volumes, revenue and profits for Use #1 IVD kits in 2017 are presented in the table below.

#D

Table 3-9: Sales volumes and value of IVD kits linked to Use #1 by Siemens Marburg

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

In order to project sales over the requested review period, assumptions have been made by Siemens Healthineers' Finance Department on the growth of IVD kit sales. The projections are subject to uncertainty and show the projected year-on-year change in sales of the #E IVD kits. Some key notes should be made:

- The projections are assumed to apply equally to numbers of kits sold and revenues/profits made; and
- Projections are only available for the period 2018-2028 (based on a strategic #D business plan developed by the Finance Department of Siemens Healthineers). For the year #D, it is assumed that no change (0%) for the #D kits will occur but on the other hand a significant reduction is assumed for #D.

The annual changes are shown in the following table.

Table 3-10: Projected year-on-year change on the number of kits sold – All IVD kits linked to Use #1 by Siemens Marburg		
Year	#D	#D
2018	#C, Column	#C, Column
2019		
2020		
2021		
2022		
2023		
2024		
2025		
2026		
2027		
2028		
2029		

Using these percentages and a discount rate of 4%, it can be estimated that the Present Value of gross profits that Siemens Marburg anticipates making over the requested review period is in the range of €10-100 million.

Table 3-11: Net present value of profits from sales of IVD kits relevant to Use #1, 2021-2029, 4% discount		
Customer group	NPV, All Use #1 kits	#D
EEA customers		
Non-EEA customers	#C	
All customers		

Sales of IVD kit reagents (Use #2)

The sales volumes, revenue and profits for Use #2 IVD kits in 2017 are presented in the table below.

Table 3-12: Use #2 - Profits from sales of Siemens Marburg's products in the EEA, 2017						
Product group	No. kits/year		Sales, €/year		Gross profits, €/year	
	EEA	Non-EEA customers	EEA	Non-EEA customers	EEA	Non-EEA customers
#D, Column	#C, Column	#C, Column	#D, Column	#D, Column	#D, Column	#D, Column
Grand total						

A higher-level summary, which also splits sales between UK customers and non-UK EEA customers is provided for the readers convenience below.

Table 3-13: Sales volumes and value of IVD kits linked to Use #2 by Siemens Marburg – Summary of all kits		
Sales by volume (No. kits/year)	Sales by value (€/year)	Profit after standard cost by value (€/year)
#D	#D	#D

In order to project sales over the requested review period, assumptions have been made by Siemens Healthineers' Finance Department on the growth of IVD kit sales. The projections are subject to uncertainty and show the projected year-on-year change in sales of the IVD kits falling within different market segments #D. Some key notes should be made:

- The projections are assumed to apply equally to numbers of kits sold and revenues/profits made; and
- Projections are only available for the period 2018-2028. For the purposes of the present analysis, for the years 2029-2032, it is assumed that no change (0%) will occur.

The annual changes are shown in **Table 3-14**.

Table 3-14: Projected year-on-year change on the number of kits sold – Market segments for IVD kits linked to Use #2 by Siemens Marburg				
Year	#D, Table			
2018				
2019				
2020				
2021				
2022				
2023				
2024				
2025				
2026				
2027				
2028				
2029				
2030				
2031				
2032				

For OEM kits (those comprising reagents made by #I and for which a separate AfA is submitted by #I), #G.

Using these percentages and a discount rate of 4%, it can be estimated that the Present Value of gross profits that Siemens Marburg anticipates making over the requested review period is in the range of €10-100 million #D.

Table 3-15: Net present value of profits from sales of IVD kits relevant to Use #2, 2021-2032, 4% discount					
Customer group	**NPV, 4% discount, All kits**	**NPV, 4% discount, [redacted]**	**NPV, 4% discount, [redacted]**	**NPV, 4% discount, [redacted]**	**NPV, 4% discount, OEM kits ([redacted])**
EEA customers	#D, Table [redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Non-EEA customers	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
All customers	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Sales of IVD wash solutions (Use #3)

The sales of the wash solutions rely on the OPEs under Use #3 in Marburg are shown in the following table. The table presents the corresponding sales volumes, revenue and profits in 2017.

Table 3-16: Sales volumes and value of wash solutions linked to Use #3 by Siemens Marburg						
IVD wash solutions	**Sales by volume (No. kits/year)**		**Sales by value (€/year)**		**Profit after standard cost by value (€/year)**	
	EEA	**Non-EEA**	**EEA**	**Non-EEA**	**EEA**	**Non-EEA**
#D, Table [redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

In order to project sales over the requested review period, assumptions have been made by Siemens Healthineers' Finance Department on the growth of the wash solution sales. The projections are subject to uncertainty and show the projected year-on-year change in sales of the wash solutions falling within different market segments ([redacted]). A few notes should be made:

- The projections are assumed to apply equally to numbers of wash solution units sold and revenues/profits made; and
- Projections are only available for the period 2018-2028. For the purposes of the present analysis, for the years 2029-2032, it is assumed that no change (0%) will occur.

The annual changes are shown in the following table.

Table 3-17: Projected year-on-year change on the number of wash solution units sold – Market segments for wash solutions linked to Use #3 by Siemens Marburg				
Year	#D, Table [redacted]		[redacted]	
2018	[redacted]	[redacted]	[redacted]	[redacted]
2019	[redacted]	[redacted]	[redacted]	[redacted]
2020	[redacted]	[redacted]	[redacted]	[redacted]
2021	[redacted]	[redacted]	[redacted]	[redacted]
2022	[redacted]	[redacted]	[redacted]	[redacted]
2023	[redacted]	[redacted]	[redacted]	[redacted]
2024	[redacted]	[redacted]	[redacted]	[redacted]
2025	[redacted]	[redacted]	[redacted]	[redacted]
2026	[redacted]	[redacted]	[redacted]	[redacted]
2027	[redacted]	[redacted]	[redacted]	[redacted]
2028	[redacted]	[redacted]	[redacted]	[redacted]
2029	[redacted]	[redacted]	[redacted]	[redacted]
2030	[redacted]	[redacted]	[redacted]	[redacted]
2031	[redacted]	[redacted]	[redacted]	[redacted]
2032	[redacted]	[redacted]	[redacted]	[redacted]

Using these percentages and a discount rate of 4%, it can be estimated that the Present Value of gross profits that Siemens Marburg anticipates making over the requested review period is in the range of €10-100 million #D .

Table 3-18: Net present value of profits from sales of wash solutions relevant to Use #3, 2021-2032, 4% discount			
Customer group	**NPV, 4% discount All wash solutions**	**NPV, 4% discount #D, Table**	**NPV, 4% discount**
EEA customers			
Non-EEA customers			
All customers			

Importantly, if wash solutions were not available, kits that depend on the concomitant use of the wash solution would also not be possible to use. The following table summarises data on the sales (and profits) of the combined wash solutions and kits.

Table 3-19: Sales volumes and value of wash solutions plus dependent IVD kits linked to Use #3 by Siemens Marburg						
IVD products	**Sales by volume (No. kits/year)**		**Sales by value (€/year)**		**Profit after standard cost by value (€/year)**	
	EEA	**Non-EEA**	**EEA**	**Non-EEA**	**EEA**	**Non-EEA**
#D, Table						

Using the percentages shown in **Table 3-17** and a discount rate of 4%, it can be estimated that the Present Value of gross profits that Siemens Marburg, Siemens Llanberis and Siemens Healthineers USA anticipate making over the requested review period from selling the combined sets of wash solutions and IVD kits is in the range of €1-10 billion #D .

Table 3-20: Net present value of profits from sales of wash solutions and dependent kits relevant to Use #3, 2021-2032, 4% discount			
Customer group	**NPV, 4% discount All wash solutions & dependent kits**	**NPV, 4% discount, #D, Table wash solutions & dependent kits**	**NPV, 4% discount wash solution & dependent kits**
EEA			
Non-EEA			
All customers			

3.2.4 Markets for relevant Siemens Healthineers analysers

Analysers relevant to the use of OPE at the Marburg site

Appendix 2 (Section 10) presents some basic background information on the different analysers that use the OPE-dependent IVD kits that are made in Marburg. The analysers are shown in **Table 3-21**.

Table 3-21: Analysers relevant to Uses #1, # 2 and #3 – Number of analysers in 2017						
Analysers			Customer location			
Platform	Analyser	Relevant website link (where available)	*	EEA	Non-EEA	All
[redacted]						
		#C, D				
[redacted]						

Further detail on the number of analysers currently in the EEA, their average age, typical lifetime and projected sales plan is given in **Table 3-22** overleaf.

Table 3-22: Number of analysers currently operated in the EEA – Use #1,# 2, #3 (2017) (NB. brown cell colour indicates analysers off sale in 2021)						
Analyser	**Number of analysers in the EEA in 2017**	**Average age of analysers in the EEA**	**Typical lifetime of analysers**	**Currently in use**	**Currently on sale**	**On sale in Jan 2021**
#C, D (table)						

Numbers of analysers per Use

Current (2017) stock of relevant analysers

In terms of which analysers are relevant to each of the three Applied for Uses, **Table 3-23** provides a summary. IVD kits that rely on Use #1 (protein isolation) are used in the largest group of analyser models, including third-party analysers which are generally excluded from the analysis in this AoA-SEA document. For each one of the Applied for Uses, 1,000-10,000 analysers are currently (2017 stock) active in the EEA, with the higher number belonging to the Use #1 group.

Table 3-23: Relevant analyser models per Applied for Use

Applied for Use	Requested review period (years)	Relevant analyser models	Number of existing (2017 stock) analysers in use by customers	
			EEA	Non-EEA
Use #1	9	#D, Column	#C, Column	#C, Column
Use #2	12			
Use #3	12			

Projected future sales of relevant analysers

It can be calculated that #D (range: 100-1,000) #D and #D (range: 10,000-100,000) #D analysers are expected to be sold over the requested review periods in the EEA and non-EEA markets. The following table presents the projected sales of analysers that are relevant to each of the Applied for Uses. It should be noted that there are overlaps between uses so the numbers presented below cannot simply be aggregated.

Table 3-24: Number of affected analysers envisaged to be sold in the future per Applied for Use

EEA-sales for the year…	Use #1	Use #2	Use #3
2018	#D, Table		
2019			
2020			
2021			
2022			
Post-2022			
EEA total over the review period	**(2021-2029)**	**(2021-2032)**	**(2021-2032)**

Table 3-24: Number of affected analysers envisaged to be sold in the future per Applied for Use			
Non-EEA sales for the year…	**Use #1**	**Use #2**	**Use #3**
2018	[redacted]	[redacted]	[redacted]
2019	[redacted]	[redacted]	[redacted]
2020	[redacted]	[redacted]	[redacted]
2021	[redacted]	[redacted]	[redacted]
2022	[redacted]	[redacted]	[redacted]
Post-2022	[redacted]	[redacted]	[redacted]
Non-EEA total over the review period	[redacted] **(2021-2029)**	[redacted] **(2021-2032)**	[redacted] **(2021-2032)**
Grand total over the review period	[redacted] **(2021-2029)**	[redacted] **(2021-2032)**	[redacted] **(2021-2032)**

The two figures that follow present the changes in the number of relevant analysers sold from 2018 onwards in the EEA and non-EEA markets.

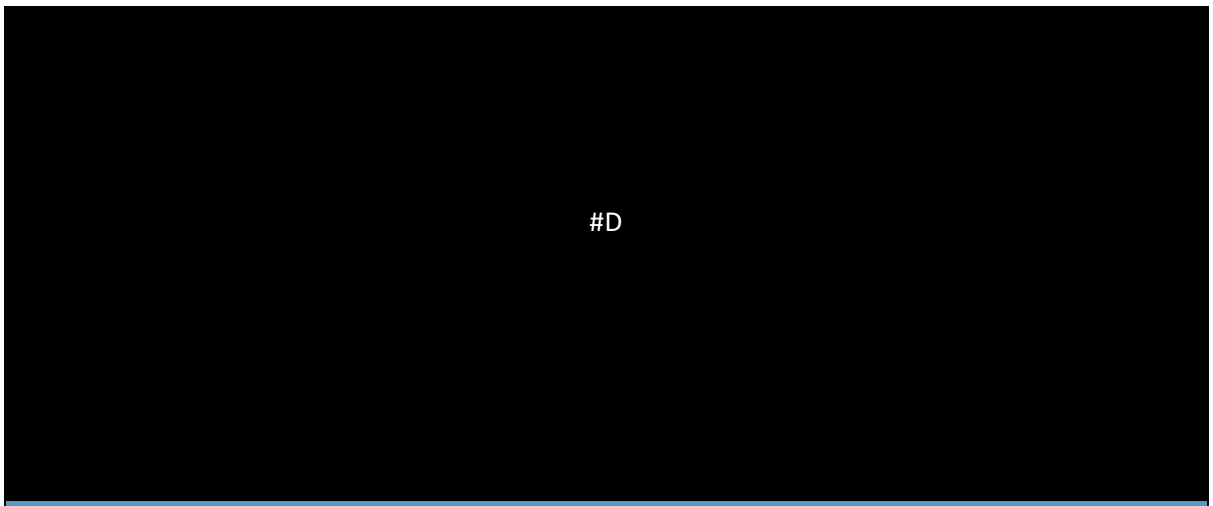


Figure 3–13: Projected annual shipments of analysers that employ OPE-dependent IVD products made by Siemens Marburg – EEA sales

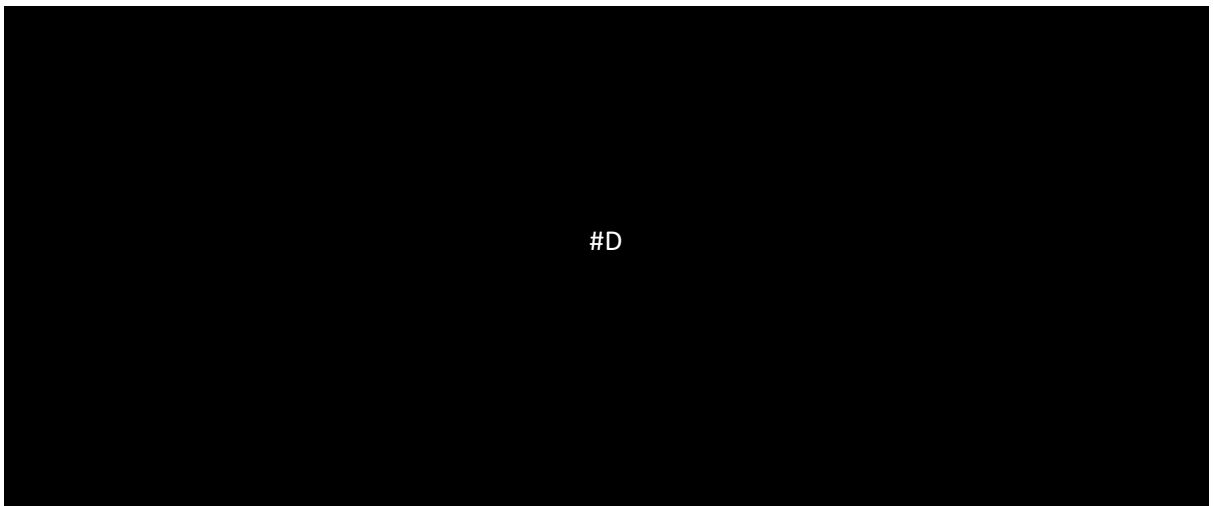


Figure 3–14: Projected annual shipments of analysers that employ OPE-dependent IVD products made by Siemens Marburg – Non-EEA sales

In terms of profit made from the sales of analysers, it should be noted that Siemens Healthineers analysers are provided as platforms to run the diagnostic tests and are often financed by the sales of the test components (IVD kits and wash solutions). In other words, the profit from the sales of the analysers themselves is not considered to be a large component of Siemens Healthineers overall profit in the "Applied for Use" scenario. The stock of analysers and its development over time will, on the other hand, be a determinant for the future sales of IVD kits. The pre-tax profits from the sales of analysers over the requested review period are presented in **Table 3-25** below.

Table 3-25: Number of affected analysers envisaged to be sold in the future and associated pre-tax profit – Analysers relevant to Uses #1, #2 and #3				
EEA-sales shipments for the year…	**Pre-tax profit made/projected (€million) for the [redacted] #D, Table analysers only**	**Pre-tax profit made/projected (€million) for the remaining Marburg-related analysers only**	**Discount factor (4%)**	**NPV, 4% discount profits from sales of analysers to EEA customers**
2018	[redacted]	[redacted]	[redacted]	[redacted]
2019	[redacted]	[redacted]	[redacted]	[redacted]
2020	[redacted]	[redacted]	[redacted]	[redacted]
2021	[redacted]	[redacted]	[redacted]	[redacted]
2022	[redacted]	[redacted]	[redacted]	[redacted]
2023	[redacted]	[redacted]	[redacted]	[redacted]
2024	[redacted]	[redacted]	[redacted]	[redacted]
2025	[redacted]	[redacted]	[redacted]	[redacted]
2026	[redacted]	[redacted]	[redacted]	[redacted]
2027	[redacted]	[redacted]	[redacted]	[redacted]
2028	[redacted]	[redacted]	[redacted]	[redacted]
2029	[redacted]	[redacted]	[redacted]	[redacted]
2030	[redacted]	[redacted]	[redacted]	[redacted]
2031	[redacted]	[redacted]	[redacted]	[redacted]
2032	[redacted]	[redacted]	[redacted]	[redacted]
Non-EEA sales shipments for the year…	**Pre-tax profit made/projected (€million) for the [redacted] analysers only**	**Pre-tax profit made/projected (€million) for the Marburg analysers only**	**Discount factor (4%)**	**NPV, 4% discount profits from sales of analysers to non-EEA customers**
2018	[redacted]	[redacted]	[redacted]	[redacted]
2019	[redacted]	[redacted]	[redacted]	[redacted]
2020	[redacted]	[redacted]	[redacted]	[redacted]
2021	[redacted]	[redacted]	[redacted]	[redacted]
2022	[redacted]	[redacted]	[redacted]	[redacted]
2023	[redacted]	[redacted]	[redacted]	[redacted]
2024	[redacted]	[redacted]	[redacted]	[redacted]
2025	[redacted]	[redacted]	[redacted]	[redacted]
2026	[redacted]	[redacted]	[redacted]	[redacted]
2027	[redacted]	[redacted]	[redacted]	[redacted]
2028	[redacted]	[redacted]	[redacted]	[redacted]
2029	[redacted]	[redacted]	[redacted]	[redacted]
2030	[redacted]	[redacted]	[redacted]	[redacted]
2031	[redacted]	[redacted]	[redacted]	[redacted]
2032	[redacted]	[redacted]	[redacted]	[redacted]

The above table shows that the overall profit to be made under the "Applied for Use" Scenario from sales of the relevant analyser models has a present value of ca. #D (Range: €0.1-1 billion) of which ca. #D will arise from sales to EEA-based customers and #D would arise from sales to non-EEA customers.

As shown in **Table 3-22**, there is significant overlap between the three Applied for Uses as regards the types of analysers that are relevant to each one of them (and thus the associated numbers of analysers expected to be sold and profits to be made). Using the projected numbers of analysers sold per Applied for Use as shown in **Table 3-24** and with a focus on the EEA market, this AoA-SEA makes the following rough assumptions:

- Use #1 accounts for #D % of the EEA-derived profit, or ca. € #D (range: €10-100 million);
- Use #2 accounts for #D % of the EEA-derived profit, or ca. € #D (range: €10-100 million); and
- Use #3 accounts for #D % of the EEA-derived profit, or ca. € #D (range: €10-100 million).

Again, these are rough estimates which take into account of the overlaps and cannot be aggregated. The correct overall profit figure is € #D, as shown above.

Sales of EEA-made analysers

Notably, the models that are manufactured #D in the EEA include:

- ;
- ;
- #D ;
- ; and
- .

The numbers of these analyser models envisaged to be sold in the future within and outside the EEA is shown in **Table 3-26**. The information in **Table 3-22** is used to identify which analysers are relevant to which use. These are:

- Use #1: ;
- Use #2: #D ; and
- Use #3: .

It can thus be calculated that over the requested review periods, the following numbers of EEA-made analysers will be sold globally:

- Use #1: #D (range: 1,000-10,000) analysers;
- Use #2: #D (range: 1,000-10,000) analysers; and
- Use #3: #D (range: 1,000-10,000) analysers.

Table 3-26: Number of affected EEA-made analysers envisaged to be sold in the future– Analysers relevant to Uses #1, #2 and #3									
Year	Total EEA-made analysers sold to EEA customers	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Use #1	Use #2	Use #3
2018	#D, Table								
2019									
2020									
2021									
2022									
Post-2022									
Year	Total EEA-made analysers sold to non-EEA customers	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Use #1	Use #2	Use #3
2018									
2019									
2020									
2021									
2022									
Post-2022									

3.2.5 OPE-independent activities at Marburg

Siemens Marburg activities other than those that involve OPEs include the manufacture of all other IVD kits in the #D portfolio, as well as all the peripheral support services at a manufacturing site, e.g. warehousing, maintenance, waste management, cleaning etc. In terms of profit, OPE-dependent kits reflect ca. #D % (range: <20%) of the profit made by Siemens Marburg through sales of IVD kits.

These products are sold as a kit (in one box) or virtual kit (ordered separately). Each kit includes multiple components, calibrators, controls and auxiliary products like buffers and washing solutions. OPE's are used for some products but not all. However, the products which use OPE cannot be used without the corresponding non-OPE using products like calibrator, control or auxiliary products (buffers, wash solutions, etc.).

In all likelihood, these operations would be impacted as a reduction in the overall #D portfolio could make the entire portfolio less attractive to customers. It can be estimated that in 2017 the profit made by Siemens Marburg from global sales of OPE-independent IVD products was ca. #D (range: €0.1-1 billion). Assuming that the volume of sales of these kits does not change in the period 2021-2032, a Present Value profit of #D (range: €1-10 billion) can be estimated (4% discount rate).

3.2.6 Other Siemens Healthineers operations in the EEA

Siemens Healthineers manufacturing and sales from the site in Llanberis in the UK is completely reliant on the continued use of OPEs at the Siemens Marburg site in Germany. As described above, the main component of the #D kit, the protein, is produced by Siemens Marburg, and is in the

scope of Use #1. Furthermore, the wash solution covered by Use #3 is used with all of the #D IVD kits, and is therefore integral to the continued operations at Siemens Llanberis. Sales of the #D IVD kit , the #D #D solution and of #D analysers have been presented in **Table 3-9**, **Table 3-11**, **Table 3-16** and **Table 3-18**.

By way of reminder, the #D kit is exclusively used with the #D analysers. Siemens Healthineers do not plan to reformulate the #D kit as the #D . Similarly, the manufacture and sales of the #D #D module needs to continue #D ; without the #D , the #D analysers cannot be operated. It can be estimated that the total Present Value profit for Siemens Llanberis over the period 2021-2029 is € #D (range: €0.1-1 billion).

3.2.7 Suppliers

For majority of consumables Siemens would be able to use several suppliers. There is no supplier who is dependent only on sales to Siemens Marburg.

Table 3-27: Suppliers related to the manufacture of OPE-containing kits in Marburg

Materials sourced upstream for the manufacture of OPE-containing kits in Marburg	EEA		Non-EEA	
	Number of suppliers	Location (country)	Number of suppliers	Location (country)
#D, Table				

Table 3-27: Suppliers related to the manufacture of OPE-containing kits in Marburg				
Materials sourced upstream for the manufacture of OPE-containing kits in Marburg	EEA		Non-EEA	
	Number of suppliers	Location (country)	Number of suppliers	Location (country)
[redacted]				

For completeness, the consumables that are relevant to the manufacture of IVD products (kits and wash solution) for the #D analysers are presented below.

Table 3-28: Suppliers related to the manufacture of OPE-containing products for #D, Table				
Chemical components sourced upstream for the manufacture of OPE-containing [redacted] in Marburg	EEA		Non-EEA	
	Number of suppliers	Location (country)	Number of suppliers	Location (country)
[redacted]				
Chemical components sourced upstream for the manufacture of OPE-containing [redacted] in Marburg	EEA		Non-EEA	
	Number of suppliers	Location (country)	Number of suppliers	Location (country)
[redacted]				

Finally, the respective table of suppliers relevant to the manufacture of OPE-free kits by Siemens Marburg is provided below.

Table 3-29: Suppliers related to the manufacture of OPE-free kits in Marburg				
Materials sourced upstream for the manufacture of OPE-free kits in Marburg	EEA		Non-EEA	
	Number of suppliers	Location (country)	Number of suppliers	Location (country)
#D, Table				

It can be seen that tens of different suppliers are involved, the vast majority of which is located within the EEA.

3.2.8 Customers

Siemens Marburg's customers are the operators of the analysers presented above. Over the last three years (2016-2018), Siemens Healthineers Diagnostics has shipped reagents to over #C, D (range: 10,000-100,000) locations in EEA countries (as distinct from customers, e.g. some locations may be distributors supporting multiple end-users).

These DUs will have to be granted an Authorisation for their own uses of OPEs within the EEA, which is covered under the Use #4 and Use #5 in Siemens Marburg's AfA. Additionally, they are relying on the supply of IVD kits and wash solutions from Siemens Healthineers in the USA and Siemens Llanberis. Under the "Applied for Use" scenario, Siemens Marburg customers would not experience any disruptions in the supply of OPE-dependent products, and their operation can continue as usual.

The avoided impacts for Siemens' customers and the corresponding impacts for society if an Authorisation is granted, is further described in Section 5.1.

3.2.9 Employment in the "Applied for Use" scenario

There are currently #D (range: 1,000-10,000) directly employed at Siemens Marburg. Additionally, there are #D (range: 10-100) third-party contractors associated with the operations at Marburg. #D/#G

There are also #D (range: 100-1,000) employees and #D (range: 10-100) contractors at the Siemens Llanberis, which are indirectly linked to the continued use of OPEs at Marburg. As described in the separate AfA submitted by Siemens Llanberis, #D .

The number of people directly or indirectly employed throughout Siemens Marburg's supply chain has not been possible to ascertain. Neither is it possible for Siemens Marburg to know the number of relevant number of jobs at OEMs who may have business links to the Marburg operations.

The number of avoided job losses and the corresponding impacts to society over the review period is further described in Section 5.3.

3.2.10 The wider IVD market and business trends

Information below is obtained from a Kalorama Information market review report.

Clinical lab medicine plays an integral role in healthcare and disease management. Lab-quality molecular tests and immunoassays at the point-of-care require some interpretation and consultation for appropriate disease management. On the supply side, labs are challenged to add new tests with little increase in financial and human resources. For most labs it may even mean doing more with less. There is also a lack of trained lab technologists, so there is a decreasing availability of human resources needed to run the more complex new set of molecular and histological tests and immunoassays. Therefore, there has been a proliferation of test and lab automation tools launched that remove precious human resources from mundane pre-analytical and sample-tracking tasks to make time for more sophisticated ones. This phenomenon was once thought to be the purview of core lab biochemistry and immunoassays but automation is becoming a common feature in the areas of haematology, blood banking, microbiology, and histology (Kalorama Information, 2016).

This emphasis on automation has created further consolidation of laboratory testing to large core labs. More and more assays in coagulation, infectious diseases, proteins, diabetes and even HPV are developed for automated clinical analysers used in the core lab. Systems for urinalysis, coagulation and microbiology are ready to take their place alongside the haematology, chemistry and immunoassay instruments – all located in a single core lab. In larger labs they may be linked to a common track line.

Getting information to care givers and patients is now not an added plus, it is a prerequisite of all lab operations. Thus, over the coming year we will see an intensification of the healthcare industry's emphasis on informatics, wireless communications, data networking and cost/effective healthcare delivery. The reorganisation of decentralised healthcare delivery worldwide and patient-focused medicine are having an enormous impact on the role of medical devices and diagnostic services in healthcare. Technological advancements, specifically those in device miniaturization, data digitisation, wireless communications and the Internet, form a technical synergy that will permit IVD tests and devices to maintain a central role in disease management.

In the area of test economics, outcomes-based disease management establishes guidelines and directives for patient care. This is having a significant effect on the use of new tests, which have to prove their added value to patient care. It also affects how many and which tests are recommended and thus reimbursed for a specific disease group. Health insurance companies such as Kaiser Permanente, Aetna and UnitedHealth along with pharmacy benefit organizations such as Medco are mining their extensive databases to look for correlations between testing patterns and patient outcome. It is expected that these would then be translated into test usage guideline.

None of the above would be happening without significant forces in the market driving them.

The global IVD market was estimated at €53 billion in 2016 and is expected to reach €55 billion by 2021. This is a slow-down of growth as compared to previous year, due to economic pressures in Europe, USA and Japan. As continued healthcare reforms in Europe, USA and Japan result in further

rationing of diagnostics, emerging markets will continue to drive growth due to increased government and private sector investment as well as an increased presence of top vendors.

Headwinds are economic conditions and testing decrease in developed markets as well as price erosion due to lab consolidation and test migration onto integrated analysers. Growth segments include molecular, microbiology, histology/cytology and Point-of-Care (POC).

Siemens Healthineers commands a leading position in the global laboratory diagnostics market, as shown in the data summarised in the table below. It is known that at least some of Siemens Healthineers' competitors will be submitting AfAs for their use of alkylphenol ethoxylates; however, Siemens Marburg has no specific information on the range of products that will be covered by those competitors' AfA submissions.

Table 3-30: Overview of the competitive position of Siemens Healthineers in the global Laboratory Diagnostics (LD) market - 2016

#C/#D, Table	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]				

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, is given in the following table.

Table 3-31: 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 and Triton™ X-405 are used at the site in Marburg as part of three separate processes (Uses #1, #2 and #3). Solid waste from the site (potentially including gloves, pipettes, etc.) is incinerated.

All OPE-containing wastewaters flow to the drain and further to the municipal sewage treatment plant in Marburg/Biedenkopf. This way uncontrolled releases to the local environment at Marburg site can be excluded. The installation and procedures for formulation of OPE-containing solutions aim at minimisation of losses to waste water. This includes low dead volumes of the installation in order to achieve high a high yield and the use of disposable connection tubes in order to avoid cross contamination of buffers.

In addition, as explained in Appendix 3 (Section 11), Siemens Marburg has investigated the feasibility and proportionality of additional Risk Management Measures (RMMs) and has reached the conclusion that for both Use #1 and Use #2 is feasible and desirable to implement additional actions to further reduce the releases of Triton™ X-100/Triton™ X-405 before the Sunset Date (although for Use #2 the associated costs could be substantial, Siemens Marburg is prepared to cover those to achieve further reduction in its releases of OPE/4-tert-OP).

The following measures are planned to be implemented before the Sunset Date:

- Use #1: implementation of a system to collect fraction of OPE-containing buffer, classify as hazardous waste and send for incineration; and
- Use #2: implementation of disposable bulk containers, classification of empty containers as hazardous waste and disposal by incineration.

Following the implementation of these measures, for Use #1 it is assumed that only 5% losses of the amount of Triton™ X-100 consumed in the manufacture of #D products will be occurring after the Sunset Date (in reality, the percentage is likely to be much lower); no Triton™ X-100 losses to the environment occur in the formulation of the #D. Before the implementation of this additional RMM, the entire 100% amount of Triton™ X-100 used was assumed to be released to the municipal STP, so the reduction achieved is very substantial.

On the other hand, for Use #2 the generation of only modest volumes of wastewater which can be handled separately allows the implementation of disposable bulk containers which will further reduce releases of OPEs. At present, an emission factor of 0.5% is assumed. Following the implementation of the additional RMM, this emission factor is expected to decrease by an additional factor of 95%.

Finally, about 0.5% of the Triton™ X-100 used in Use #3 currently ends up in the wastewater and the STP, where it is degraded to 4-tert-OP, which is partly released to the environment. The cost of implementing additional RMMs for this use is disproportionate (see analysis in Appendix 3 (Section 11)) and implementation could not be achieved before the Sunset Date. Therefore, no further improvement on the early low emission factor shown above will be possible.

The following table summarises the emissions to the environment.

Table 3-32: Summary of emission sources associated with the use of Triton™ X-100/Triton™ X-405 in Marburg	
Environmental compartment	**Release method**
Water	Via municipal STP discharge into the River Lahn, which flows further to the River Rhein
Soil	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 OPEs to the environment include environmental permitting for waste. 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 River Lahn (waterbody id number 258) (WRRL, 2017). According to the 2015 management plan, the overall waterbody status is unsatisfactory, with good chemical status but unsatisfactory status for fish and diatoms, and moderate status for invertebrates. Classification data have not been identified for the individual components that make up the chemical status.

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 following table summarises emission factors that have been used in the CSR for the estimation of releases of OPE/OP to the environment that are associated with the use of OPEs in the three Applied for Uses.

Table 3-33: Key emission parameters for the estimation of environmental impacts under the "Applied for Use" Scenarios				
Emission parameter		**Use #1**	**Use #2**	**Use #3**
Number of release days per year (2021) – decreasing thereafter		#H	#H	#H
% of consumed Triton™ X-100 released to water (as 4-tert-OP)	Current (Q1 2019)	**26.5%** #D	0.5% x 26.5% = **0.1325%**	0.5% x 26.5% = **0.1325%**
	Sunset Date and later	5% x 26.5% = **1.325%** #D	5% x 0.5% x 26.5% = **0.0066%**	
% of consumed Triton™ X-100	Current (Q1 2019)	**6.5%** #D	0.5% x 33% x 19.5% = **0.0322%**	0.5% x 33% x 19.5% = **0.0322%**

Table 3-33: Key emission parameters for the estimation of environmental impacts under the "Applied for Use" Scenarios				
Emission parameter		**Use #1**	**Use #2**	**Use #3**
released to sludge (as 4-tert-OP)	Sunset Date and later	5% × 6.5% = **0.325%** #D	5% x 0.5% x 33% x 19.5% = **0.016%**	
% of consumed Triton™ X-405 released to water (as 4-tert-OP)	Current (Q1 2019)	N/A	0.5% x 9.5% = **0.0475%**	N/A
	Sunset Date and later		5% x 0.5% x 9.5% = **0.0024%**	
% of consumed Triton™ X-405 released to sludge (as 4-tert-OP)	Current (Q1 2019)	N/A	0.5% x 11.8% x 19.5% = **0.0115%**	N/A
	Sunset Date and later		5% × 0.5% x 11.8% x 19.5% = **0.00058%**	
Is sludge applied to agricultural soil?		No	No	No

Estimated releases of 4-tert-OP under the Applied for Use" Scenarios

Use #1

The total emissions of 4-tert-OP to the environment under the "Applied for Use" 1 Scenario are shown in **Table 3–34**. No releases of Triton™ X-100 occur during the formulation of the #D (which is sent to Siemens Llanberis), so only the volumes of Triton™ X-100 used in the preparation of the #D is relevant to release estimation. 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. #H (range: 0.1-1) kg over 9 years. The table below does take into account the additional RMM that Siemens Marburg will be implementing before the Sunset Date.

Table 3–34: Projections of environmental releases of 4-tert-OP as a result of the continued use of Triton™ X-100 in Marburg – Use #1			
Year	**OPE amount used (kg) Triton™ X-100** #D #D	**4-tert-OP releases to aquatic environment (kg/y)**	**4-tert-OP releases to sludge (kg/y)**
2018	#A, Column		
2019			
2020			
2021		**#H, Column**	**#H, Column**
2022			
2023			
2024			
2025			
2026			
2027			
2028			
2029			
Total, 2021-2029			

Use #2

The total emissions of 4-tert-OP to the environment under the "Applied for Use" 2 Scenario are shown in **Table 3–35**. 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. #H (range: 1-10) g over 12 years. The table below does take into account the additional RMM that Siemens Marburg will be implementing before the Sunset Date.

Table 3–35: Projections of environmental releases of 4-tert-OP as a result of the continued use of Triton™ X-100/Triton™ X-405 in Marburg – Use #2				
Year	OPE amount used (kg)		4-tert-OP releases to aquatic environment (kg/y)	4-tert-OP releases to sludge (kg/y)
	Triton™ X-100	Triton™ X-405		
2018	#A, Column	#A, Column		
2019				
2020				
2021			#H, Column	#H, Column
2022				
2023				
2024				
2025				
2026				
2027				
2028				
2029				
2030				
2031				
2032				
Total, 2021-2032				

Use #3

The total emissions of 4-tert-OP to the environment under the "Applied for Use" 3 Scenario are shown in **Table 3–36**. 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. #H (range: 1-10) kg over 12 years.

Table 3–36: Projections of environmental releases of 4-tert-OP as a result of the continued use of Triton™ X-100 in Marburg – Use #3			
Year	OPE amount used (kg) Triton™ X-100	4-tert-OP releases to aquatic environment (kg/y)	4-tert-OP releases to sludge (kg/y)
2018	#A, Column		
2019			
2020			
2021		#H, Column	#H, Column
2022			
2023			
2024			
2025			
2026			
2027			
2028			
2029			
2030			
2031			
2032			
Total, 2021-2032			

Latest research values for ecotoxicity

Table 3-37 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 3-37: Latest research values (as presented in the CSR)	
Environmental domain	**Latest research values**
Freshwater sediment	28 µg/kg dry weight
Freshwater	0.034 µg/litre
Marine water	0.0034µg/litre
Marine sediment	0.28 µg/kg dry weight
Soil	5.6 µg/kg dry weight

Predicted environmental concentrations

Table 3-38 provides the predicted local concentrations of 4-tert-OP in the **local and regional environment** over the requested review periods 2021-2032, as presented in the CSR. All values provided (for the year 2021) are below the respective latest research values shown in **Table 3-37**.

Table 3-38: Predicted environmental concentrations, local and regional, Uses #1-3 (2021)						
Compartment	**Latest research value**	**Local PECs**				**Regional PECs Uses #1-3**
		Use #1	**Use #2**	**Use #3**	**Worst-case daily release, Uses #1-3**	
Fresh water	0.034 µg/L	0.000#H, Table µg/L	E-5 µg/L	0.00 µg/L	0.00 µg/L	0.000 µg/L
Sediment (freshwater)	0.028 mg/kg dw	0.000 mg/kg dw	E-6 mg/kg dw	0.00 mg/kg dw	0.00 mg/kg dw	0.000 mg/kg dw
Marine water	0.0034 µg/L	0.0000 µg/L	E-6 µ/L	0.000 µg/L	0.000 µg/L	0.0000 µg/L
Sediment (marine water)	0.0028 mg/kg dw	0.0000 mg/kg dw	E-7 mg/kg dw	0.000 mg/kg dw	0.000 mg/kg dw	0.0000 mg/kg dw
Agricultural soil	0.0073 mg/kg dw	E-10 mg/kg dw	E-10 mg/kg dw	E-10 mg/kg dw	E-10 mg/kg dw	0.000000 mg/kg dw
Post-2021 trends		Modest decline until end , dramatic decline thereafter	Modest increase until end , dramatic fall and stable thereafter	Significant decline throughout review period	Significant decline throughout review period (dominated by large relative consumption of OPEs under Use #3)	

The 4-tert-OP concentrations calculated for the local aquatic compartment and sediment are slightly or even significantly below the latest research values for risk characterisation. Yet, risks for aquatic and sediment organisms cannot be excluded. Overall the calculated PECs are considered reasonable worst-case, since, based on the following considerations, the real 4-tert-OP emissions resulting from the use of OPEs in the production of IVD kit reagents and wash solutions are expected to be lower:

- The effectiveness of the planned segregation of OPE-containing solutions after protein extraction (Use #1) and formulation of IVD kit reagents (Use #2) is expected to be higher than 95%. However, since the additional RMMs have not yet been implemented, the actual effectiveness cannot be determined;

- The Marburg STP is a very large and modern STP with high standards. Longer retention times than considered in the calculation can be assumed and these would reduce the 4-tert-OP released from the STP, while the retention of 4-tert-OP in the sludge will increase;

- 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 calculations shown in the CSR; and

- Siemens Marburg is in the process of phasing out the use of OPEs in the manufacture of IVD kit reagents and wash solutions. This will not necessarily reduce the maximum daily use volume, but the number of lots and release events and thus the environmental burden will be reduced year on year. This progressive reduction has been taken into account in the estimates of releases but also in calculating the environmental stock of 4-tert-OP, as shown below.

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

Introduction

The information in the following table, taken from the CSR, has been used as the basis for developing a decay curve for 4-tert-OP in the aquatic compartment.

Table 3-39: Daily maximum consumption and release amounts for 4-tert-OP (in grams)			
Use	**OPE consumed**	**OPE released**	**4-tert-OP released**
Use #1	#H, Table		
Use #2			
Use #3			
Total			

Half-lives of 8 to 54 days have been determined for 4-tert-OP in water samples within laboratory microcosms (BAuA, 2011). By way of example, the following figure indicates the decay of the #H kg of 4-tert-OP released in 2021 under Applied for Use #1, assuming a half-life of 8 days (NB. This amount is 26.5% of the maximum daily usage for Use #1, as shown in **Table 3-33**). It shows the amount left is approaching zero within eight weeks.

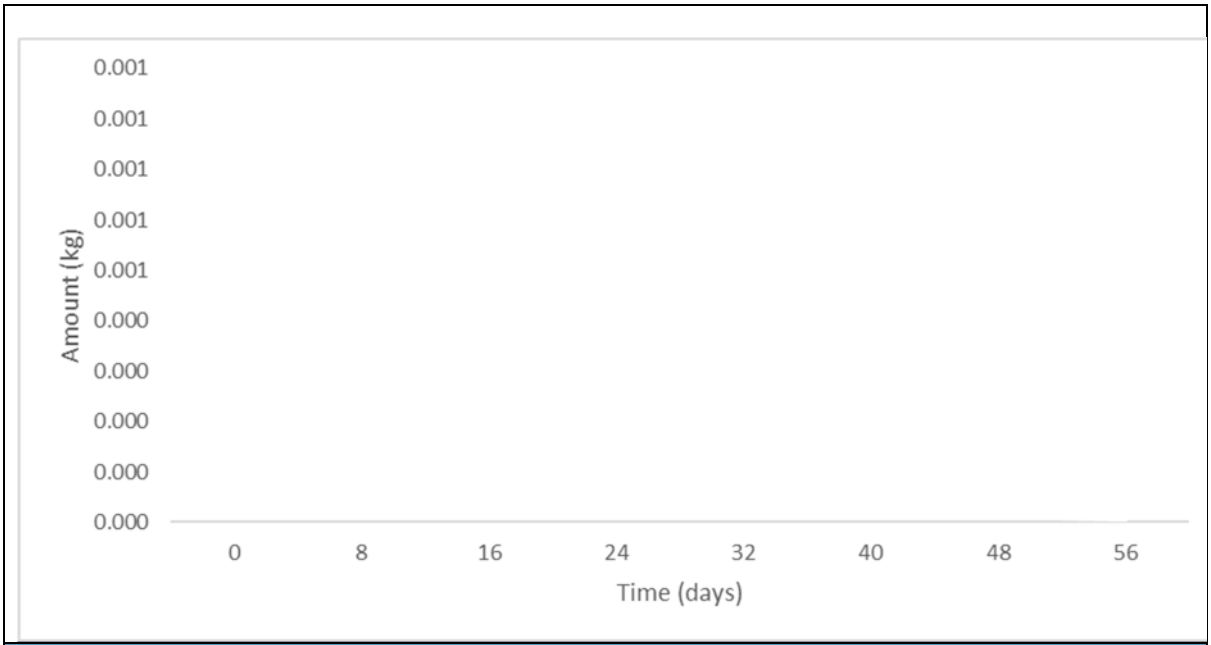


Figure 3-15: Degradation of [redacted] kg of 4-tert-OP assuming a half-life of eight days

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 only on a limited number of years due to the batch-wise manufacturing processes in Marburg. The number of release days assumed for the year 2021 were shown in **Table 3-33**.

Given that usage is anticipated to decline each year, the number of days over which batches will be processed will decline too. The approximate year-on-year decreases in the level of Triton™ X-100/Triton™ X-405 used at the Marburg plant for the coming years and the associated number of active days (i.e. days when releases of OPE/OP occur) are given in **Table 3-40**. This table assumes that the percentage reduction in Triton™ X-100/Triton™ X-405 consumption is the same as the percentage reduction in the number of batches of products and the amount of 4-tert-OP discharged.

Table 3-40: Anticipated decrease in usage of Triton™ X-100/Triton™ X-405 and release of 4-tert-OP

Use #1				
Year	**Amount used (kg) Triton™ X-100** [redacted] **#H**	**Amount of 4-tert-OP discharged per release (kg)**	**Number of release days assumed**	**Amount of 4-tert-OP released per 'active' day**
2021	#A, Column	#H, Column	#J, Column	#J, Column
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]

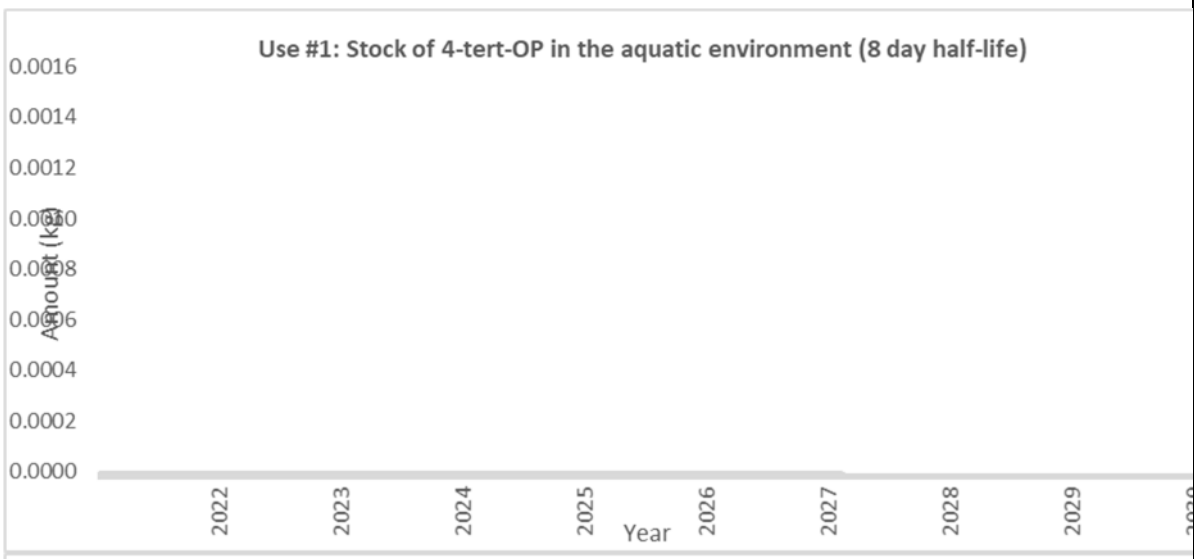
Table 3-40: Anticipated decrease in usage of Triton™ X-100/Triton™ X-405 and release of 4-tert-OP				
Use #2				
Year	**Amount used (kg) Triton™ X-100 Triton™ X-405**	**Amount of 4-tert-OP discharged per release (kg/y)**	**Number of release days assumed**	**Amount of 4-tert-OP released per 'active' day**
2021	[redacted]	[redacted]	[redacted]	[redacted]
2022	[redacted]	[redacted]	[redacted]	[redacted]
2023	[redacted]	[redacted]	[redacted]	[redacted]
2024	[redacted]	[redacted]	[redacted]	[redacted]
2025	[redacted]	[redacted]	[redacted]	[redacted]
2026	[redacted]	[redacted]	[redacted]	[redacted]
2027	[redacted]	[redacted]	[redacted]	[redacted]
2028	[redacted]	[redacted]	[redacted]	[redacted]
2029	[redacted]	[redacted]	[redacted]	[redacted]
2030	[redacted]	[redacted]	[redacted]	[redacted]
2031	[redacted]	[redacted]	[redacted]	[redacted]
2032	[redacted]	[redacted]	[redacted]	[redacted]
Use #3				
Year	**Amount used (kg) Triton™ X-100**	**Amount of 4-tert-OP discharged per release (kg)**	**Number of release days assumed**	**Amount of 4-tert-OP released per 'active' day**
2021	[redacted]	[redacted]	[redacted]	[redacted]
2022	[redacted]	[redacted]	[redacted]	[redacted]
2023	[redacted]	[redacted]	[redacted]	[redacted]
2024	[redacted]	[redacted]	[redacted]	[redacted]
2025	[redacted]	[redacted]	[redacted]	[redacted]
2026	[redacted]	[redacted]	[redacted]	[redacted]
2027	[redacted]	[redacted]	[redacted]	[redacted]
2028	[redacted]	[redacted]	[redacted]	[redacted]
2029	[redacted]	[redacted]	[redacted]	[redacted]
2030	[redacted]	[redacted]	[redacted]	[redacted]
2031	[redacted]	[redacted]	[redacted]	[redacted]
2032	[redacted]	[redacted]	[redacted]	[redacted]

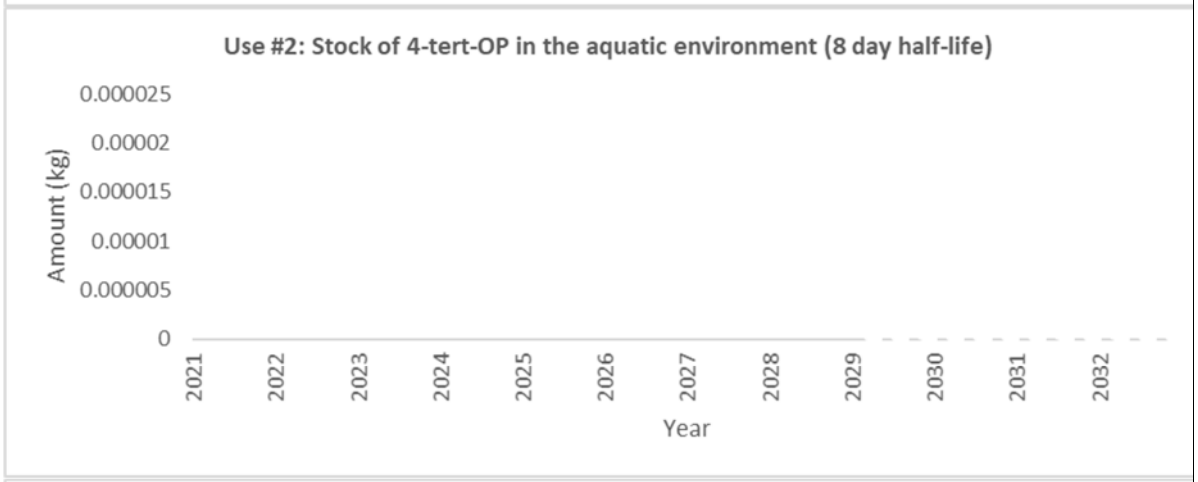
The following two figures indicate the 4-tert-OP stock in the freshwater environment assuming a release occurs for each of the three Applied for Uses from the municipal STP. **Figure 3-16** indicates the stock level assuming a half-life of eight days, whilst **Figure 3-17** shows the situation for a 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. #H kg for each of the Applied for Uses. For Use #1, stock levels are very low and only marginally increase in the period 2021-#H before they become practically zero before the end of the review period. For Use #2, releases are even lower; stock levels are extremely low but generally remain stable until the cessation of the use of Triton™ X-100/Triton™ X-405. For Use #3, due to degradation and reducing frequency of input over the period 2021-2032, stock levels decrease over time and become very low very soon after use of Triton™ X-100 ceases; and

- With a half-life of 54 days, 4-tert-OP stock levels peak at around #H kg, but they then start to decline due to the decreasing input and reducing frequency of input combined with the ongoing degradation of 4-tert-OP. By 2035, the remaining stock in the environment

reduces to near zero. For Use #1, reduction of stock to practically zero occurs before the end of the review period.





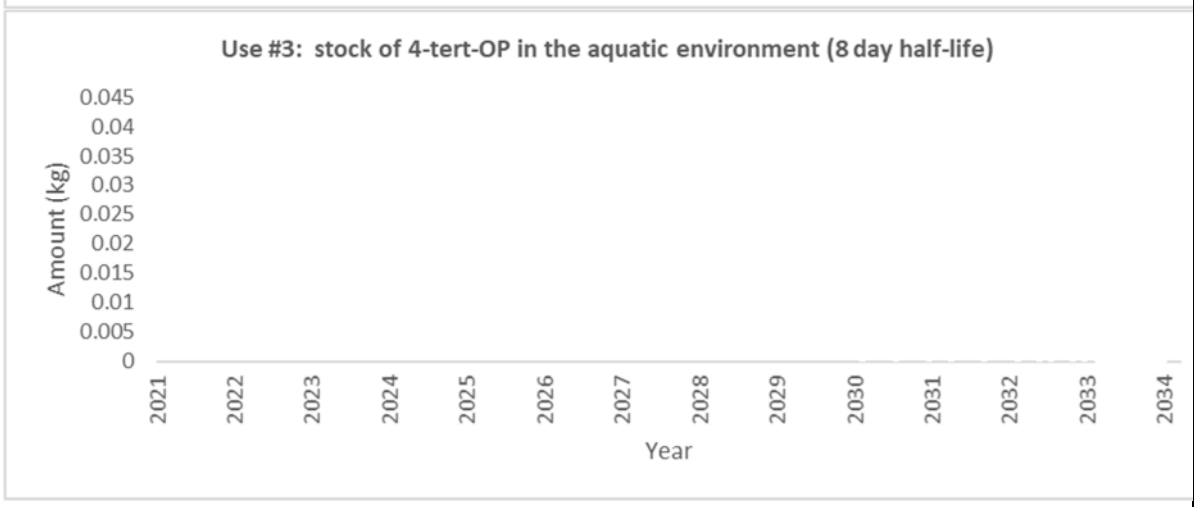
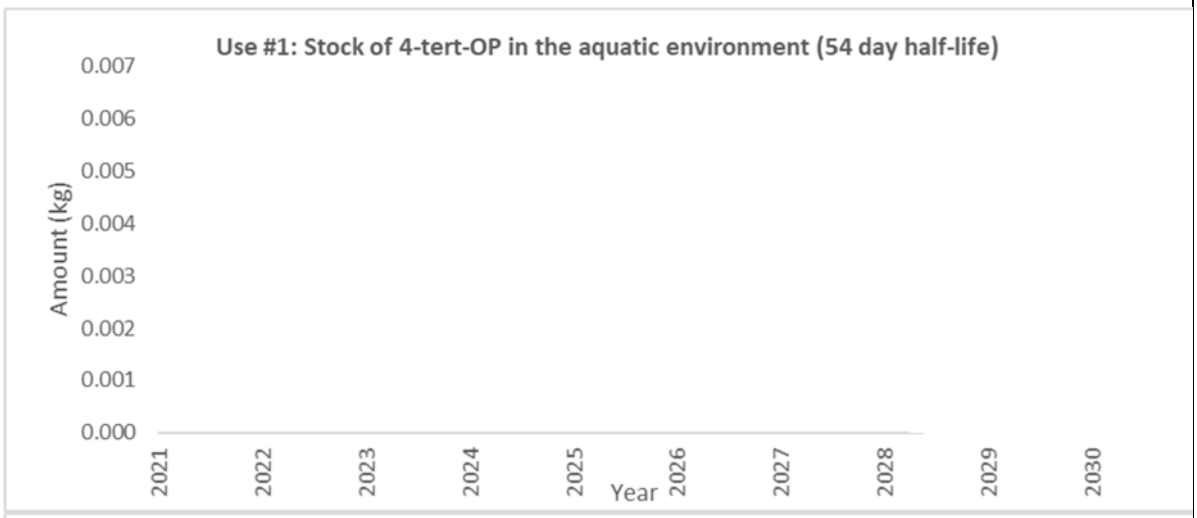
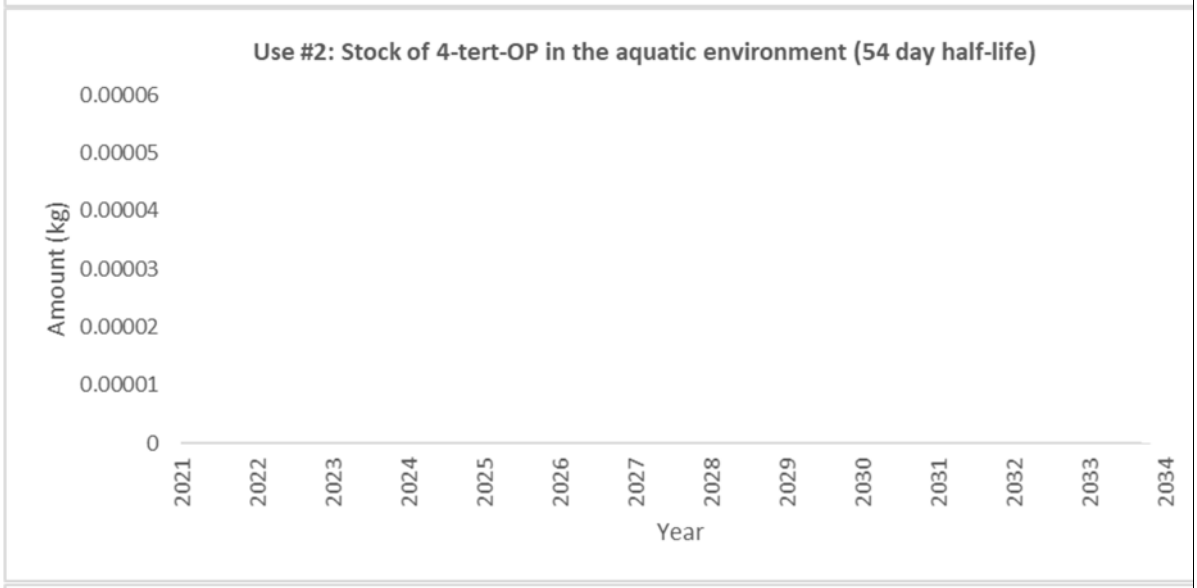


Figure 3-16: Illustrative 4-tert-OP stock in the freshwater environment assuming a half-life of 8 days – Uses #1, #2 and #3





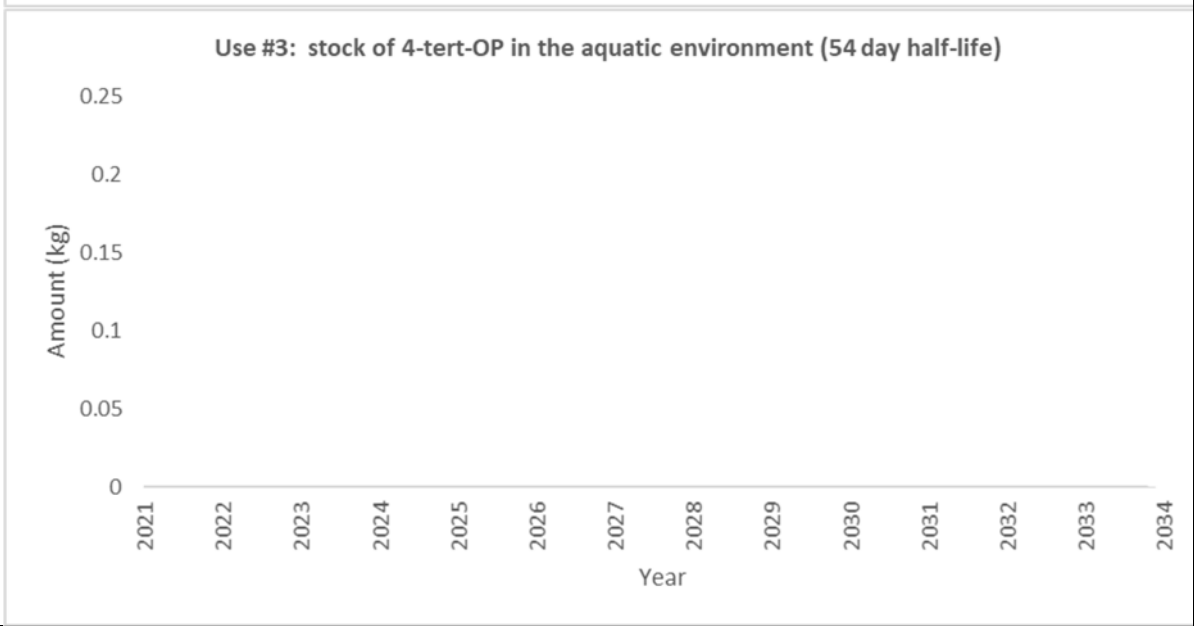


Figure 3-17: Illustrative 4-tert-OP stock in the freshwater environment assuming a half-life of 54 days – Uses #1, #2 and #3

Table 3-41: Maximum 4-tert-OP levels in the freshwater environment for each Applied for Use		
Use	**Maximum stock (kg) with 8-day half-life**	**Maximum stock (kg) with 54-day half-life**
Use #1	#H, Table	
Use #2		
Use #3		

3.3.4 Summary

In summary, the percentage of total OPE used that is assumed to be emitted to the aquatic environment as 4-tert-OP ranges from 1.325% of the Triton™ X-100 amount consumed for Use #1 down to 0.0024% of the Triton™ X-405 consumed for Use #2. No other environmental discharges are believed to occur (sludge from the STP is assumed not to be spread to agricultural land). Based on an annual usage of OPEs of #H, J for Uses #1, #2 and #3 respectively for 2021 (NB. with notable decreases from the 2018 levels), this equates to a total release of #H kg of 4-tert-OP per year per Applied for Use to the aquatic environment depending on the Applied for Use. Over the requested review period, the releases of 4-tert-OP to the aquatic environment account for a total of ca. #H (range: 0.01-10) kg per Applied for Use over the respective review periods. **Table 3-42** summarises the releases of 4-tert-OP to the aquatic environment for all three Applied for Uses. Over the period 2021-2032, the total release is #H (range: 1-10) kg 4-tert-OP.

Whilst the local assessment indicates that concentrations in the water are below the latest research values, the releases are not occurring every day manufacture 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 remains at very low levels. If a half-life of eight days is assumed, then the maximum total 4-tert-OP in the environment resulting from each Applied for Use is ca. #H kg. If the upper end half-life of 54 days is assumed, then 4-tert-OP stock levels peak at around #H kg per Applied for Use prior to declining over time due to decreased usage and 4-tert-OP breakdown.

Table 3-42: Estimated total release of 4-tert-OP to the aquatic environment from Uses #1, #2 and #3	
Year	**4tert-OP release to aquatic environment for all three Applied for Uses**
2021	#H, J (table)
2022	
2023	
2024	
2025	
2026	
2027	
2028	
2029	
2030	
2031	
2032	
Total	

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 and Triton™ X-405 fall 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.

4-(1,1,3,3-tetramethylbutyl)phenol, ethoxylated (OPnEO) is considered a substance of very high concern due to the degradation to 4-(1,1,3,3-tetramethylbutyl)phenol (4-tert-OP), a substance with endocrine disrupting properties.

OPnEO 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 OPnEO 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 OPnEO, 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 Marburg consumes a low and diminishing volume of Triton™ X-100/Triton™ X-405 (for all three Applied for Uses collectively projected to be ca. #A kg in 2021) and the annual releases of 4-tert-OP to the aquatic environment can be estimated to be a total of #H (range: 0.1-1) kg in 2021 and decreasing thereafter. The stock levels of 4-tert-OP in the environment are particularly low with a maximum level associated with each of the Applied for Uses of #H kg, depending on the Applied for Use considered and 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

Introduction

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;
- **The Challenging Nature of Identifying an Alternative Substance to OPE's –** 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 OPE's from its product-lines; and
- **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 product-lines performing a variety of functions, and therefore the technical and regulatory processes and challenges can vary between Design Projects. While every design project must move through certain prescribed steps, there are some steps which will only apply in some cases; also, the technical challenges will vary between designs. 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 OPE's, 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 absolutely 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.

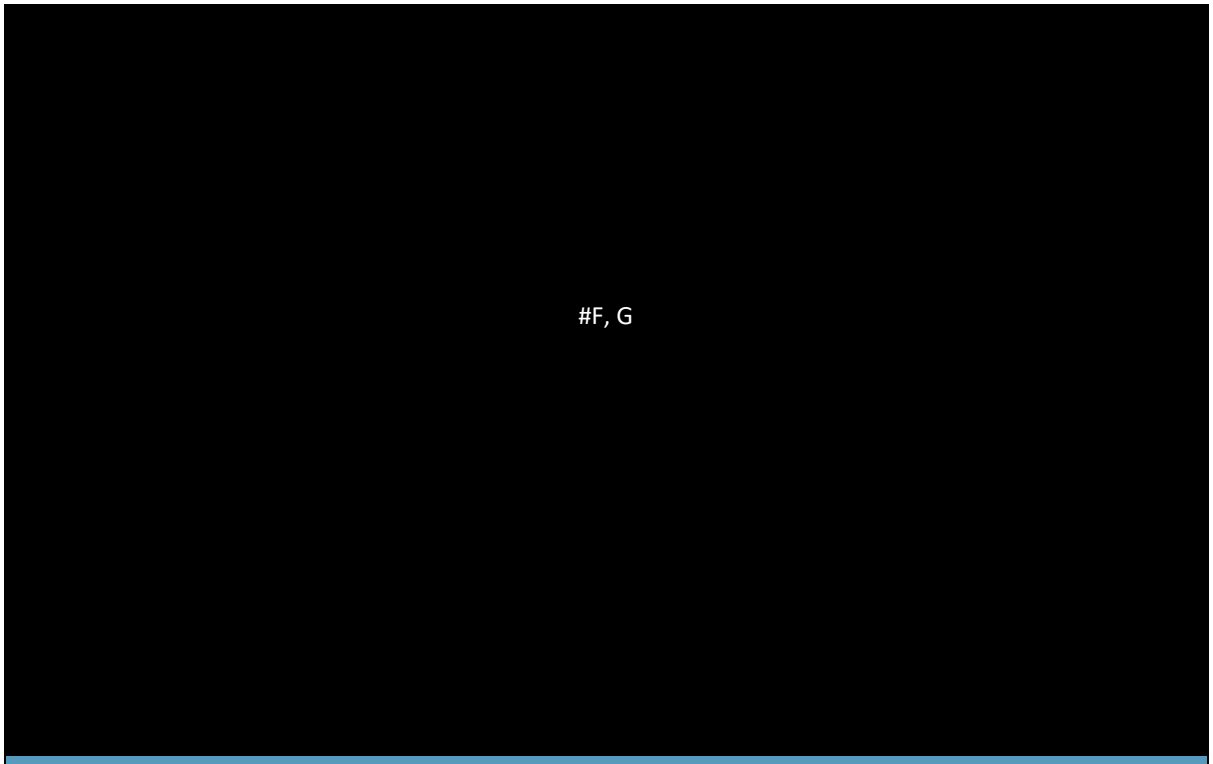


Figure 4–1: Product Design and Design Change Process Steps

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 OPE's 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 #F), and these have 38 supporting documents to direct and support the responsible personnel through each task in a prescribed way which can be clearly tracked and documented. When one considers that each manufacturing site also adopts a local version to implement this global procedure, also addressing any regional or national regulatory requirements, the number of working documents significantly increases.

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 OPE's), 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 4-8**.

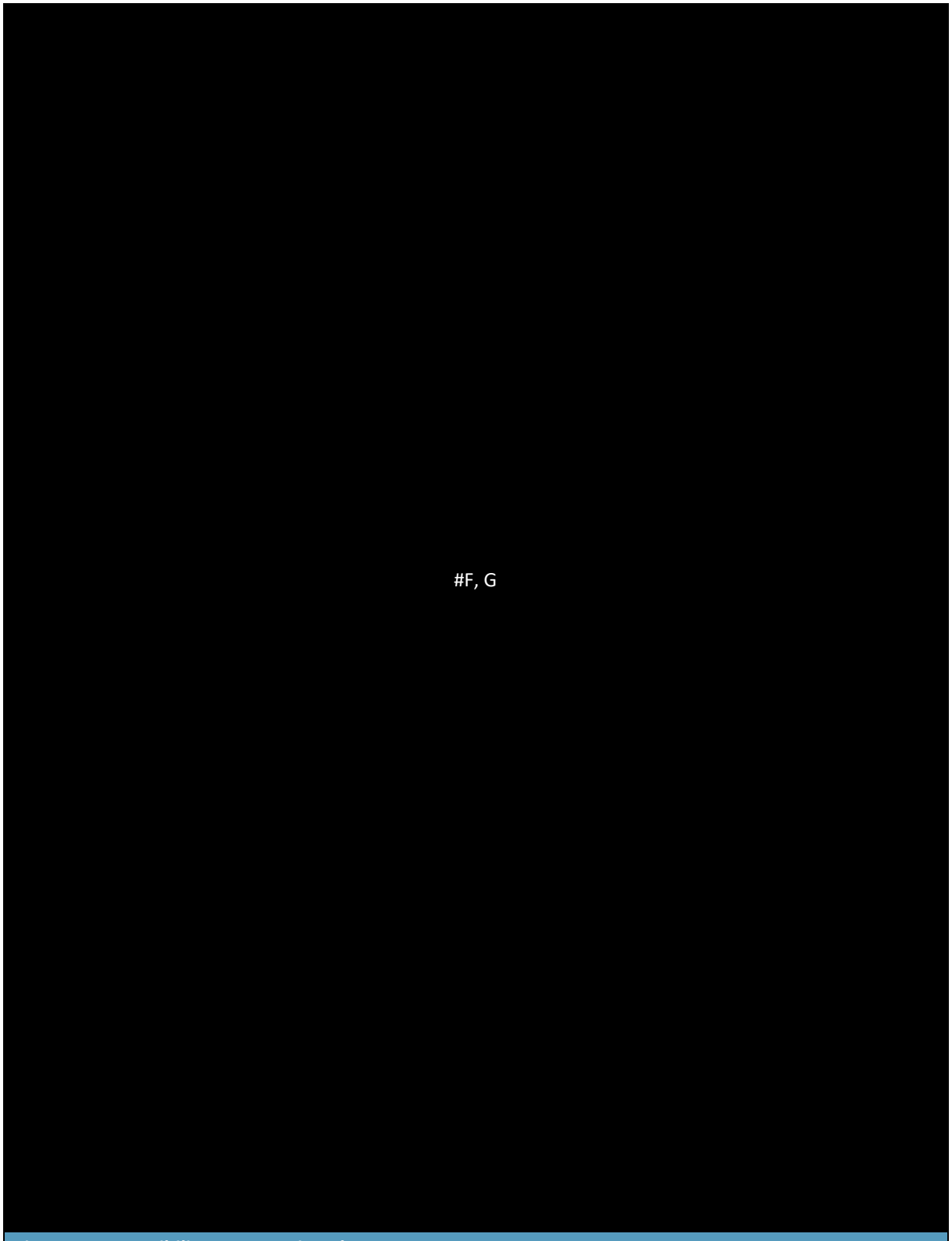


Figure 4–3: Feasibility Stage Design Phase

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 processing of a change project that results in a regulatory re-registration of an IVD kit includes the following steps:

1. A Change Project initiated by the central Siemens Healthineers change team;
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. 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 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 on the periods it takes (on average) to get the regulatory permit. 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. Given the long periods that bind significant research resources it is not possible to start the substitution activities for all products produced in Marburg at the same time.

Overall, the entire re-registration process can be expected to take up to #B , or ca. 4 years[6].

[6] 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; Report and Technical Documents for Assays; Risk Management Report; Product Summary; Clinical Trial / Study Data / Method Comparison).

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.

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 Timeframe for IVDR unknown
North America	USA (including Puerto Rico)	Code of Federal Regulations (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

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.

  An anlogy could be - 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. 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 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 #D use OPE (and #D) and within the wider Siemens Healthineers portfolio #D formulations use OPE, the scale of the project-work and resources required to phase out OPE's is a huge undertaking and requires skilled coordination across functions, countries and #D 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 OPE's in an IVD reagent or a formulation used to manufacture an IVD Product (such as in the case of the reagents and wash formulations 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.

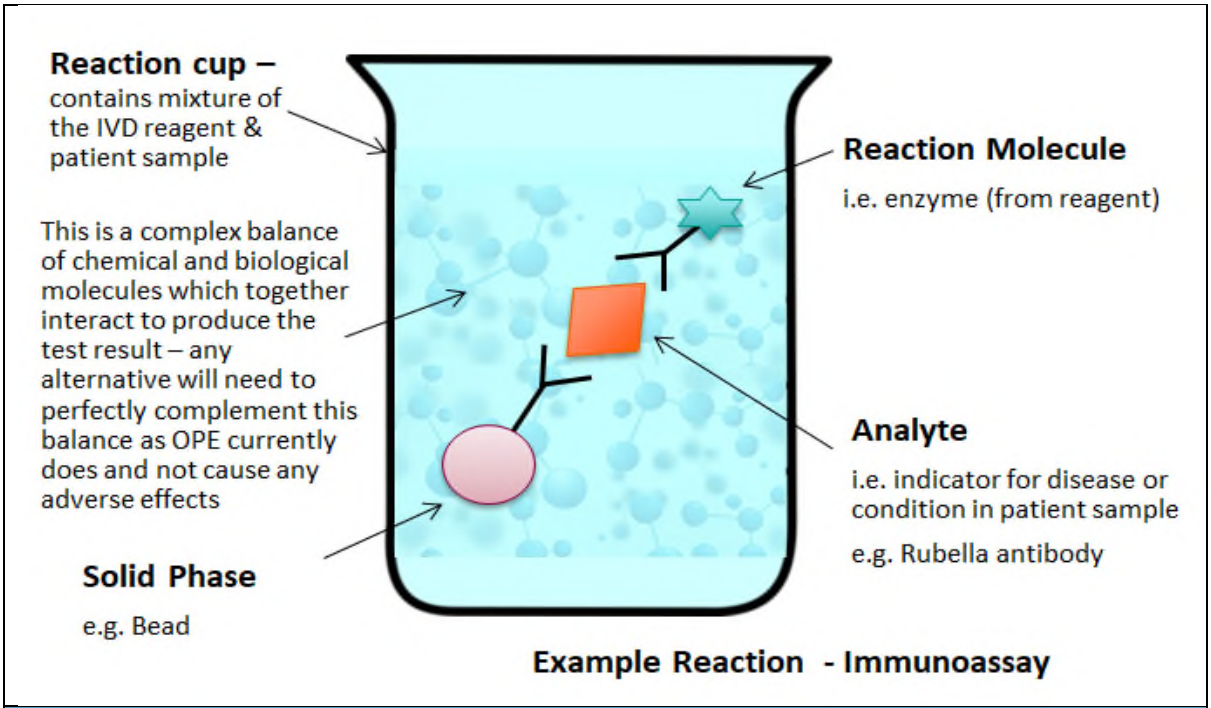


Figure 4–4: Example of the reaction in an immunoassay test
NB. When referring to many IVD products within the scope of this AfA, OPE is typically found in the IVD reagent itself

In addition to the immunoassay example, there are several ways to perform such measurements, one example is the #D assay described in Section 3. Additional IVD kit reagent technologies utilise enzymes as the reporter system while other IVD kit reagent technologies utilise light-emitting molecules such as #D as the reporter system.

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. 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 target protein in the patient sample.

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 in regard to 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 used in scope of this AfA facilitate protein purification, ensure the sensitivity and specificity of tests and in the case of the wash solutions act as a cleaning agent. 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, and often followed by 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 OPE's 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 involved in the reaction, 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 (in terms of specificity and sensitivity).

Additional Consideration – Use#3 Wash Solutions

In regard to the technical challenge described above, an additional challenge is introduced when reformulating wash solutions. Wash solutions are used with every IVD test performed on an analyser, and therefore residues from the wash formulations can be retained on the analyser system which then interact with the chemical and biological constituents of the reagents used in the IVD formulations which perform the tests. As a result, any change in the design of an IVD Wash Solution must be tested with every single IVD product used on each 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 (#D), 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 with regard to 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 physico-chemical 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 #D IVD products (representing #D formulations) affected across #D 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 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 through 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 #D platform (e.g. #D , #D & #D products where the same reagent formulations are used on the #D platform) or which are expected to have a longer life-cycle[7] 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 #D platform, which will over time be replaced by the #D , 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 far 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.

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

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

Figure 4–5: Siemens Healthineers REACH Response Plan overview

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, three 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.

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 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**.

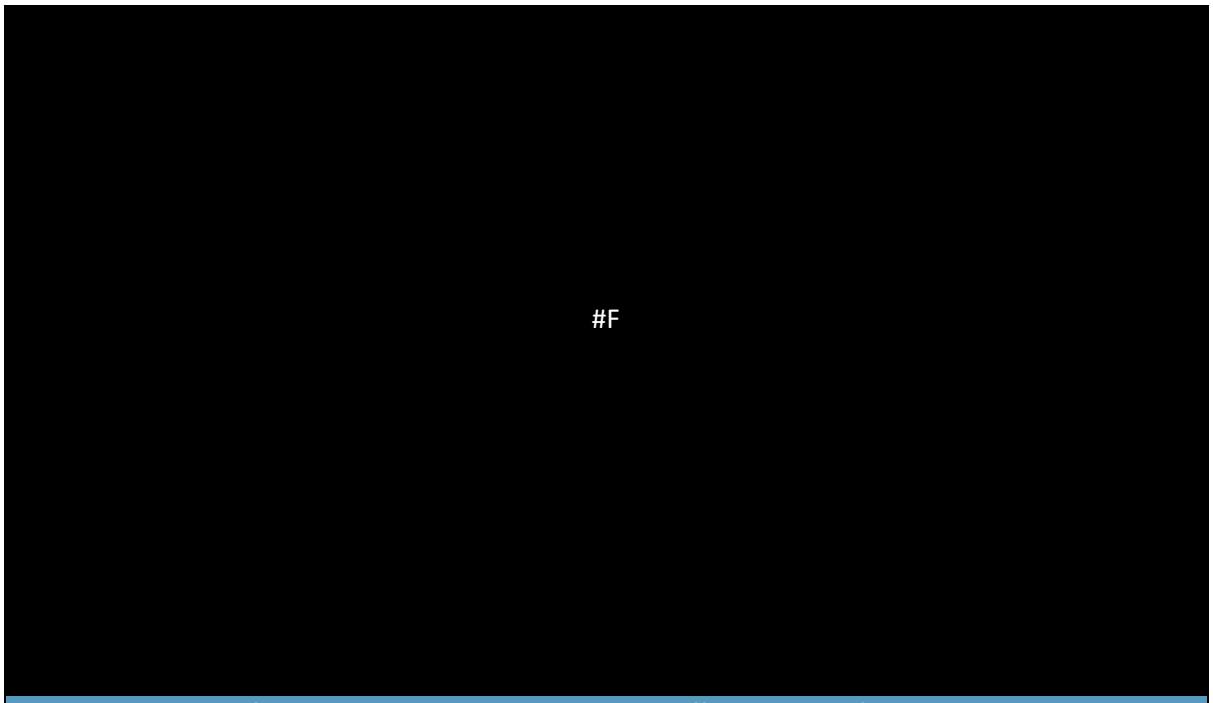


Figure 4-6: Excerpt from communication with US EPA in efforts to identify suitable low or non-hazard alternatives to OPE

- In May 2014 Siemens Healthineers initiated a collaborative project with the #F (bullet point) [8]. The challenge presented by OPEs in terms of the widely impacted Siemens Healthineers product portfolio, and the strong

[8] #D

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] 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] 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: **#F**

#F and #F were chosen to pursue due to their surface tension properties and more favourable toxicity and biodegradation results. This was later narrowed to #F 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 #F R&D site.

This work with #F 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 #F , to focus specifically on the substitution of octylphenol ethoxylates in IVD kit reagents and IVD wash solutions. #F 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** below. #F report is provided as Appendix 4 (Section 12) to this AfA; 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 #F , 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 4-1** 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 / 9036-19-5	Reference
1-Oleoyl-rac-glycerol	111-03-5	#F (table)
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	
Tween® 20	9005-64-5	
Tween® 60	9005-67-8	
Tween® 80	9005-65-6	

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	#B, D, F (table) Assay
Product Description	The assay is for *in vitro* diagnostic use in the quantitative measurement of in human serum or plasma using the system. The assay can be used to aid in the diagnosis of .
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,
Development Team	Assay Development Team, R&D,
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, % 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 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[9] 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 , 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	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	#B, D, F (table) Assay
Product Description	The) assay is for *in vitro* diagnostic use in the quantitative measurement of in human serum or plasma ( ) using the Analyser. The assay can be used to aid in the diagnosis of acute)
New or Existing Product?	New
Year Development Initiated	2011
Development Location	Siemens Healthcare
Development Team	Assay Development Team,
Background	The initial reagent design contained % (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 . The idea was to maximise the and the assay , removing as well. A few low end were also added to collect and . Background 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) with the two formulations and sample recovery comparisons. A portion of each detergent formulation was also set aside to check and . When another critical IVD performance parameter, , 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 . Finally, it was necessary to label with all available s and understand the influence of and . was the only one that was effective but it also incurred issues - the stuck to the as it was not completely. As a result, over time on replicate measurement using , the reagent became irreversibly raising the background. The addition of to the whose mimic and increasing the probe's 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 (and further . In total, all these efforts to identify an alternative to the OPE added a year to the development of the assay.

IVD Product Name	#B, D, F (table)
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] [redacted] **Condition B** [redacted] [redacted] **Condition C** [redacted] 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 [redacted] Clinical Chemistry analyser using commercial reagents including the [redacted] calibrator and [redacted], 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 [redacted] 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, [redacted], 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	[redacted] #B, D, F (table)
Product Description	The [redacted] assay is for *in vitro* diagnostic use in the quantitative determination of [redacted] in human serum and plasma ([redacted]) using the [redacted] Analyser. Measurements of [redacted] produced by the [redacted] are used in the diagnosis of [redacted] disorders. The commercial [redacted] assay in an important [redacted] test and requires one of the lowest [redacted] in the portfolio
New or Existing Product?	Existing
Year Development Initiated	2016
Development Location	Siemens Healthcare, [redacted]
Development Team	CPS Team, R&D, [redacted]
Background	This product contains [redacted] 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	#B, D, F (table) [redacted]
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	#B, D, F (table) Assay
Product Description	The assay is another important blood test measuring , improving patient care in individuals suspected of having). Measurements of are used as an aid in the diagnosis and assessment of severity. The test is further indicated for the risk stratification of patients with acute .
New or Existing Product?	Existing
Year Development Initiated	2017
Development Location	Siemens Healthcare,
Development Team	Assay Development Team, R&D,
Background	This product is composed of four separate reagents, three containing w/w OPE (Reagents) and the other reagent (Reagent containing 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 ( )**: Lowered OPE to % w/w within Reagents ; and Replaced OPE % w/w with Triton™ X-100 reduced % w/w (Reagent). Results Summary: patient samples were tested for method comparison showing % shift in patient sample recovery vs commercial reagents. There is a much greater shift (under recovery for test lot) for samples above units. Assay range is /mL. **Revision B ( )**: Replaced OPE % w/w with Triton™ X-100 reduced % w/w within Reagents ; and Replaced OPE % w/w with Triton™ X-100 reduced % w/w (Reagent). Results Summary: patient samples were tested for method comparison and showed % shift in the patient sample analyte values vs commercial reagent - similar analyte recovery to Revision A. Samples greater /mL showed a much greater shift (low patient sample analyte values for the test reagent). Since Reagent is formulated with the greatest OPE concentration %), the team has now focused only on Reagent in the short-term. **Revision C ( )**: Lowered OPE to % w/w; and Replaced remaining OPE with Tergitol™ 15-S-9 % w/w. Results Summary: patient samples were tested for method comparison against commercial reagents. A familiar recovery of % 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 /mL in each instance and shared a similar pattern. **Revision D ( )**: Lowered OPE to % w/w; and Replaced remaining OPE with Tergitol™ 15-S-9 % w/w and Triton™ X-100 reduced. Results Summary: method comparison testing was completed with samples showing ca. patient sample shift between test and commercial reagents. Again, the familiar pattern of patient samples higher than

	/mL show greater under-recovery for the test reagent. It was noted that the separation was closer than previous experiments. **Revision E ( );** **Revision F ( ):** Lowered OPE to %; and Replaced remaining OPE with Triton™ X-100 reduced % 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 has a significant impact. Lowering the Triton™ X-405 concentration in Reagents , however, had an insignificant impact. It is clear that the Triton™ X-100 at % w/w in Reagent 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:

#D, F

#D, F

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 #D . 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 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, physico-chemical 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.

4.1.1 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

Before potential alternatives to the Applied for Uses of OPEs are considered, it should be noted that each of these alternatives cannot be seen in isolation. Two major considerations should be kept in mind:

- The Siemens Marburg production site (and with this the legal entity that is applying for Authorisation) is only one part of a world-wide operating corporate (Siemens Healthineers); and

- The Applied for Uses within the scope of this AoA/SEA document are mainly preparatory steps for the final application of IVD products at the DUs' sites (customers in the healthcare sector). In this regard, it is important to mention that other IVD kit reagents and IVD wash solutions containing OPEs are imported into the EEA, primarily originating from Siemens Healthineers' US-based manufacturing operations. The continuation of supply of these IVD products is equally relevant to customers of Siemens Marburg as the supply of IVD products from Marburg manufacturing.

The use of those imported IVD products also requires REACH Authorisation and Siemens Marburg is submitting a separate AfA for their use by DUs (Uses #4 and #5). Therefore, resources for research and development and for later product quality testing and licensing of the various products under different worldwide relevant IVD regulations are limited. As a consequence, initiating substitution of OPEs across all impacted IVD products immediately is not feasible. However, if an Authorisation was not granted, besides the economic damage for Siemens Marburg, the DUs would face the prospect of being unable to deliver diagnostic services they currently perform, which would have significant knock-on effects on the healthcare syetem and patients.

From Siemens Marburg's perspective, the following theoretical alternatives to the use of OPEs in the production of protein (Use #1), IVD kit reagents (Use #2) and IVD wash solutions (Use #3) could be considered:

1. Substitution of OPE by an alternative (environmentally-friendly) substance.
2. Relocation of relevant Siemens Marburg operations to a location outside the EEA.
3. Discontinuation of supply of OPE-dependent IVD kits and wash solutions made in Marburg.
4. Discontinuation of supply of all IVD kits and wash solutions made in Marburg.

These four scenarios are discussed in detail below in order to identify the most realistic "Non-use Scenario", which will form the basis for the impact assessment in Section 5 of this AoA-SEA document.

4.3 Assessment of shortlisted alternatives

4.3.1 Alternative 1: Substitution of OPE with an environmentally friendly substance

Description

This scenario explores in more detail the feasibility of substituting Triton™ X-100 and Triton™ X-405 with alternative substances under the "Non-use" Scenario. As described in Section 4.1.1, extensive research and development work has been conducted by Siemens Healthineers over the past 6 years to identify and test suitable alternative substances to OPEs. With #D IVD products and processes to find alternatives for, it was clear from the outset that one alternative substance would not be suitable for every case, and therefore a range of substances are included in this assessment.

The actual alternative that could be successfully implemented in the case of any of the OPE-dependent IVD products at Siemens Marburg will not be known until completion of the Feasibility and real-time Stability Testing phases of the Design Change projects specific to each of those products.

The focus for Siemens Healthineers has been the development of a list of potential alternatives which could be used as a starting point in any IVD Product Design Change or Product Development Process. The list was developed as described in Section 4.1 taking into consideration a range of factors including:

- Surfactants known to be effective in other IVD products;
- Surfactant Properties comparable to those of OPE – these include similar
  - HLB values;
  - Critical Micelle Concentration ranges; and
  - Cloud points;
- A lower hazard classification and thus an indication that any alternative substance would not become restricted or subject to REACH Authorisation in the future – substances with a classification as CMR, acute or chronic effects on the aquatic environment cat.1 according to the CLP Regulation and other properties that might give reason to have equivalent concern were excluded, including those suspected of having endocrine disrupting properties.

Substance ID and properties

At this point in time, there has not been a successful substitution of OPEs in an existing IVD product manufactured or process used at Siemens Marburg. However, there have been extensive research and development activities undertaken within the wider Siemens Healthineers portfolio to identify alternatives to OPE and substitute its use in IVD products, as described in Section 4.1.1.

Based on this work, a number of new IVD products have been developed since 2013 without the use of OPE, where normally Triton™ X-100 or Triton™ X-405 would have been utilised given their proven track record in effective IVD product design and manufacture. A number of these products were subsequently introduced to the market after the Siemens Healthineers' decision to eliminate OPEs in 2013.

The work thus far indicates that it is technically possible to substitute OPEs with other non-ionic detergents available on the market or under development; however, it will not be known which substance can directly substitute the OPEs in the Uses under discussion in this AfA until the Feasibility and real-time Stability Testing phases have been completed. Therefore, the discussion of this alternative cannot focus on any one specific alternative substance and is by necessity accompanied by several assumptions.

From a very general perspective, a substitution process of an OPE in one of the processes or products under discussion would cover the following steps:

- The established list of non-ionic detergents would be screened for the most likely candidates, based on the technical and expert knowledge of the R&D scientists who understand the products in question;
- An initial testing series would be performed to see if each alternative substance works under the conditions of the current process/IVD test;
- Alternative substances that show promising results in initial testing might be used for further optimisation;
- One or more alternative substance would then be subject to extensive quality testing.

As previously noted, currently no existing processes or products have undergone an active substitution process. The closest experience in this regard is the #D [redacted] Assay shown in Section 4.1.1, where a kit reagent has been changed after it was close to product release.

Table 4-3 overleaf provides a wider overview of non-ionic surfactants that in principle can be used in IVD protein isolation, kit reagents and washing solutions. The substances shown in this table have been already used successfully in product development or have been applied to screening tests. The colours of the fields reflect whether key technical parameters as shown in Section 4.1 are met.

Table 4-3: Key information on detergents that have been tested as alternatives in comparison to Triton™ X-100[10]							
Name	**CAS No.**	**Trade name (s)**	**HLB**	**CMC[11]**	**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[12])	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[13]	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	

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

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

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

[13] 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[10]							
Name	**CAS No.**	**Trade name (s)**	**HLB**	**CMC[11]]**	**Cloud Point [°C]**	**Classification Supplier safety data sheets**	**H-phrases**
Ethoxylated lauryl alcohol	9002-92-0	Brij® 35	16	0.091 mM[14] (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[15]	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[16]	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

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

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

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

Results from research and development conducted within the wider Siemens Healthineers portfolio and presented in Section 4.1.1 show that there are substances on the market that might be suitable alternatives, however this would need to be proven for the Siemens Marburg products through testing on a 'per product' basis.

Technical feasibility of Alternative 1

Use #1: Isolation of proteins from recombinant cell cultures

The technical feasibility of different alternative substance for this use would vary between the protein types that are isolated.

In the case of the #D protein, the main challenge is to ensure a high harvest of protein that remains stable until the purification process has been completed. For the function of Triton™ X-100 this means it has to disrupt the cells from the cell cultures efficiently and then stabilise the protein until it has bound to the purification column. After this step, molecules that could influence the protein yield are removed, e.g. proteases that might originate from cell strains and could degrade the protein. If a substance can be found that keeps the #D protein stable during purification, a substitution could be implemented without additional requalification by authorities.

For substitution of Triton™ X-100 in the isolation process of #D proteins, the process would need to undergo initial screening tests. Several of the substances listed in **Table 4-3** are well known substances that have been widely used in protein isolation activities in the past. Given their key parameters and their availability, no direct preferences can be derived from the list. Since the HLB and the CMC only serve as a vague orientation, the suitability of a substance has to be determined empirically. This refers to the identity of the substance and the optimal concentration. Regarding the availability it can be stated that all substances can be sourced from at least one supplier in the EEA. As it would be preferable to find substances that have better intrinsic properties, it might be reasonable to try unclassified substances as a start (potentially even by extending the indicative list presented above).

In case of the #D the situation differs, because only a raw extract is produced without immediate further purification. Therefore, in principle all molecules that could interfere with the #D remain in solution until further processing at Siemens Llanberis in the UK. So, an alternative surfactant has to mediate a good protein yield but also stabilise the #D over a relevant timeframe until further processing can be performed. It should further be noted that the Triton™ X-100 not only is relevant during protein isolation and transport but also in the subsequent process step performed at Llanberis. Here it has an important role when the #D is bound to a #B bead in a bead coating process. In principle, the identification of a substitute would use the same criteria as discussed for the #D proteins. The main difference is that functionality also has to be ensured in the Siemens Llanberis Applied for Use too (see separate AfA).

The future of the #D product is complex. It is sent to Siemens Llanberis for the coating of beads in one of Siemens Llanberis' IVD kits. But it is also intended to be used for #D kits – #C, D . Since the #D IVD kit is used on #D analysers, the continued use of this test (as well as all other #D IVD kits) are linked to Use #3 and the substitution (or Authorisation of the continued use) of OPE in the #D wash solution (#D).

To conclude, the technical feasibility of the substitution does not only depend on the potential to find an alternative substance in this use but also in uses that are performed down in the supply chain (during production and upon end use of the resulting #D IVD kit)[17].

Use #2: Formulation of IVD kit reagents

While work to substitute OPE in IVD kit reagents has been initiated at the Siemens Marburg site, feasibility testing has not yet identified a single specific alternative substance. Since some of the substances that have been applied in screening testing for other products have been proven to be (at least partially) promising, the identification process of alternative substances could also be directly started with similar screening experiments.

According to the Siemens Healthineers REACH Response Plan, substitution efforts will take place in two tranches:

- The so-called Panel 1 of high priority will include #D, G ; and
- The so-called Panel 3 (Panel 2 refers to reformulation of the Use #3 wash solution products) of lower priority will include #D, G

Panel 1 substitution R&D work is expected to finish in early #G and Panel 3 R&D work is planned to finish in mid #G .

Once a substance is found that could replace the OPEs under consideration (either Triton™ X-100 or Triton™ X-405), product re-registration would be necessary worldwide. The re-registration process must also be included in the "technical feasibility" assessment of this alternative as it impacts the time before any alternative to OPE can be introduced to the market and products produced with the alternative substance can be sold to customers that operate the relevant analysers.

As described earlier in Section 4.1.1, the entire re-registration process can be expected to take up to #C , or ca. 4 years.

It is also important to note that there are other complexities to consider in terms of assessing the technical feasibility, in some cases the resources for substitution of OPEs are also limited by other internal and external activities. These are:

- Siemens Marburg does receive IVD kit reagents from an OEM that also contains OPEs. This supplier sells very specific products to Siemens Marburg that represent one part of the IVD kit but the final IVD kit is assembled by Siemens Marburg. This supplier has also initiated activities to substitute OPEs from these products. If these activities are successful, Siemens Healthineers has to qualify the resulting final IVD kits as well under the specific regional regulatory regimes which binds resources of Siemens Healthineers. Such processes have preferences because until the relevant permits have been granted, the supply chain would be interrupted and end users might not be able to perform diagnostic tests and treat patients accordingly;

[17] It should be noted that such dependencies occur quite often, when substitution needs to be considered in the Siemens Healthineers product portfolio and is one of the main causes of the overall complexity of the substitution of the OPEs in this sector.

- Apart from the IVD kit reagents manufactured in Marburg and the ones supplied by OEMs, Siemens Healthineers manufactures a #D of IVD kit reagents that contain OPEs in the USA and imports them into the EEA. These imported IVD kits that contain OPEs are also subject to substitution activities however, these activities will be performed at the US R&D site (followed by the same worldwide re-registration procedure as no EEA-specific variants are produced). This also increases the workload that is needed to organise the substitution of OPEs in the product portfolio of Siemens Healthineers and makes it necessary to spread the substitution activities over a longer time period; and

- Researchers within Siemens Healthineers that are qualified to do substitution work are also involved in activities to develop new IVD kits. This activity on the one hand binds resources for substitution work on existing IVD kits (including the ones produced at Marburg) but on the other hand forms a relevant and important component in the overall substitution strategy of Siemens Healthineers. In reaction to this, Siemens Healthineers has decided to phase out older products and since 2013 the company only starts development of new products without OPEs. New products in development can measure the same diagnostic parameter but maybe by another mechanism or measures another diagnostic parameter that gives an indication for the same disease. Products that are subject to such a phase out would not be within the scope of substitution and re-registration activities but have to be authorised for a bridging period until the new product lines are capable of replacing the existing one with OPE.

As a conclusion of these considerations on the substitution of OPEs in the kit reagents that are produced in Marburg and on the background of the overall Siemens Healthineers strategy to replace OPEs, it can be stated that substitution in each kit reagent might prove to be technically possible based on the experiences acquired already for a few IVD kits. However, the R&D and regulatory burden of substituting Triton™ X-100 in all relevant kits, even if some of them are phased out, would be very onerous and time consuming. Regulatory bodies require a re-registration after substitution of substances in an IVD kit, like Triton™ X-100. This re-registration includes testing of all performance parameters of a test and demonstration of comparability to the already existing kit – a very labour and cost intensive path.

Use #3: Formulation of wash solutions

The substitution of OPEs in IVD wash solutions is accompanied by the same technical considerations as the IVD kit reagents. The already tested substances might also qualify for the IVD wash solutions. A significant difference is that the performance testing needs to be undertaken with every kit that is applied to the analyser under discussion and not for one IVD kit only. While the stabilisation of molecules in the IVD kit reagent is not important for the IVD wash solution, the IVD wash solution must be capable of removing all residues from each IVD kit and the different types of patient samples extremely thoroughly to ensure no carry-over from one diagnostic measurement to another. Therefore, once a potential substitute substance is identified, the screening process needs to be followed with a verification measurement series for each IVD kit that is used alongside the reformulated IVD wash solution. This understandably generates a significant R&D workload.

For IVD wash solutions intended for use on #D analysers #D reformulation is planned and it is the intention to ensure these platforms can be used in the future. However, reformulation cannot be undertaken immediately. Progress with substitution of OPE under Use #2 would be required before reformulation of the wash solution can start and compatibility testing with #D assays would be required. Re-registration activities following reformulation would take until the end of 2032 to complete.

On the other hand, the #D will not be subject to substitution efforts. The Siemens Healthineers' strategy is to #D. If substitution were to be undertaken, this could not have been given priority and would take a sufficiently long time, so there would be the real risk of the #D. Clearly, reformulation would make no business nor practical sense. Therefore, it is not foreseen to search for an alternative substance and to undergo requalification as described. Nevertheless, the importance of the testing that is performed on that platform (among other #D) it will be necessary to continue to supply this wash solution for several years (with OPE) to ensure the end users (e.g. hospitals and laboratories) can continue using the #D analysers.

In conclusion it can be stated that a substitution of OPEs in the #D #D could theoretically be technically feasible, however as with Use #2 the technical and regulatory activities will be very time-consuming and represent a high cost.

Economic feasibility and economic impacts of Alternative 1

As described above, Siemens Healthineers is not planning to carry out reformulations for all the affected products, but will focus on the products that are expected to be in production/sale over a longer period of time. The cost of reformulation is therefore only calculated for this subset of products.

Use #1: Isolation of proteins from recombinant cell cultures

Siemens Healthineers is planning to reformulate all #D formulations under Use #1, representing #D products #D. The time to successfully transition to one or more alternatives for this use is estimated to be #G years from the beginning of 2019 or #G years from the Sunset Date. The cost of R&D is difficult to specify; the resources needed will be part of a larger project, are difficult to separate and are therefore difficult to estimate.

For most products under Use #1 there will be no IFU change since there is no change in composition. Triton™ X-100 is only used during production but not present in the final product. As such it can be assumed that no significant re-registration effort or cost would be needed.

Even if it were to be assumed that implementation of alternative substance(s) could be achieved in a much shorter timeframe than Siemens Marburg anticipates, the actions of Siemens Marburg's customers (but also those of Siemens Llanberis) could still render the manufacture of the impacted IVD kits redundant.

On the Sunset Date and with full range of IVD kits and IVD wash solutions within the scope of Uses #1 (but equally Use #2 and #3) unavailable, the customers using the impacted analysers would have to seek alternatives, at least for the period of reformulation. These alternatives would be competitor products run on competitor analysers and diagnosing the same range of diseases in patients as those diagnoses provided by the Siemens Healthineers platforms (the reader is reminded that many of the Siemens Healthineers' analysers **do not** run on third-party IVD kits[18]). It can be assumed that none of

[18] #C, D

Siemens Healthineers' competitors would develop kit reagents that are dedicated to be used on Siemens Healthineers analysers. All competitors, including Siemens Healthineers, aim to develop their own IVD kits for use on their own analyser platforms as this is the standard business model for profitability in this field.

Customers need at least 6 months for the validation of a new analyser. If disruption to the supply of Siemens Marburg's IVD kits and wash solutions were to last substantially longer, customers would be strongly encouraged to swiftly move on to an alternative, third-party platform.

Assuming customers made this change to competitor IVD kits and analysers so as to be able to continue providing the same patient diagnostic services, it is quite probable that most, if not all, customers would continue to use these alternatives rather than switch back to the affected Siemens Marburg kits. In short, if Siemens Marburg was forced to keep its IVD products off the market for several years, there would be no market left for these kits to come back to after substitution of OPEs is complete.

As such, for the purposes of the calculation of economic cost, we will assume that the profits projected to be made under the "Applied for Use" Scenario for Use #1 would be lost. It is pertinent to note that Siemens Healthineers typically maintains a very limited stock of kits (for some kits only #C, D 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.

Based on **Table 3-11**, the economic cost to Siemens Marburg would be € #D, E (range: €10-100 million) (PV, 4%, 2021-2029). This does not include the market value of the #D kits that should be allocated to Siemens Llanberis as it is the UK site that places the final IVD kit on the market and thus any associated profits should be allocated to the UK operations.

Use #2: Formulation of IVD kit reagents

Siemens is planning to reformulate #D, G formulations under Use #2. The remaining formulations are to be phased out. The time to successfully transition to one or more alternatives for formulation of reagents is estimated to 12 years from the Sunset Date. During this period a total of #G FTEs are expected to be needed to complete the substitution process. It is assumed that each FTE is equivalent to a cost of #G. This would bring the overall cost to #G (range: €1-10 million).

After the reformulation stage the performance of the products must be verified and any performance changes will require a re-registration in most countries. If there is no performance change, some countries may still require re-registration due to an IFU change related to composition. As described earlier, in the case of reformulation of the OPE-dependent kits, approximately 50 re-registrations would be envisaged. For each submission around two months of preparation time is needed, in addition to the time necessary for the regulatory authorities to complete the reviews.

As a very rough estimate, for each product consider 120 hours for the Business line, and 40 hours per country that has a submission requirement, and additional 120 hours each for USA and China. This means that the entire re-registration process is expected to require 120 + (50 × 40) + (2 × 120) = 2,360 hours of work for Siemens Healthineers for each product. The average hourly wage can be assumed

to be € #D /hr, meaning that the added costs related to the internal work with preparing re-registration documents would amount to #G (range: €1-10 million).

In addition to the necessary person-hours there will also be a filing fee in some countries. For example, in 2018 the US FDA 510(k) filings fee was US$10,566 per submission. Fees can range across the board, it is not possible to estimate without conducting the required paperwork and submitting this to the country as the fee is based on the change requested. This will not be known until the Design Change work is undertaken and largely completed per product.

Table 4–4: Estimate of OPE substitution cost at Siemens Marburg (R&D and re-registration cost) for Use #2	
Cost element	**Estimated cost**
Internal R&D (reformulation) cost	#E, G
Internal re-registration submission preparation cost	
Total cost	**(range: €1-10 million)**

As discussed for Use #1 above, a long R&D period without concurrent sales of the impacted IVD kits would simply mean that customers would rapidly be lost as they would seek alternative kits/analysers. Without a REACH Authorisation, there will most probably be no market left for Siemens Marburg to return to after a lengthy substitution period. Based on **Table 3-15**, the economic cost to Siemens Marburg would be € #E, G (range: €10-100 million) (PV, 4%, 2021-2032).

Use #3: Formulation of wash solutions

Siemens Healthineers are planning to reformulate #D under Use #3, representing two commercial products that are relevant to #D assays. The #D platform will be phased out, with a complete stop of supply of #D products, including the #D , in 2030. Even though only must be tested across all IVD kits, so the time to transition to is expected to take at least 12 years from the Sunset Date due to the prioritisation of other IVD kits and also the dependencies of this substitution work on the substitution efforts for other IVD kits manufactured in Marburg. During this period a total of #G FTEs are will be needed to complete the substitution process. The associated internal cost would be #E, G = #E, G (range: €1-10 million).

The cost of re-registrations can be estimated following the same approach as for Use #2 above for one product, leading to a re-registration submission preparation cost of € #E, G (range: €0.1-1 million).

As discussed for Uses #1 and #2 above, a long R&D period without concurrent sales of the impacted IVD kits would simply mean that customers would rapidly be lost as they would seek alternative kits/analysers. Without a REACH Authorisation, there will most probably be no market left for Siemens Marburg to return to after a lengthy substitution period.

Based on **Table 3-18**, the economic cost to Siemens Marburg from the loss of sales of wash solutions would be € #E (range: €10-100 million) (PV, 4%, 2021-2032). Very importantly, sales all IVD kits that are used on the analysers that depend on the use of the affected IVD wash solutions would be affected. For example, #D analysers cannot be operated without the #D #D that is manufactured in Marburg. Inability to sell the #D or DUs to use would mean that no #D kits could be sold and used either. **Table 3-20** shows that sales of the combined wash solutions and dependent IVD kits over the period 2021-2032 are projected to generate profits of #E (range: €1-10 billion) (PV, 4%, 2021-2032). This involves #D IVD kits made in Llanberis but also products made in Marburg and in the USA by Siemens Healthineers.

In short, it should be clear that inability to sell IVD wash solutions would have far reaching repercussions for the operation of the analysers that depend on these solutions.

Conclusion on economic feasibility of Alternative 1

Summary of economic cost

Table 4–5 summarises the analysis above. It is clear that the key economic cost would be the lost profit during the period of the implementation of an alternative substance or combination of substances. Particularly the absence of the IVD wash solutions from the market would have extensive detrimental impacts on Siemens Healthineers businesses due to the critical role they play in the operation of the relevant analysers.

Table 4–5: Summary of costs associated with the implementation of Alternative 1			
Cost element	**Use #1**	**Use #2**	**Use #3**
Internal R&D (reformulation) cost	Unspecified	#D (table)	[redacted]
Internal re-registration submission preparation cost	-	[redacted]	[redacted]
Downtime losses for Siemens Marburg	[redacted]	[redacted]	[redacted]
Indirect losses for Siemens Healthineers	-	-	[redacted]
Total cost (PV, 4%)	**€** [redacted]	**€** [redacted]	[redacted]

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

Availability of Alternative 1

The availability of potential alternative substances may vary since it seems very likely that no "universal" solution can be found for all IVD kits and wash solutions. 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 and can be sourced from several suppliers, other alternative substances have not passed the laboratory testing stage and therefore may not be available on the market. On the other hand, relatively small amounts of an alternative substance would be needed per year to substitute the OPEs. The amount of OPEs used in all three Applied for Uses will be ca. #A kg/y and of this the majority (#A kg/y) will be used in the formulation of the #D #D (under Use #3), for which no intention for reformulation exists. As such, market availability of the alternative substance might not prove to be a major stumbling block, regardless the identity of the alternative (unless it is an entirely novel solution).

The discussion above has explained the long timeframes that would be required for the implementation of substitutes for OPEs for each of the Applied for Uses. In case of IVD wash solutions (Use #3), the substitution of OPEs would need to be followed by testing with all IVD kits that can potentially be applied to the relevant analyser platforms.

Hazard and risk of Alternative 1

A general evaluation of an OPE free alternative kit reagent is very difficult, since the specific alternative is highly reagent specific. Whether or not an alternative reagent has less hazardous properties cannot be evaluated on a generic level as there is no "universal" solution for all Applied for Uses and for each of IVD kits and wash solutions within those Applied for Uses.

For the substances presented in **Table 4-3**, the available hazard classification information suggests a lower hazard profile compared to the OPEs used in Siemens Marburg's IVD kit reagents and wash solutions. More generally, it is to be expected that Siemens Healthineers would only switch to a safer detergent substance in comparison to OPEs.

Conclusions on Alternative 1

This alternative is an important component of the overall Siemens Healthineers REACH Response Plan for the phase out of OPEs, which aims to substitute OPEs in the majority of the IVD products that fall within the scope of the three Applied for Uses.

However, in the case of non-Authorisation of the continued use of OPEs, it would not be possible to implement this alternative for the following reasons:

- Substitution efforts would be lengthy. This would mean that the IVD kits and wash solutions undergoing OPE substitution would be kept off the market for several years;

- Profits losses due to unrealised sales of IVD kits during the substitution projects would be substantial. These would encompass not only the sales of the kits/wash solutions that would be subject to design change, but also numerous other kits the use of which would be impacted due to the unavailability of the needed accompanying wash solution; and

- Customers of Siemens Marburg would not be prepared to wait for years until the IVD kits and wash solutions they need are introduced onto the market free from OPE dependencies. Soon after the IVD kits/wash solutions became unavailable, customers would investigate, identify and migrate to a competitor platform (or abandon in-house testing and resort to outsourcing of testing) in order to maintain their diagnostic capabilities.

Overall, implementing alternative substances under conditions of non-Authorisation is not economically feasible.

4.3.2 Alternative 2: Relocation of relevant Siemens Marburg operations to a location outside of the EEA

This alternative considers the relocation of the Applied for Uses of OPE from the Siemens Marburg site to a site outside the EEA. Only non-EEA Siemens Healthineers manufacturing sites within the Laboratory Diagnostics division are considered within this scenario. These are primarily based in the USA, as they already have US FDA Registration as IVD manufacturing sites.

Substance ID and properties

Use #1: Isolation of proteins from recombinant cell cultures

Substance ID is not relevant for this use. The assumption is that the process will be performed in the same way as currently in Marburg. This means OPE will still be used in protein isolation.

Use #2: Formulation of IVD kit reagents

Substance ID is not relevant for this use. The assumption is that the process will be performed in the same way as currently in Marburg. This means OPE will still be used in the formulation of the same IVD kit reagents.

Use #3: Formulation of wash solutions

Substance ID is not relevant for this use. The assumption is that the process will be performed in the same way as currently in Marburg. This means OPE will still be used in the formulation of the #D [redacted] wash solutions.

Technical feasibility of Alternative 2

Outline of the likely relocation process and timeframe

To transfer each of the Applied for Uses out of the EEA would involve the following activities and estimated timeframes:

- Identification of a non-EEA Siemens Healthineers site with US FDA Registration to cover the types of uses/products manufactured and the capacity to take on all or some of the Marburg operations, i.e. cell extraction, reagent formulation and wash solution manufacture – anticipated timeframe of maximum 6 months;

- Pre-Submission Notification to US FDA regarding planned change in location of manufacture – involving significant upfront preparatory work to describe proposed change and could take up to 150 days for a US FDA response – anticipated timeframe of maximum 6 months;

- Transfer of production equipment to the site and re-validation of processes and products at the new site. This is a lengthy and strictly regulated process, involving Installation Qualification, Process Qualification and Operational Qualification – anticipated timeline of maximum 12 months; and

- If full IVD product manufacture was to be transferred, i.e. with all kit components transferred and not only the kit reagent, a Site Change Supplement would need to be submitted to the US FDA – anticipated timeline of maximum 12 months.

Re-registration activities will be triggered worldwide, especially if country of origin and/or legal manufacturer change. Place of manufacture is also registered in some countries. A change of the legal manufacturer would also cause a complete rework of the entire labelling (e.g. Box Labels, Bottle Labels, Instruction for use).

The overall potential timeframe in relation to this process would therefore be a minimum 36 months. Stockpiling the affected IVD products would not be an adequate solution. The shortest shelf-life of the OPE-dependent products associated with each Applied for Use has been reviewed and is confirmed to be 12 months. Generally, customers also will not accept product with a shelf-life of less than 12 months.

This would mean that the period during which customers would be unable to receive IVD products could be up to 30 months.

Some use-specific commentary is further provided below.

Use #1: Isolation of proteins from recombinant cell cultures

The key knowledge required for performing the Applied for Use relates to the specific recombinant cell culture and the exact protocol that needs to be followed. The production itself (cultivation and growth of the cells) is performed with standard laboratory equipment. The same applies for the

isolation itself. The space needed for these operations is also rather small. The purification of the #D is performed in a standard cooling chamber usually used in protein chemistry to avoid enzymatic activity that might lead to degradation. Such instrumentation already exists at other Siemens Healthineers production sites. As a result, the operation could be implemented in another laboratory without significant technical obstacles. However, as noted in the general discussion above, the regulatory activities that would be required in order to validate the relocation of production would take a substantial amount of time.

Siemens Healthineers could take some practical measures to mitigate impacts:

- #D: Siemens Healthineers could aim to build up a stock of the protein to mitigate disruption to the supply to customers (this would also mean that the volume of OPE used would initially increase). Importantly, for the end user, the relocation of the production process of the #D to a non-EEA location would not have noticeable consequences. Since the protein itself does not contain any OPE anymore, after processing it could be imported to the EEA and used without any technical implications;

- #D: the situation would be slightly different to that described for the #D. This protein is not OPE-free after processing in Marburg but is shipped with a certain OPE content in the #B to the production site of Siemens Llanberis in the UK. Here it is used in a coating process of a carrier material that also relies on the presence of OPEs. So, the OPE has an extended function also to protect the #D protein is this subsequent use. In the coating process, the OPE is removed from the process so the resulting product (the bead made in Llanberis) will not contain OPE. Thus, it has to be concluded that in principle a shift of the production process and the isolation process would be possible but its realisation depends on further subsequent uses in the supply chain. These uses would either

  - Need to be outsourced to a non-EEA location too, or
  - Rely on a separate REACH Authorisation (for which Siemens Llanberis is currently applying for separately).

  If either of these scenarios materialised, the products produced from the #D could in principle be used by end users in the EEA, because they also do not contain OPEs anymore. Still, in practice they would face the problem that the resulting IVD kit that contains the #D-coated bead would need to be applied on an #D analyser system that is operated with an IVD wash solution that contains OPE (Applied for Use #3). Thus, a REACH Authorisation for the continued use of the #D wash solution is required for the end user to continue the operation of their #D analysers without interruption. This is Applied for Use #5.

  It would perhaps be considered that both the relevant Marburg and Llanberis operations would be relocated to a non-EEA facility. However, this could trigger significant re-registration activities if the legal manufacturer(s) and / or Country of Origin had to be changed. This could be avoided as only part of the production process would have to be relocated for the #D products. Still, such relocation would be dependent on the downstream use of the #D wash solution being authorised (Use #5).

Use #2: Formulation of IVD kit reagents

Formulation of IVD kit reagents is performed with standard laboratory equipment (scales, stirrers, vessels, etc.). The packaging is performed on filling lines that are not specific to a specific reagent (several are packaged on such a line) but rather to the types of vials used. Nevertheless, the filling line can be adapted to different types of vials. Since comparable packaged reagents are already

imported from the US sites into the EEA, the relocation of the formulation process to a non-EEA facility would appear feasible without significant obstacles from a technical perspective.

Since the formulation of IVD kit reagents involves the use of OPEs with the intention that these remain in the produced reagents until their end-use on an analyser at a customers' site, this alternative does not provide an alternative for Applied for Use #4 by end users in the EEA. These customers could not continue to use kit reagents currently formulated in Marburg after a relocation of manufacture outside the EEA unless an Authorisation for Applied for Use #4 was also granted.

As for Use #1 above, relocation of Use #2 to a non-EEA facility could trigger significant re-registration activities if the legal manufacturer(s) and / or Country of Origin had to be changed. These could not be avoided if the entire production is moved to another country. Therefore, such relocation could not be given real consideration.

Use #3: Formulation of wash solutions

Formulation of the IVD wash solution is performed in a larger vessel with fixed pipes and a stirrer. It is not specific to each IVD wash solution but can be used for all solutions that are formulated in larger volumes than kit reagents. The formulation vessel is connected to a filling line via fixed pipes and hoses so the IVD wash solution can directly be filled into vials for shipment to customers. As a result, the operation could be implemented in another laboratory without significant technical obstacles.

Again, as for Use #2, the aim of the addition of OPEs to the washing solution is to mediate a function in the end use. Therefore, end users in the EEA would not be able to perform diagnostics that are linked to the OPE-containing wash solutions under consideration (#D), unless the downstream use of these IVD wash solutions (Use #5) is authorised separately.

As for Uses #1 and #2 above, relocation of Use #3 to a non-EEA facility could trigger significant re-registration activities if the legal manufacturer(s) and / or Country of Origin had to be changed. These could not be avoided if the entire production is moved to another country. Therefore, such relocation could not be given real consideration.

Economic feasibility and economic impacts of Alternative 2

As described above, the overall potential timeframe in relation to this process could be ca. 36 months. Stockpiling the affected IVD products would not be an adequate solution due to the shelf-life of the impacted IVD products and also due to the fact that for Uses #2 and #3 stockpiling would not resolve the issue of the continued use of OPE by the customers (separate Authorisations would still be required). The period during which customers would be unable to receive IVD products from Marburg (via the European Distribution Centre) could be up to 30 months.

If the disruption to the supply of these products were to be so long-term, customers who are currently using the impacted analysers (see full range of impacted analysers per Applied for Use in **Table 3-21**) would need to make alternative arrangements and would have to seek alternatives. These alternatives might include:

- Moving to alternative analysers, i.e. third-party platforms – downstream users need at least 6 months for the validation of a new analyser. If disruption to the supply of Marburg-made IVD kits and wash solutions were to last substantially longer, customers would be inclined to look into this option. Importantly, it is not known if any competitor analysers diagnose the identical set of

diseases as the Siemens Healthineers ones, so multiple competitor analysers might be required to provide the same range of diagnostic services; or

- Outsourcing of diagnostic testing services – a theoretical, solution would be that Siemens Marburg's customers explore the possibility of outsourcing their diagnostic tests, possibly in the short term. Whether this is possible within the EEA (with platforms/kits that do not rely on OPE or are covered by a third-party Authorisation) or outside the EEA, it is not possible to ascertain. It is also not clear whether capacity exists either within or without the EEA or how practical and costly such outsourcing might be (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)).

Ultimately, if Siemens Marburg initiated the relocation of its manufacturing activities, it would engage in a lengthy process which would keep its IVD products off the market for a period of time too long for the customers to persevere. Customers would move to alternative means of delivering their diagnostic services (certainly hospitals could not afford to wait until Siemens Healthineers sorted out its manufacturing relocation issues). Once such operation changes and investments would be made, those customers would not return to Siemens Healthineers' analysers and IVD products. In other words, absence from the market for up to 30 months would mean that the market would be lost.

Therefore, the direct cost Alternative 2 would include:

- **Cost of relocation**: this would include the engineering/start-up cost of re-location itself and the regulatory cost of re-registrations. The latter could not be avoided, particularly for Uses #2 and #3, as it would not be possible to keep Germany as the country of origin. The engineering/start-up cost of re-location can be estimated to cost between € #E [redacted] per Applied for Use; and

- **Loss of profit due to loss of market share:** Siemens Marburg would lose the entire profit from sales of the IVD kits and wash solutions manufactured under Uses #1, #2 and #3. As a matter of fact, Siemens Healthineers typically maintains a very limited stock of kits (for some kits only [redacted] Days Inventory on Hand (DIOH) is maintained at the EDC), thus in the event of non-Authorisation sales of the impacted IVD kits would practically cease soon after the Sunset Date. **Importantly, for sales of IVD kits and wash solutions to EEA-based customers (Use #2 and #3) to materialise, an Authorisation of these downstream users would be required under the separately Applied for Uses #4 and #5**.

The associated costs in terms of Present Value of profits that would not materialise would be those shown below, These are based on estimates presented in **Table 3-11**, **Table 3-15** and **Table 3-18**.

Table 4-6: Direct economic costs of Alternative 2 for Siemens Marburg – Uses #1, #2 and #3				
Cost element	**NPV, € Use #1 [redacted] kits* (2021-2029)**	**NPV, € All Use #2 kits (2021-2032)**	**NPV, € All Use #3 wash solutions (2021-2032)**	**Total, €**
Cost of relocation	#E (table)	[redacted]	[redacted]	[redacted]
Loss of profit from sales to EEA customers	[redacted]	[redacted]	[redacted]	[redacted]
Loss of profit from sales to Non-EEA customers	[redacted]	[redacted]	[redacted]	[redacted]
Total direct cost	[redacted]	[redacted]	[redacted]	[redacted]
* profits from sales of [redacted] IVD kits are allocated to Siemens Llanberis and thus are not included here to avoid double-counting				

The overall cost from effectively losing these markets completely would be over #E [redacted] (range: €100-1,000 million).

The collapse of Siemens' Marburg's manufacturing operations would have significant repercussions for other Siemens Healthineers operations, as summarised in **Table 4-7**.

Table 4-7: Indirect economic costs of Alternative 2 for Siemens Healthineers – Uses #1, #2 and #3		
Applied for Use	**Indirect impacts on Siemens Healthineers' operations**	
Use #1	#D [redacted]	Without manufacture and sale of several IVD kits which are used on a range of analysers such as #D [redacted], sales of OPE-independent kits for these analysers would also be impacted. The extent of the impact and the ultimate effect on the marketability and future use of these analysers is uncertain
	#D	Siemens Llanberis would also be affected since the #D protein is the main component of the #D [redacted] kit
Use #2	Without manufacture and sale of several IVD kits which are used on a range of analysers such as #D [redacted], sales of OPE-independent kits for these analysers would also be impacted. The extent of the impact and the ultimate effect on the marketability and future use of these analysers is uncertain	
Use #3	#D [redacted]	Without manufacture and sale of the #D [redacted] wash solution, #D [redacted] analysers could no longer be used. This means that the operations of Siemens Llanberis would cease. As described in **Table 3-20**, the Present Value profit that would not materialise if #D [redacted] wash solutions and kit sales stopped would be #E [redacted] (range: €0.1-1 billion). These losses would be allocated to Siemens Llanberis and Siemens Healthineers USA (Los Angeles)
	#D [redacted] wash solutions	Without manufacture and sale of the #D [redacted] wash solutions, #D [redacted] analysers would no longer be possible to operate. As such, sales of all IVD kits used on these analysers would cease. As described in **Table 3-20**, the Present Value profit that would not materialise if #D [redacted] wash solutions and dependent kit sales stopped would be ca. #E [redacted] (range: €1-10 billion)

It is clear that relocation of Siemens' Marburg's operations would not be economically feasible for any of the Applied for Uses.

Availability of Alternative 2

Since Siemens Healthineers already has production sites for products similar to the ones produced in Marburg and the equipment is not specialist or unique, comparably small it seems reasonable that the alternative could be implemented in a non-EEA location as well.

Hazard and risk of Alternative 2

Since OPEs will be used in the same way as at the Marburg site shifting the three uses to non-EEA locations will not change the overall global risk of the uses. While the local risk in Marburg is eliminated the local risk at the alternative production sites will be increased in a corresponding fashion. Some further considerations on the risk per Applied for Use will be given in detail below.

Use #1: Isolation of proteins from recombinant cell cultures

In the case of the #D proteins, it can be assumed that there would be no changes to the overall risk in the EEA, beside the local risk reduction at the Marburg site.

The shift of the production of the #D protein does eliminate the risk in Marburg but the risk from subsequent use at the Siemens Llanberis production site would in principle remain the same. However, if implementation of a relocation strategy would precipitate the collapse of the #D Business Line, then the associated use of OPE and release of 4-tert-OP to the environment in Llanberis would cease.

Use #2: Formulation of IVD kit reagents

The risk on the local level in Marburg would be eliminated but the risk in the EEA from subsequent uses of the IVD kit reagents (if authorised) would remain. Non-EEA uses would not be affected; therefore, the risk would remain stable. However, if implementation of a relocation strategy would precipitate the permanent cessation of sales of the impacted IVD kits, then the associated use of OPE and release of 4-tert-OP to the environment at the customers' sites would cease.

Use #3: Formulation of wash solutions

The risk on the local level in Marburg would be eliminated but the risk in the EEA from subsequent uses of the IVD wash solution (if authorised) would remain. Non-EEA uses would not be affected; therefore, the risk would remain stable. However, if implementation of a relocation strategy would precipitate the collapse of the #D Business Line and the retirement of the #D analysers (#D), then the associated use of OPE and release of 4-tert-OP to the environment at the customers' sites would cease.

Conclusions on Alternative 2

A shift to non-EEA regions of the three Applied for Uses would not pose an insurmountable challenge from a technical perspective. Given that the activities involved in transferring each of the Applied for Uses outside of the EEA would involve a potential timeframe of ca. 36 months, coupled with the far shorter shelf-life of the products which would prevent stockpiling of IVD products to cover the supply gap, this alternative could not be an economically feasible option.

Customers, and ultimately patients awaiting results in the healthcare system, would lose supply of the IVD products for an unacceptably long period of time, potentially up to 30 months in some cases. It is the expectation that customers would be forced to move to alternative platforms or perhaps out-

source tests at significant cost in the short-term, and then would move on to new platforms to overcome the supply gap.

Ultimately, Siemens Healthineers would invest money and resources towards the relocation and validation of the manufacturing process involved in the three Applied for Uses only to find out that there would be no market left for the non-EEA-made products to be sold to.

Importantly, the future of these three Applied for Uses is also dependent on the outcome of separate AfAs submitted by Siemens Llanberis and Siemens Marburg's Applied for Uses #4 and #5.

4.3.3 Alternative 3: Shutdown of the Siemens Marburg operations involving the use of OPE

This alternative covers the option that Siemens Marburg ends its operations that involve OPEs without replacing it by one of the other discussed alternatives.

Substance ID and properties

Substance ID is not relevant for this alternative.

Technical feasibility of Alternative 3

Technically, cessation of Marburg activities that are linked with OPEs is not challenging, although the impact would be significant.

As described above, if these operations stopped, other operations of Siemens Healthineers would be impacted, as shown in **Table 4-7**. The impact would be particularly significant for those analysers and their accompanying IVD kits (whether they depend or not on OPE) which rely on the continued use of IVD wash solutions, namely [redacted]. All end users of these test systems would immediately need to stop their diagnostic activities due to a loss of supply of the wash solutions as these cannot be replaced by other market actors.

Economic feasibility and economic impacts of Alternative 3

The economic cost of Alternative 3 would follow the pattern shown for Alternative 2 above with a key difference: the engineering/start-up cost of relocation would not arise.

Thus, the direct cost to Siemens Marburg from the cessation of the use of OPE in the three Applied for Uses would be as shown below. The overall direct cost is estimated at #E [redacted] (PV, range: €0.1-1 billion).

Table 4-8: Direct economic costs of Alternative 3 for Siemens Marburg – Uses #1, #2 and #3

Customer group	NPV, € Use #1 [redacted] proteins (2021-2029)	NPV, € All Use #2 kits (2021-2032)	NPV, € All Use #3 wash solutions (2021-2032)	Total, €
Loss of profit from sales to EEA customers	#E (table)	[redacted]	[redacted]	[redacted]
Loss of profit from sales to Non-EEA customers	[redacted]	[redacted]	[redacted]	[redacted]
Total direct cost	[redacted]	[redacted]	[redacted]	[redacted]

As far as indirect costs are concerned, those presented in **Table 4-7** would similarly apply to Alternative 3 and amount to a significant loss due to the indirect impacts on profits from sales of IVD kits that depend on the continued availability of IVD wash solutions (range: €1-10 billion).

Overall, Alternative 3 is not economically feasible for any of the three Applied for Uses.

Availability of Alternative 3

Not relevant for this alternative.

Hazard and risk of Alternative 3

This alternative would eliminate risks to the environment associated with releases of 4-tert-OP arising from the use of OPEs under Applied for Uses #1, #2 and #3 in Marburg.

Conclusions on Alternative 3

To shut down all activities that are linked to the use of OPEs in Marburg would lead to significant losses in the diagnostic capacity in the health system in the EEA. Similar to Alternative 2, this alternative would lead to significant economic losses for Siemens Marburg, Siemens Llanberis and more widely Siemens Healthineers. Ultimately however, Alternative 3 could prove to be less costly than Alternative 2 as it would avoid the predictably ineffective relocation of the Marburg uses of OPEs to non-EEA facilities.

4.3.4 Alternative 4: Shutdown of the entire Siemens Marburg IVD product operations

This alternative covers the option that Siemens Marburg ends its entire IVD product manufacturing operations.

Substance ID and properties

Substance ID is not relevant for this use.

Technical feasibility of Alternative 4

Technically-speaking, stopping of all IVD product manufacturing activities could be carried out; however, the repercussions across all operations of Siemens Healthineers and the healthcare system would be immense. OPE-dependent products account for only #D % of Siemens Marburg profits, meaning that the OPE-independent products are far more important for Marburg and the wider Siemens Healthineers operations than the products within the scope of Applied for Uses #1, #2 or #3.

Economic feasibility and economic impacts of Alternative 4

Section 3.2.5 explained that in 2017 the profit made by Siemens Marburg from global sales of OPE-independent IVD products was ca. #E (range: €0.1-1 billion). Assuming that the volume of sales of these kits does not change in the period 2021-2032, a Present Value profit of #E (range: €1-10 billion) can be estimated (4% discount rate). This profit would be lost under Alternative 4. In addition, Siemens Llanberis' operations would also be discontinued and the wider global operations of Siemens Healthineers would come under serious risk.

Overall, Alternative 4 is economically infeasible.

Availability of Alternative 4

Not relevant for this alternative.

Hazard and risk of Alternative 4

This alternative would eliminate risks to the environment associated with releases of 4-tert-OP arising from the use of OPEs under Applied for Uses #1, #2 and #3 in Marburg.

Conclusions on Alternative 4

Alternative 4 would have extreme economic consequences for all operations of Siemens Healthineers. The economic cost of this alternative is extremely high and therefore entirely disproportionate to the impacts on the environment from the continued use of OPEs in Marburg. Siemens Marburg would not contemplate the shutdown of its entire operations in response to non-Authorisation.

4.4 The most likely non-use scenario

Based on the analysis presented above, the most likely "Non-use" scenario would be based on Alternative 3, i.e. the shut-down of the parts of Siemens Marburg manufacturing which involve the use of OPEs. The justification for this is:

- Alternative scenarios 1 and 2 would result in the cessation of the supply of IVD products for a period of time during which it is anticipated that all the market share relating to these products would be irrevocably lost;
- Alternative 2 would additionally entail a certain cost for the unsuccessful relocation of Siemens Marburg's operations to non-EEA facilities; and
- Alternative 4 would have an economic cost too high to contemplate as a realistic proposition.

5 IMPACTS OF GRANTING AUTHORISATION

5.1 Economic impacts – benefits of continued use

5.1.1 Introduction

Under the "Non-use" Scenario, Siemens Marburg would cease its use of OPE for protein isolation, manufacture of reagents and manufacture of wash solutions. These operations would not be relocated to non-EEA facilities and the associated sales, profits and customer base would be lost.

The full range of impacts that would be avoided if an Authorisation was granted and which will be presented below can be summarised as follows:

Table 5-1: Overview of (direct) economic benefits for the Siemens Marburg supply chain under the "Applied for Use" Scenario

Impacted stakeholder	Use #1	Use #2	Use #3
Siemens Marburg	Profits from sale of [redacted] #D (table) IVD kits would be preserved	Profits from sale of [redacted] OPE-dependent products would be preserved	Profits from sale of [redacted] OPE-containing IVD wash solution products would be preserved
Siemens Llanberis	Profits from sale of [redacted] IVD kits would be preserved	No direct impact	Profits from sale of all [redacted] IVD kits solutions would be preserved
Siemens Healthineers operations in the USA	Profits from sales of [redacted] analysers would be protected from losing access to several assays	Profits from sales of [redacted] analysers would be protected from losing access to several assays	Profits from sales of [redacted] analysers would be protected from losing access to the critical wash solutions Profits from sales of kits used in the above analysers would be preserved
EEA-based manufacturers of Siemens Healthineers analysers	Profits from sales of [redacted] analysers would be protected from losing access to several assays	Profits from sales of [redacted] analysers would be protected from losing access to several assays	Sales of [redacted] analysers would be preserved – without a wash solution the analysers would not be operational
Suppliers to Siemens Marburg and Siemens Llanberis	Profit associated with sales of products and services to Siemens Marburg associated with this "Applied for Use" would be preserved	Profit associated with sales of products and services to Siemens Marburg associated with this "Applied for Use" would be preserved	Profit associated with sales of products and services to Siemens Marburg and Siemens Llanberis associated with this "Applied for Use" would be preserved
Customers of Siemens Marburg	Continued access to a range of IVD kits that rely on OPEs and which will allow full functionality for a range of analyser platforms: [redacted]	Continued access to a range of IVD kits that rely on OPEs and which will allow full functionality for a range of analyser platforms: [redacted]	Continued ability to operate [redacted] analysers which depend on the use of the two wash solutions made in Marburg

Table 5-1: Overview of (direct) economic benefits for the Siemens Marburg supply chain under the "Applied for Use" Scenario			
Impacted stakeholder	**Use #1**	**Use #2**	**Use #3**
	[redacted]		
Customers of Siemens Llanberis	Continued access to the [redacted] IVD kit that relies on OPEs and which will allow full functionality for the [redacted] analysers	No direct impact	Continued ability to operate [redacted] analysers which depend on the use of the [redacted] IVD wash solution made in Marburg

Most of the products within Uses #1-3 contain OPEs, (the #D protein, IVD kit reagents and IVD wash solutions), which means that the downstream users would also have to obtain an Authorisation for the continued use of these IVD products in the EEA. Use #4 and Use #5 applied for by Siemens Marburg cover end use of the reagents and the wash solutions, while the use of the #D protein in the relevant #D IVD kit is covered by a separate AfA submitted by Siemens Llanberis.

The inter-dependencies of the products make it more complicated to accurately track and allocate the impacts to the correct entity. The profits of sales of IVD kits is allocated to the manufacturer of the end product. This implies that the profits from sales of the #D kit, which depends on the #D carried out by Siemens Marburg, will be allocated to the manufacturer of the #D kit, that is, Siemens Llanberis. The costs to human health and the environment and social impacts will only cover effects within the EEA.

The chosen "Non-use" Scenario is Alternative 3, which will form the basis for the calculations of benefits and costs to society from granting an Authorisation. The main assessment periods used are the requested review periods, 9 years, 12 years and 12 years, for Use #1, #2 and #3 respectively.

5.1.2 Economic Impacts for Siemens Marburg

Use #1

As described in Section 4.3.3, cessation of the manufacture of the IVD kits within the scope of Use #1 would mean the loss of future profits with a Present Value of #E (2021-2029) (range: €10-100 million). #D, E [redacted]. As such, future business prospects would be affected on the global scale rather than within the limits of the EEA where the REACH Regulation applies.

Therefore, continued use of Triton™ X-100 would allow Siemens Marburg to generate substantial future profits from the sale of the relevant #D® IVD kits.

It is important to note that:

- Being unable to sell certain kits would well impact the sales of other kits too, as specific customers might have particular interest/need in the impacted ones and therefore this could lead them to abandon their analysers, thus causing further loss of profit for Siemens Marburg; and

- The #D platform encompasses #D analysers. If the availability of key IVD kits used on them is impacted #D, the prospects of future sales could be very much damaged (least of all due to reputational impacts).

Use #2

As described in Section 4.3.3, cessation of the manufacture of the IVD kits reagents within the scope of Use #2 would mean the loss of future profits with a Present Value of #D (2021-2032) (range: €10-100 million). #D. As such, future business prospects would be affected on the global scale rather than within the limits of the EEA where the REACH Regulation applies.

Therefore, continued use of Triton™ X-100 and Triton™ X-405 would allow Siemens Marburg to generate substantial future profits from the sale of the relevant #D IVD kits.

The comments made above on indirect effects arising from the removal of certain IVD kits from the market would also apply here.

Use #3

As described in Section 4.3.3, cessation of the manufacture of the three IVD wash solutions within the scope of Use #3 would mean the loss of future profits with a Present Value of #D, E (2021-2032) (range: €10-100 million). #D. As such, future business prospects would be affected on the global scale rather than within the limits of the EEA where the REACH Regulation applies.

More importantly, if wash solutions cannot be sold to the users of these analysers, no other relevant IVD kit made in Marburg (with or without the use of OPEs) could be sold. The impacted analysers could not be operated without a wash solution and therefore the analysers would become non-operational and sales of all kits needed on #D analyser systems would stop. It can be estimated using the figures shown in **Table 3-20** that the Present Value of profits made from sales of all #D wash solution-dependent kits for the two analysers in the period 2021-2032 at € #D, E (range: €1-10 billion).

Therefore, continued use of Triton™ X-100 would allow Siemens Marburg to generate substantial future profits from the sale of the relevant #D IVD kits.

All Applied for Uses

It is possible that Siemens Marburg may face penalties if the company becomes unable to distribute products it is contracted to provide. However, this will 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 the affected products from a contractual perspective. In this sense, the estimates provided above may underestimate the overall economic impact on Siemens Marburg.

Finally, the discussion above must also be considered to cover the Siemens Healthineers European Distribution Centre in Duisburg.

5.1.3 Economic Impacts for other Siemens operations in the EEA

Use #1

Economic impacts for Siemens Llanberis

The #D kit is exclusively used with the #D analysers. In the "Non-use" Scenario, the process of isolating the #D protein would stop. This protein is normally shipped with OPE in the #B, D to Siemens Llanberis in Wales for further processing (bead washing/coating where the final product does not contain OPEs). Even if Siemens Llanberis was granted an Authorisation to continue to use OPE (under its separate AfA), the "Non-use" Scenario for Use #1 of Siemens Marburg would mean that sales of the #D kit by Siemens Llanberis would not materialise after 2021.

Naturally, if Siemens Llanberis was not granted an Authorisation, use of the OPE-containing #D protein in Llanberis would cease anyway and therefore no impact would arise under the "Non-use" Scenario for Siemens Marburg's Use #1. The Present Value of profits made by Siemens Llanberis in the period 2021-2029 is as shown below.

Table 5-2: Use #1 - Net present value of profits from sales of #D kits by Siemens Llanberis, 2021-2029, 4% discount

Customer group	NPV, #D kits
EEA customers	#E (table)
Non-EEA customers	
All customers	

Therefore, the benefits of continued use of OPE in Marburg under Use #1 for Siemens Llanberis would be:

- If Siemens Llanberis is granted an Authorisation for its own use of OPE, #E (range: €1-10 million, Present Value, 2022-2029); and

- If Siemens Llanberis is not granted an Authorisation for its own use of OPE, nil (i.e. the use of OPE in Marburg for the manufacture of the #D protein would be pointless and loss of profit would not be associated with the Siemens Marburg "Non-use" Scenario).

Economic impacts for other Siemens Healthineers operations (sales of analysers)

If the use of OPE in Marburg under Use #1 was allowed to continue, profits from sales of #D analysers would be protected from losing access to several assays. Here, only sales to EEA-based customers are considered, however, sales will take place outside the EEA too, therefore, the economic benefits that are quantified below underestimate the real benefit for the EEA-based manufacturer and Siemens Healthineers, the re-seller of the analysers.

As shown in **Table 3-24**, Use #1 is associated with the future sales of #D (range: 1,000-10,000) analysers to EEA customers in the period 2021-2029 with an associated Present Value profit of ca. € #D, E (range: €10-100 million, estimate only due to overlaps between Applied for Uses). Sales to non-EEA customers will be #D. This profit could be in jeopardy if the sale of #D relevant IVD kits are impacted. The exact extent of impacts cannot be estimated so the profit figure

shown above should be assumed to be the maximum benefit achieved through the continued use of OPE in Marburg under Applied for Use #1.

Use #2

Economic impacts for Siemens Llanberis

The formulation of reagents does not affect Siemens Llanberis' operations, so no additional benefits are expected.

Economic impacts for Siemens EDC

It is assumed that as long as Uses #4 and #5 (separately applied for by Siemens Marburg on behalf of its DUs) are granted an Authorisation and the use of OPE-dependent IVD products in the EEA continues, the Siemens EDC (part of the Siemens Marburg legal entity) would not be materially impacted, as the volume of IVD products distributed by the EDC would remain largely unaffected.

Economic impacts for other Siemens Healthineers operations (sales of analysers)

If the use of OPE in Marburg under Use #2 was allowed to continue, profits from sales of #D analysers would be protected from losing access to several assays #D . Here, only sales to EEA-based customers are considered, however, sales will take place outside the EEA too, therefore, the economic benefits that are quantified below underestimate the real benefit for the EEA-based manufacturer and Siemens Healthineers, the re-seller of the analysers.

As shown in **Table 3-24**, Use #2 is associated with the future sales of #D (range: 1,000-10,000) analysers to EEA customers in the period 2021-2032 with an associated Present Value profit of ca. € #D, E (range: €10-100 million, estimate only due to overlaps between Applied for Uses). Sales to non-EEA customers will be #C, D . This profit could be in jeopardy if the sale of #D relevant IVD kits are impacted. The exact extent of impacts cannot be estimated so the profit figure shown above should be assumed to be the maximum benefit achieved through the continued use of OPE in Marburg under Applied for Use #2.

Use #3

Economic impacts for Siemens Llanberis

As previously explained, the #D #D that is made in Marburg needs to be used with every test conducted on #D analysers. If the #D is not available, there can be no #D IVD kit sales nor any #D analyser sales. In other words, if Use #3 of Siemens Marburg was not authorised, the #D business line would collapse and the Siemens Llanberis plant would #D .

As is described in the separate Siemens Llanberis AfA, the profit made by the Llanberis plant from sales of all #D kits (whether these depend on OPE or not) is substantial. Based on Tables 3-6 and 3-7 of the corresponding AoA-SEA document, the following table can be generated. This shows that the continued use of OPE by Siemens Marburg under Use #3 would benefit Siemens Llanberis to a tune of #D, E (range: 0.1-1 billion) in the period 2021-2029, even if Siemens Llanberis itself was granted an Authorisation for its own continued use of Triton™ X-100.

Table 5-3: Net present value of profits from sales of [redacted] IVD kits by Siemens Llanberis, 2021-2029, 4% discount (rounded)			
Customer group	**OPE-dependent kits made in Llanberis**	**OPE-independent kits made in Llanberis**	**Total Siemens Llanberis sales**
EEA customers	#E (table)	[redacted]	[redacted]
Non-EEA customers	[redacted]	[redacted]	[redacted]
All customers	[redacted]	[redacted]	[redacted]

If Siemens Llanberis was not granted an Authorisation for its own Applied for Use of OPE, the benefit from the continued use of OPE in Marburg would still be substantial at up to #E (range: €0.1-1 billion) as Siemens Llanberis would aim to continue selling OPE-independent IVD kits. However, without the OPE-dependent #D IVD kits on sale, the assumption that the sales of the remaining #D IVD kit portfolio would continue without a discernible impact is overoptimistic.

Economic impacts for other Siemens Healthineers operations (sales of wash solution-dependent kits and analysers)

The following table summarises information from **Table 3-20** and **Table 5-3** and shows that over the key period of 2021-2029, sales of #D kits that originate from Siemens Healthineers USA (i.e. beyond Llanberis) are estimated at #D, E (range: €0.1-1 billion) as Present Value. This projected profit would be preserved if Applied for Use #3 was authorised.

Table 5-4: Net present value of profits from sales of [redacted] IVD kits by Siemens Healthineers, 2021-2029, 4% discount (rounded)			
Customer group	**Total sales of all #D [redacted] IVD wash solutions and dependent kits**	**Total Siemens Llanberis sales**	**#D kit sales from the USA**
EEA customers	#D (table)	[redacted]	[redacted]
Non-EEA customers	[redacted]	[redacted]	[redacted]
All customers	[redacted]	[redacted]	[redacted]

If the use of OPE in Marburg under Use #2 was allowed to continue, profits from sales of #D [redacted] analysers would be protected from losing access to the critical wash solutions their operation relies upon. Here, only sales to EEA-based customers are considered, however, sales will take place outside the EEA too, therefore, the economic benefits that are quantified below underestimate the real benefit for the EEA-based manufacturer and Siemens Healthineers, the re-seller of the analysers.

As shown in **Table 3-24**, Use #3 is associated with the future sales of #D (range: 1,000-10,000) analysers to EEA customers in the period 2021-2032 with an associated Present Value profit of ca. € #D, E (range: €10-100 million, estimate only due to overlaps between Applied for Uses). Sales to non-EEA customers will be #C, D lower. This profit would certainly be lost if relevant IVD wash solutions are impacted. This profit figure shown above is the benefit achieved through the continued use of OPE in Marburg under Applied for Use #3.

5.1.4 Economic impacts on EEA-based manufacturers of Siemens Healthineers analysers

Section 3.2.4 and Appendix 2 explain that the manufacture of #D (Use #2), #D (Use#2), #D (Uses #1, #2 and #3) and #D (Use #2) takes place in the EEA, more specifically in #D. Of these analysers, #D is made by Siemens Healthineers with the remaining analysers made by external vendors.

Under the "Non-use" Scenario their wholesale supply of these analysers to Siemens Healthineers after the Sunset Date would be impacted. As Siemens Marburg is not privy to the profit margins of these companies these impacts cannot be quantified. However, it is worth reiterating the number of these analysers that are expected to be sold globally in the period 2021-2032:

- Use #1: #D;
- Use #2: #D (range: 1,000-10,000) analysers; and
- Use #3: #D.

5.1.5 Economic Impacts for Siemens' suppliers

Suppliers of raw materials for IVD product manufacture

The suppliers of Siemens Marburg are likely to experience reduced profits, if they can no longer supply their goods to the Marburg plant. **Table 3-27** has provided a list of supplied materials and indicates that the suppliers are mostly based in the EEA.

The total lost profit for the EEA suppliers is not known and not included in the total benefits estimated below. This will clearly lead to an underestimation of the total benefits to society, but the size of the underestimation has not been possible to establish.

Original Equipment Manufacturer (OEM) suppliers

#D IVD kit reagents #D #D which fall within the scope of Use #2 of this AfA are products that are manufactured by #D. #D uses Triton™ X-100 in the formulation of the reagents and is submitting a separate AfA that covers the manufacture of these #D (and any other associated) IVD kit reagents. #D would not be impacted under the "Non-use" Scenario for Siemens Marburg's Applied for Uses #1, #2 or #3, as OPE is not used for these products in Marburg. On the other hand, #D would be impacted if an Authorisation were not to be granted to Siemens Marburg for downstream Use #4, as then the end users would not be permitted to continue using the OPE-containing reagents in the EEA and in turn Siemens Marburg could not sell them and thus #D would have to abandon the EEA market. #D would thus be impacted even if its own internal use of OPE would be authorised.

Details on profit generated by #D from the sale of these IVD kits to Siemens Marburg is not available to the applicant and can only be sought within #D's separate AfA documents.

On the other hand, Siemens Marburg is supporting #D's Authorisations by providing (through an independent third-party acting as a trustee) confidential information on the likely impacts on Siemens Healthineers' operations from non-Authorisation of #D's own use of Triton™ X-100. This confidential information which is intended to be reviewed alongside #D's AfA documents is presented in Appendix 5 (Section 13) at the end of the present AoA-SEA document.

5.1.6 Economic impacts for Siemens Marburg customers

Introduction to the "Non-use" Scenario

The use of the OPE-dependent products is covered in Use #4 and Use #5 of Siemens Marburg's set of Applications for Authorisation. However, the customers would be affected by non-Authorisation of Applied for Uses #1-3, even if Siemens Marburg were to obtain an Authorisation for the customers' own downstream use of OPEs under Uses #4 and #5, as they are relying on the supply of these products from Siemens Marburg.

Analysers/systems are either 'Open' or 'Closed' channel, which indicates whether a third-party IVD kit could technically be used on that analyser should one be specifically designed for that purpose by a competitor. It is possible that for some of the 'open channel' analyser systems, e.g. the #D platforms, there may be third-party IVD kits available which are OPE-free and could be used on the system but these are used at the customer's responsibility. Closed systems, e.g. the #D platform will not work with any IVD kits other than those designed by Siemens Healthineers. Typically, the #D systems are open while the #D systems tend to be closed (although there are exceptions).

However, while this possibility to use third-party IVD kits exists on the 'open channel' analysers, there are some key factors to note:

- It is not known by Siemens Healthineers which of the OPE-containing IVD kits have OPE-free (if any) alternatives providing the same diagnostics tests – customers would have to conduct market research to identify alternative IVD kits and determine whether they contain OPEs. This would likely take some time, thus delaying testing of patient samples and provision of results. In the immediate aftermath of non-Authorisation, emergency tests (e.g. those requiring a 1-hour turnaround time) would be severely delayed;

- Searching for alternative supplier reagents may be locally difficult, as not all reagents are available in every country (i.e. through local suppliers);

- If any third-party IVD kits providing the same diagnostic tests were sourced, customers would be responsible for performing validation of third-party tests on the analysers and confirming performance parameters. This can take a significant amount of time and delay results, particularly in larger labs where larger groups of people may need additional training. Alternative IVD kits could produce different reference ranges, which are used by healthcare providers/physicians to assess results and provide diagnoses. New reference ranges mean a significant communication exercise throughout the healthcare system to ensure results are not mis-read and thus incorrect diagnoses are made;

- Adaptation of the reagents to the system ("method") only works with specific assay parameters that can require a significant development and validation effort by the customer. The IVD compliance development, testing and documentation typically takes 6-24 months[19], depending on the complexity of the method. Of course, after having developed the new methods, a correlation of the new vs. the old (discontinued) method would be required. This is needed to ensure normal samples as well as pathologic samples are identified correctly. This includes the

[19] This testing activity needs to be distinguished from the activities aimed at finding an alternative substance. Here the testing refers to a testing of an already developed IVD kit system and its adaptation to a Siemens Healthineers analyser.

achievement for comparable results especially for the follow up of patients. This implies that the old material remains available for testing after the adaptation work is done; and

- It should be noted that Siemens Healthineers is currently working on implementing its REACH Response Plan for the phase out of OPEs so that all IVD kits offered will have an OPE-free alternative available; however, this will not be in time for the January 2021 Sunset Date and is therefore not relevant for the "Non-use" Scenario. The complexity of substituting OPEs for the full range of products in the Siemens Healthineers portfolio is significant, as described in Section 4.1, and therefore, such substitution will happen over an extended period of time.

It is worth noting the complexities that would arise for certain among Siemens Healthineers customers. In the case of research centres/universities, these customers might need to restart their research as the output data would change once third party IVD products were introduced.

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 Siemens Healthineers analyser, they could possibly outsource some of the tests to other (reference) laboratories or they might have to 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 Siemens Marburg OPE-dependent IVD kits. Consequently, it is not possible to establish a single "Non-use" Scenario for Siemens Marburg's customers. The range of possible "Non-use" Scenarios is presented below and the most likely one is identified.

Scenario 1: Switch to an alternative Siemens Healthineers analyser

Siemens Healthineers' #D analysers aim to gradually replace several older analysers models in the Siemens Healthineers portfolio. #D

It would also be fair to assume that if Siemens Marburg failed to obtain an Authorisation for its use of modest volumes of OPE in the manufacture of a relatively small number of IVD kits and wash solutions, it would be most likely that the prospects of Authorisation for the more voluminous and dispersive uses of OPE applied for by Siemens Marburg under Uses #4 and #5 would face a similar non-Authorisation outcome.

Moreover, if Siemens Healthineers were to suddenly become unable to service the stock of a large number of existing analysers in January 2021 (and note that some of those analysers 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 likelihood of customers switching to an alternative Siemens Healthineers analyser is extremely low.

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

Taking into account the introductory text above, 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 Marburg) produce OPE-dependent kits but because their production takes place outside the EEA, the use of OPE in the manufacturing process is not subject to REACH Authorisation.

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

Even if the availability of suitable kits from third-party suppliers was a given, switching analysers would not be a straightforward process. A typical customer in a large hospital reference lab may be running up to #D (range: 10-100) analysers from a particular platform, or potentially a range of analysers from different platforms. Faced with the situation whereby they can no longer utilise some or all of their existing analysers because the tests they need to run contain OPEs, these are the steps they would need to follow to purchase new analyser systems:

1. **Define their testing needs**: this would require a full review of all the tests they are required to perform across the range of analysers currently in use, looking at numbers and types of tests, throughput, turnaround times, performance requirements, reference ranges, available staff numbers, etc.

2. **Analyse capacity**: this could potentially be compared to 'building a new house', plans and schematics are normally drawn up of the laboratory areas to calculate how much space is available. Analysers, and especially groups of analysers, can take up quite a lot of space, as well as the adjacent space required for peripheral services for sample prep, hand-washing, waste management, etc.

3. **Put the contract out to tender**: IVD companies (suppliers of analysers) are invited to tender. The laboratory's requirements are reviewed, analysers within each supplier's range are identified and confirmed as to whether they meet the customer's needs from a testing and capacity perspective. This can involve several rounds of site visits and exchanges of information to ensure all needs are fully known and understood.

4. **Discuss contract details**: contractual arrangements are discussed, for example the ongoing purchase of IVD products for specific analysers (i.e. IVD kit reagents and IVD wash solutions), pricing, contractual terms and periods, ongoing sales and service arrangements, etc.

5. **Delivery and installation**: once a contract has been agreed, delivery and installation of the analyser systems take place. This can sometimes involve civil work to cater for any changes in layout or analyser size, to ensure a power supply, access to water and potentially to accommodate waste or drainage arrangements. In addition, a period of validation based on the customers' Quality Management System would be required after installation and before the start of routine testing. For larger installations this can take 8 weeks or more.

6. **Training**: training on the safe and effective operation of the new analyser systems is arranged and takes place, normally provided by the supplier IVD company.

7. **Adaptation to local procedures**: local procedures in the laboratory are updated and training on any changes are documented.

8. **Follow-up communication**: communications are arranged by the customer to their healthcare provider network to ensure any changes, for example reference ranges or turnaround times, are fully understood and incorporated into any of their local procedures or required documentation.

The above tendering process through to completion normally takes longer than 12 months, often up to 2 years in the case of larger laboratories. Providing all of the above steps were followed systematically, as is normally the case, it can be assumed the introduction of this alternative could be accomplished without a decrease of diagnostic performance of a healthcare institution.

Scenario 3: Outsource diagnostic testing

In theory, Siemens Marburg 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 brought in and has to be validated; this process of validation 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 Marburg cannot be certain that there exist third-party analysers that could deliver the assays that would become unavailable on the relevant Siemens Healthineers platforms [redacted] 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, surely it would have been already chosen by Siemens Marburg 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 to replace a Siemens Healthineers 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 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. 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 some 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 Marburg customers.

Scenario 4: Stop the delivery of diagnostic tests

If OPE-free technology is not available on the EEA market, Siemens Marburg customers would have to stop providing the diagnostic tests connected to the impacted IVD kits and wash solutions.

While there are no technical reasons as such why a laboratory could not stop diagnostic testing, clearly the impact to the healthcare system would be significant and it would be unacceptable to stop supplying healthcare providers and patients across the EEA with potentially life-changing or life-saving test results. Many customers will also have contractual obligations to supply diagnostic test results to various healthcare providers. For these reasons, Siemens Marburg customers (for example, hospitals) would do their absolute best to identify alternative solutions.

Conclusion

The above analysis presents the following key facts:

- Siemens Marburg 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;

- Siemens Marburg cannot be certain as to whether suitable third-party analysers exist and whether these can deliver the required testing. Siemens Healthineers' range of analysers cannot be relied upon to deliver the required tests due to the future of multiple platforms, new and old, being dependent on the outcome of separate AfAs.

For the purposes of the analysis here, we will assume that Siemens Healthineers' customers who use the IVD kits and wash solutions made with OPEs in Marburg would opt to prematurely invest in a new third-party analyser which can replace their existing Siemens Healthineers system. This would by no means be an ideal solution; as noted previously, switching to a new analyser could take 6-24 months. Moreover, it cannot be certain whether OPE-independent alternative technologies on the EEA market will exist on the Sunset Date. The choice of this "Non-use" Scenario is essentially based on the fact that this is the only **potentially** technically feasible option.

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 #D 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.

Key assumptions for the quantification of impacts on Siemens Marburg customers

Impacts arising from the time lag that would be required when switching from one analyser to another cannot be quantified and are therefore ignored, but it must be understood that the time lag would have very severe consequences over the course of 6-24 months. This should not be underestimated.

In terms of the impacts that can be quantified, two groups of impacted Siemens Healthineers analysers can be distinguished[20]:

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

The approach taken to quantifying the costs for each Applied for Use is based on the following:

- For existing stock, the average estimated age of the analysers is increased by 3 years (to see what their average age will be at the end of 2020) and is compared to the typical lifetime of each analyser platform to see what remaining life would be forfeited if the analysers were prematurely

[20] 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.

replaced. For new analysers (sold in 2018-2020), based on projected sales in each of these three years, the average age of the analysers at the end of 2020 is calculated and then compared to the typical lifetime of each analyser platform. This approach means that several analyser types can be omitted from the calculations as they were launched several years ago, their average age is old and thus it is assumed that these analysers would be replaced by 2021 anyway and therefore the associated replacement cost cannot be considered an impact relevant to the "Non-use" Scenario;

- Replacement analysers are expected to have comparable prices to the analysers being replaced. The analyser prices are also assumed to grow with the same pace as the inflation, which mean that the real prices are assumed to be constant throughout the review period;

- This premature investment will lead to additional costs for Siemens Marburg's customers, as they could alternatively have 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 purpose of this analysis will instead use the social discount rate of 4%; and

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

Uses #1, #2 and #3

Premature replacement of existing analyser stock

Table 5–5 summarises the calculations of the cost of premature replacement of the existing stock of analysers which are known to be relevant to the IVD kits generated through the use of OPE under Applied for Uses #1, #2 or #3. The analysers indicated in italics in the table would be at an advanced (average) age by 2021 and therefore the cost of their replacement is not considered to be relevant to the "Non-use" Scenario. Overall, #D (range: 1,000-10,000) analysers would need to be replaced prematurely and the Present Value cost (2017 prices) would be ca. #D, E (range: €1-10 million). The respective costs for each Use are #D, E (NB. simple aggregation of these three figures would amount to more than #D, E as there are overlaps with some analysers being relevant to more than one Applied for Use). It is clear that as far as existing analyser stock is concerned, customers using analysers relevant to Use #1 would be most severely impacted #D.

Table 5–5: Cost to Siemens Marburg's customers from premature replacement of existing stock (2017) of analysers relevant to Uses 1, 2 and 3									
Analyser	Relevant Applied for Uses	Number of affected analysers in the EEA	Average age EEA, years, 2017	Expected lifetime, years	Remaining lifetime in 2021, years	Average price (€)	Average cost of premature investment per analyser (€)	Total cost of premature investment (€, 2021)	Total cost of premature investment (€, 2017)
#D, E (table)									

Essentially, even though the real price of the analysers remains constant, due to discounting, there will be an added cost for Siemens Marburg's customers from having to buy a new analyser earlier than planned. Impacts would also arise for non-EEA operators of the relevant Siemens Healthineers analysers but these are not considered in the analysis here.

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. On the other hand, it is anticipated that the costs of non-Siemens IVD kits would be generally similar to those of the Siemens Marburg IVD kits.

Premature replacement of new (2018-2020) stock

Projections of sales of new analysers are available for certain models and these have been used to calculate the cost of their premature replacement; the data available are not sufficiently granular for the cost to be possible to accurately split between Applied for Use #1, #2 or #3. Splitting the costs is further complicated by the fact that there are overlaps among the three Uses in terms of which analysers are relevant to each one Use.

Table 5–6 summarises the calculations of the cost of premature replacement of the new (2018-2020) stock of analysers which are known to be relevant to the IVD kits generated through the use of OPE under Applied for Uses #1, #2 and #3. Two general categories are possible to review, #D analysers and Marburg-related analysers (all other analysers, which in the data presented include: #D).

Overall, #D (range: 1,000-10,000) analysers of a very young age would need to be replaced prematurely and the Present Value cost (2017 prices) would be ca. € #D, E (range: €10-100 million). For simplicity, we will assume that the "Non-use" Scenario for each Applied for Use will be accompanied by an analyser replacement cost (for new analysers) of ca. € #D, E .

Other costs associated with the premature replacement of Siemens Healthineers 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 tests results are measured) would have to be established.

Lost profits: Siemens Marburg's customers who engage in commercial activities will 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, but it is expected to be a substantial financial burden for the actors in questions.

Potential outsourcing costs: if the new analyser is not acquired early enough to complete the necessary validation testing before the Sunset Date, Siemens Marburg customers might need to outsource or cease the testing during the verification period. This cost cannot be quantified (but see the 2007 articled referred to above which show the increase in testing costs when testing is outsourced).

Table 5–6: Cost to Siemens Marburg's customers from premature replacement of new stock (2018-2020) of analysers relevant to Uses 1, 2 and 3								
Analyser 'group'	**Number of affected analysers in the EEA**	**Average age EEA, 2021**	**Expected lifetime (years)**	**Remaining lifetime 2021, years**	**Average price, €**	**Average cost of premature investment per analyser, €**	**Total cost of premature investment (€, 2021)**	**Total cost of premature investment (€, 2017)**
#D, E (table)								

Impacts on workflow: while the Siemens 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 analysers to their operations can be anticipated to affect the workflow of the customers.

Conclusion

Ultimately, in the EEA and globally, the critical benefit that will arise for society from an Authorisation is that diagnostic capabilities of Siemens Healthineers customers will be sustained, there will be no delays in performing diagnostic tests and delivering results to healthcare professionals and patients and there will be no increase to the cost of associated diagnostic testing activities. This sub-section has outlined the possible scenarios for Siemens Marburg customers in the EEA in the event of non-Authorisation. While the focus here is on EEA customers, the benefits will be similarly relevant globally to all Siemens Marburg customers throughout the world.

5.1.7 Economic impacts for consumers/patients

Under the "Non-use" scenario, the patients relying on tests provided by Siemens Marburg's direct customers may experience economic losses due to increased costs of testing e.g. from increased testing costs for Siemens Marburg's direct customer, hospital, commercial laboratory or other. However, this price increase would simply be a transfer of the costs from the direct Siemens Marburg's customers to the patient. This means that it is a distributional affect rather than added costs to society.

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

5.2.1 Environmental benefits

Under the "Non-use" Scenario, the environmental impacts described in Section 3.3 would be avoided. The CSR describes exposure scenarios under which only releases to the aquatic environment occur after Triton™ X-100/Triton™ X-405-containing wastewater is treated in an municipal STP.

Table 3–34, **Table 3–35** and **Table 3–36** have presented the estimated annual and daily releases of 4-tert-OP over the requested review period for each of the Applied for Uses. Annual releases of 4-tert-OP in the year 2021 are projected to be #H, J (range: 0.01-0.1), #H, J (range: 0.0001-0.001) and #H, J (range: 0.1-1) kg/y for Use #1, #2 and #3 respectively. For Uses #1 and #2, their very low annual emissions will remain largely stable until #G and #G respectively, after which years they will drastically reduce. For Use #3 usage of OPEs and emissions of 4-tert-OP will progressively decline from 2021 onwards. The total amount of 4-tert-OP released ranges between #H, J (range: 0.001-5 kg) per Applied for Use with the overall release of 4-tert-OP from the Marburg site over the period 2021-2032 reaching #H, J (range: 1-10) kg. Sludge from the municipal STP is assumed not to be applied on agricultural soil.

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 #H, J kg for Use #1, #2 and #3 respectively, 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 local and regional assessments in the CSR indicate that concentrations in the water are below the latest research values (often by a substantial margin), the releases are not occurring every day IVD kit and wash solution manufacture 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.

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

5.2.2 Health benefits for affected patients

The number of IVD kits sold in the EEA in 2017 represented approximately:

- Use #1: ca. #D kits #D (range: 10,000-100,000);
- Use #2: ca. #D kits (range: 10,000-100,000); and
- Use #3: ca. #D kits (range: 10,000-100,000).

It must be understood that each kit may deliver hundreds of different tests; some examples from the #D range IVD kits, but generally indicative of the situation across the board, are provided below:

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

Siemens Marburg is in position to translate the number of IVD kits sold to the equivalent number of diagnostic tests performed with those kits. Thus, it can be estimated that in 2017 Siemens Marburg's customers in the EEA may have performed:

- ca. #C, D (range: 10-100 million) tests using IVD kits within the scope of Use #1;
- ca. #C, D (range: 1-10 million) tests using IVD kits within the scope of Use #2; and
- naturally, the number of tests conducted alongside the wash solutions of Use #3 was even larger than the numbers shown for the two other Uses above.

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

#D

- #D

The specific IVD kits that would be affected are described in **Table 5–7** where the key characteristics of the relevant diseases diagnosed by means of these kits are presented.

Ultimately Siemens Marburg customers are using the 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. end stage renal disease). The number of kits used in the EEA is significant, in the range of tens of millions per year (as of 2017). The #D test, for instance, is one of the #C, D most important, most ordered and highly established parameter to be tested. 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, the combination of Marburg-made assays that can be run on one specific analyser could be unique. The result of this could be that a customer currently using Siemens Marburg IVD products can test them all on one analyser. If specific assays from Siemens Marburg were not available any more, the customer might (or not) find replacement third-party products on the market, nevertheless it could be (depending on the assays the customer is running in their lab) that they have to run them on different analysers. This means that the customer would need additional investment and lab space for another analyser but also the complexity of the workflow would increase and delays in obtaining test results and in diagnosis might be exacerbated. On a case-by-case basis, customers might be forced to switch to an alternative method or outsource testing to a reference laboratory. This would similarly increase the time to generate patient results, potentially delaying treatment.

Table 5–7: Disease information relating to diagnostics carried out by OPE-dependent [redacted] IVD kits manufactured in Marburg					
Impacted IVD kit (reagent name)	Diseases/conditions tested for/detected	Symptoms	Prevalence/incidence	Diagnosis/detection	Treatable?
#C, D (table) [redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 5–7: Disease information relating to diagnostics carried out by OPE-dependent [redacted] IVD kits manufactured in Marburg					
Impacted IVD kit (reagent name)	Diseases/conditions tested for/detected	Symptoms	Prevalence/incidence	Diagnosis/detection	Treatable?
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

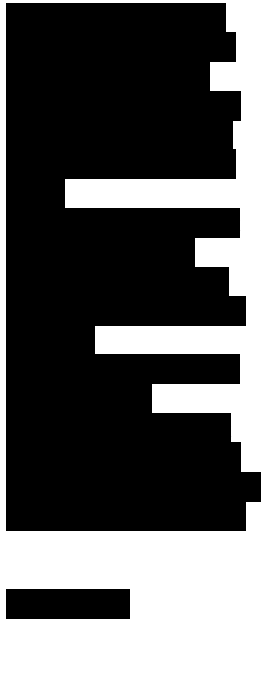
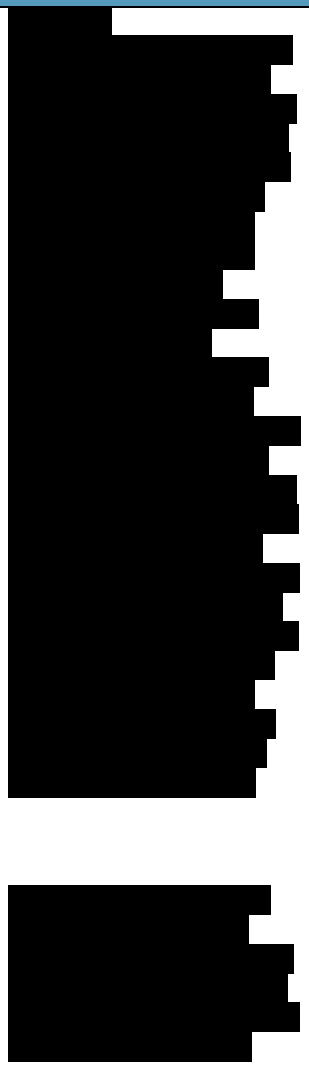
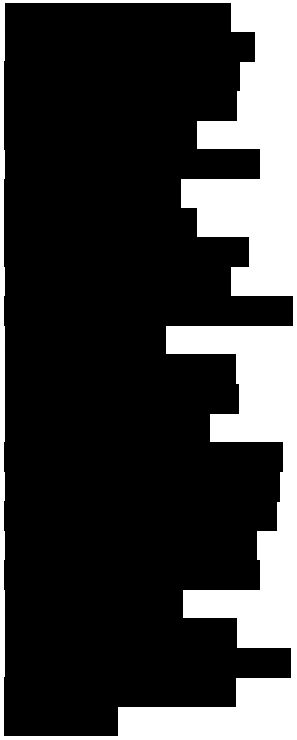
Table 5–7: Disease information relating to diagnostics carried out by OPE-dependent [redacted] IVD kits manufactured in Marburg					
Impacted IVD kit (reagent name)	Diseases/conditions tested for/detected	Symptoms	Prevalence/incidence	Diagnosis/detection	Treatable?
					

Table 5–7: Disease information relating to diagnostics carried out by OPE-dependent [redacted] IVD kits manufactured in Marburg					
Impacted IVD kit (reagent name)	Diseases/conditions tested for/detected	Symptoms	Prevalence/incidence	Diagnosis/detection	Treatable?
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 5–7: Disease information relating to diagnostics carried out by OPE-dependent [redacted] IVD kits manufactured in Marburg					
Impacted IVD kit (reagent name)	Diseases/conditions tested for/detected	Symptoms	Prevalence/incidence	Diagnosis/detection	Treatable?
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 5–7: Disease information relating to diagnostics carried out by OPE-dependent [redacted] IVD kits manufactured in Marburg					
Impacted IVD kit (reagent name)	Diseases/conditions tested for/detected	Symptoms	Prevalence/incidence	Diagnosis/detection	Treatable?
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 5–7: Disease information relating to diagnostics carried out by OPE-dependent [redacted] IVD kits manufactured in Marburg					
Impacted IVD kit (reagent name)	Diseases/conditions tested for/detected	Symptoms	Prevalence/incidence	Diagnosis/detection	Treatable?
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 5–7: Disease information relating to diagnostics carried out by OPE-dependent [redacted] IVD kits manufactured in Marburg					
Impacted IVD kit (reagent name)	Diseases/conditions tested for/detected	Symptoms	Prevalence/incidence	Diagnosis/detection	Treatable?
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 5–7: Disease information relating to diagnostics carried out by OPE-dependent [redacted] IVD kits manufactured in Marburg					
Impacted IVD kit (reagent name)	Diseases/conditions tested for/detected	Symptoms	Prevalence/incidence	Diagnosis/detection	Treatable?
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 5–7: Disease information relating to diagnostics carried out by OPE-dependent [redacted] IVD kits manufactured in Marburg					
Impacted IVD kit (reagent name)	Diseases/conditions tested for/detected	Symptoms	Prevalence/incidence	Diagnosis/detection	Treatable?
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 5–7: Disease information relating to diagnostics carried out by OPE-dependent [redacted] IVD kits manufactured in Marburg					
Impacted IVD kit (reagent name)	Diseases/conditions tested for/detected	Symptoms	Prevalence/incidence	Diagnosis/detection	Treatable?
			[redacted]		

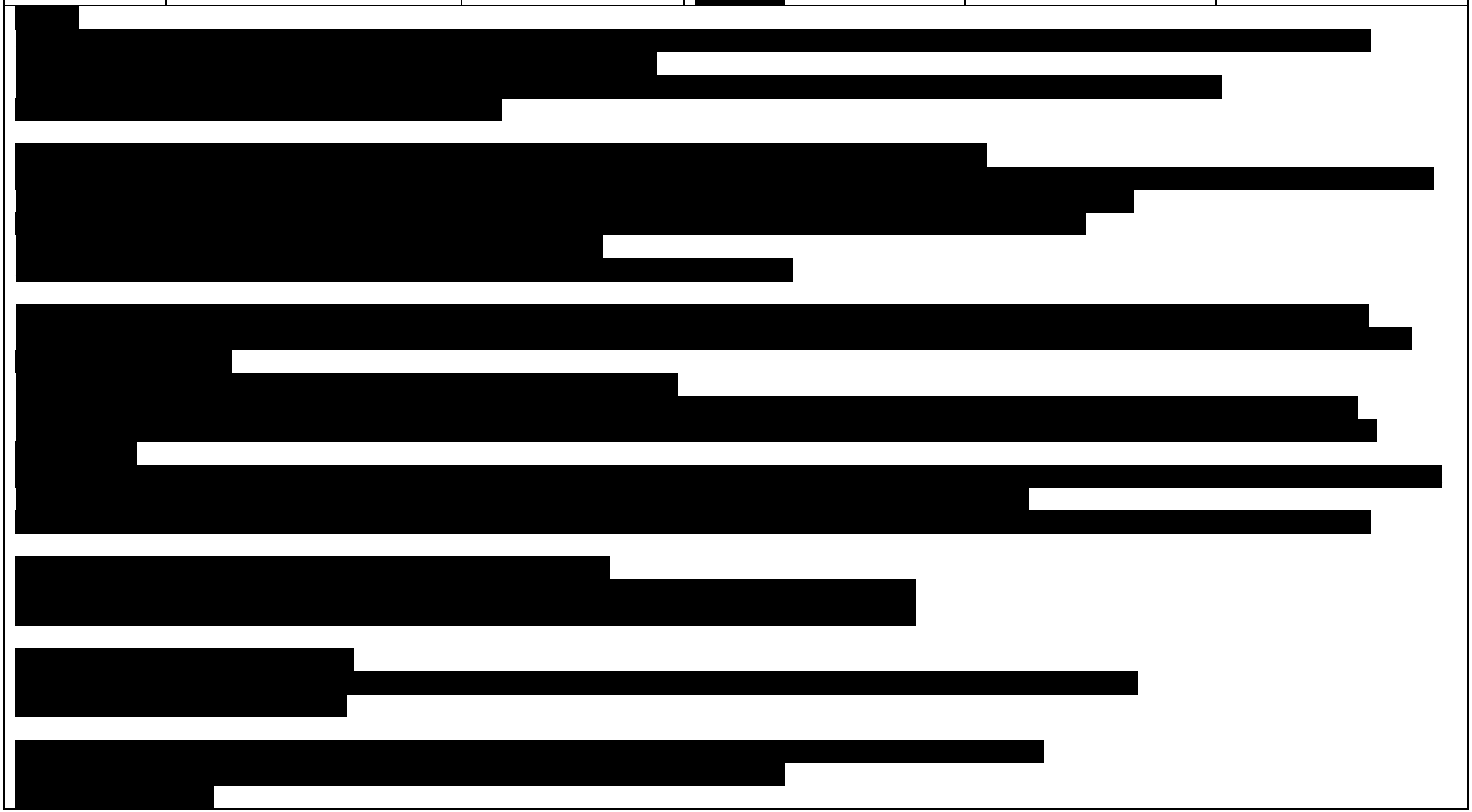


Table 5–7: Disease information relating to diagnostics carried out by OPE-dependent [redacted] IVD kits manufactured in Marburg					
Impacted IVD kit (reagent name)	Diseases/conditions tested for/detected	Symptoms	Prevalence/incidence	Diagnosis/detection	Treatable?
[redacted]					

Table 5–7: Disease information relating to diagnostics carried out by OPE-dependent [redacted] IVD kits manufactured in Marburg					
Impacted IVD kit (reagent name)	Diseases/conditions tested for/detected	Symptoms	Prevalence/incidence	Diagnosis/detection	Treatable?
[redacted]					

5.3 Social impacts

5.3.1 Avoided job losses at Siemens Marburg

Currently there are #D (range: 1,000-10,000) full-time employees at Siemens Marburg, #C, D

For the purposes of the analysis here we assume that the number of workers #D, E As previously noted (see Section 3.2.5), OPE-related operations account for % of the overall profit made by Siemens Marburg). The following table summarises the 2017 profits made from global sales of Siemens Marburg of the products within the scope of each one of the Applied for Uses #D, E

Table 5-8: Estimates of avoided job losses among Siemens Marburg employees under the "Applied for Use" Scenarios

Applied for Use	Profit made in 2017 from sales to all (EEA & non-EEA) customers	% of Siemens Marburg profit	Avoided job losses under the "Applied for Use" Scenario
Use #1	#D, E (table)		
Use #2			
Use #3			
Total			**(range: 10-100)**

As mentioned above, it is highly likely that the reduction in the production and sales of Siemens Marburg products would extend beyond the OPE-dependent products. In this case, the number of employees made redundant would be higher than estimated above. For instance, non-Authorisation for Use #3 would render #D analysers unusable. Therefore, all Marburg operations that are of relevance to this analyser would be impacted irrespective of their dependence on the continued use of Triton™ X-100.

5.3.2 Avoided job losses at other Siemens operations within the EEA

Use #1

#D, manufactured at Siemens Llanberis (UK), is dependent on the use of OPE for protein isolation at Marburg. Discontinuing the supply of the #D kit will lead to economic impacts, but is not expected to lead to any notable changes in employment at Siemens Llanberis.

Use #2

No Siemens Llanberis products are linked to Use #2, so there will be no changes in employment in either scenario.

Use #3

One of the OPE-dependent wash solutions manufactured at Siemens Marburg is the #D #D which is used alongside every single #D IVD kit manufactured at the Siemens' Llanberis site. If this wash solution could no longer be supplied, all operations at Siemens Llanberis would come to a halt as customers of Siemens Llanberis could no longer operate their #D analysers. This would lead to the #D, E (range: 100-1,000) employees at Llanberis becoming redundant (NB. this is the projected headcount #D).

Impacts on the European Distribution Centre

For the purposes of the present analysis, it is assumed that no discernible impact on the levels of employment at the EDC would arise under the "Non-use" Scenarios for any of the three Applied for Uses.

5.3.3 Avoided job losses among third party contractors

In addition to the staff directly employed by Siemens Marburg, there are third-party contractors connected to the manufacturing of #D products. The jobs of these contractors rely on the continued operations at Marburg, and would be at risk of losing their jobs if the operations at the Marburg site is reduced or discontinued. A total of #D (range: 10-100) contractors are employed at Marburg. The approach taken for estimating the avoided job losses among Siemens Marburg employees can be followed here too. These calculations show that impacts on contractors would generally be low.

Table 5-9: Estimates of avoided job losses among Siemens Marburg contractors under the "Applied for Use" Scenarios

Applied for Use	% of Siemens Marburg profit	Avoided job losses under the "Applied for Use" Scenario
Use #1	#D (column)	#D, E (column)
Use #2		
Use #3		
Total		**(range: 1-10)**

Nevertheless, under a worst-case scenario, if the entire Siemens Marburg operation were to collapse, the entire group of #D, E (range: 10-100) contractors would lose their jobs.

For Use #3, as mentioned above, if the #D #D was discontinued, all operations at Siemens Llanberis would come to a halt. As a consequence, more than #D, E (range: 10-100) third-party contractors would also be made redundant.

5.3.4 Avoided job losses among suppliers and customers

Siemens Marburg has tens of suppliers, of which the vast majority reside in the EEA. It is believed that the volumes of materials they sell to Siemens Marburg are relatively small part of their overall sales, therefore, loss of this part of their business would likely have an insignificant effect on their levels of employment.

Siemens Marburg's customers are diverse, and the impacts would likely vary. In a commercial lab or large hospitals that have staff dedicated to diagnostic testing it might be that a reduction in the product portfolio would make some staff redundant for a period of time. It is, however, unlikely that

there will be a substantial number of jobs lost amongst the Siemens Marburg customers due to a reduction in the portfolio.

5.3.5 Monetisation of social impacts

The proposed approach 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 with regard to 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 bits 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).

According to De Statis[21], the average yearly salary in Germany is €45,252. The ratio of social costs of jobs lost compared to the annual pre-displacement for Germany is 2.6 (Dubourg, 2016). Based on the average salary and a social cost to salary ratio of 2.6, the social costs of one job lost at the Marburg site is estimated at €117,655.

On the other hand, 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 expected 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, we will use the ratio for UK as a whole, which 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 at ca. €51,000.

Table 5–10 provides a summary of the expected avoided job losses and the corresponding benefits to society.

[21] Data available at: https://www.destatis.de/EN/FactsFigures/NationalEconomyEnvironment/EarningsLabourCosts/EarningsEarningsDifferences/Tables/LongTimeSeriesD.html (accessed on 11 December 2018).

Table 5–10: Estimation of social benefits from the continued use of Triton™ X-100/Triton™ X-405 in Marburg		
Use #1	**Number of jobs lost**	**Social costs**
Siemens Marburg	#D , E (table)	
Siemens Llanberis		
Suppliers and customers		
3rd party contractors - Marburg		
3rd party contractors - Llanberis		
Total avoided jobs lost		
Use #2	**Number of jobs lost**	**Social costs**
Siemens Marburg		
Siemens Llanberis		
Suppliers and customers		
3rd party contractors - Marburg		
3rd party contractors - Llanberis		
Total avoided jobs lost		
Use #3	**Number of jobs lost**	**Social costs**
Siemens Marburg		
Siemens Llanberis		
Suppliers and customers		
3rd party contractors - Marburg		
3rd party contractors - Llanberis		
Total avoided jobs lost		
Sum of all 3 Uses		
Worst-case scenario	**Number of jobs lost**	**Social costs**
Siemens Marburg		
Siemens Llanberis		
Suppliers and customers		
3rd party contractors - Marburg		
3rd party contractors - Llanberis		
Total avoided jobs lost		

The expected benefits to society from avoided job losses from granting the authorisation for all three Applied for Uses is **€** #D, E (range: €10-100 million), but there are uncertainties related to the number of workers that would be made redundant in the situation of downscaling the production at the Marburg site. The worst-case scenario would see operations at both Marburg and Llanberis cease leading to the loss of ca. #D, E (range: 1,000-10,000) jobs and a social cost of ca. **€** #E (range: €0.1-1 billion).

5.4 Wider economic impacts

5.4.1 Trade competition

Overview

A key parameter of the above analysis is that IVD kits and wash solutions made by Siemens Marburg may not be possible to replace by third-party kits/wash solutions made by competitors. Therefore, removal of the kits/wash solutions from the market could mean that Siemens Marburg customers would have to abandon their Siemens Healthineers analysers.

As is also described above, there are, in principle, several "Non-use" Scenarios for Siemens Marburg customers depending on whether OPE-free technology can be made available to customers in the EEA on the Sunset Date. As Siemens Marburg cannot be certain what alternative technologies might be available on the market, an (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 and wash solutions manufactured at Siemens Marburg 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 Marburg IVD kits and wash solutions 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.

Intra-EEA competition

Siemens Healthineers is aware that some of its competitors will be submitting AfAs for their own uses of OPE. It can also be safely assumed that competitors are actively looking into reformulating their products without OPE. Siemens Marburg has researched the market for third-party IVD kits that cover some of the assays covered by Applied for Uses #4 and #5 to establish whether OPE is mentioned as component of the kit reagent in the respective Safety Data Sheets. These searches have generated information (see **Table 5-11**) that can only be considered a snapshot of the situation at the end of 2018 and does not reflect any contemporaneous efforts that Siemens Marburg's competitors may be making towards the reformulation of their IVD kits or indeed the Authorisation of their continued use of OPE. This table cannot be seen as all-encompassing and is only used here as a limited example to underpin the arguments made.

It can be seen that for some kits, third-party replacements would also contain OPEs. It should be noted that such kits would normally need to be used on third-party analysers, they may not necessarily be used as drop-in replacements on Siemens Healthineers analyser platforms.

If Siemens Marburg's competitors were able to supply analysers which do not depend on OPE and cover the same/similar range of assays as the Siemens Healthineers impacted analysers, it can be assumed that customers would move to those third-party analysers. This would decrease Siemens Healthineers' market share while benefitting competitors and could well cause imbalances to intra-EEA competition, depending of which competitor is able to replace the Siemens Healthineers analysers (by way of example, in the field of core lab analysers, #C [redacted] If, theoretically speaking, the #C [redacted] was the only company able to substitute the Siemens analysers, its market share could well exceed 50% and could become by far the dominant player in the market.

Table 5-11: Presence of OPE in IVD kit reagents placed on the market by Siemens Marburg's competitors

Assay	[redacted]	[redacted]	[redacted]
#C, D (table) [redacted]			
[redacted]			
[redacted]			
[redacted]			
[redacted]			
[redacted]			
[redacted]			
[redacted]			
[redacted]			
[redacted]			

Table 5-11: Presence of OPE in IVD kit reagents placed on the market by Siemens Marburg's competitors				
Assay	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				

Again, as it is not possible to know to what extent competitors are dependent on OPE, whether their products cover all relevant Siemens Healthineers assays, what the competitors Authorisation and reformulation plans are and how successful their Authorisations will be, it is not possible to predict changes to intra-EEA competition under the "Non-use" Scenario.

EEA competitiveness

As previously noted, it can only be assumed that Siemens Marburg's customers would seek alternative analysers with kits that do not depend on OPE. It is possible that some of these analysers and kits could be manufactured outside the EEA. In this case, under the "Non-use" Scenario non-EEA businesses might benefit at the expense of EEA-based businesses.

In terms of IVD kit and wash solution sales, the ability of non-EEA manufacturers to place such products on the EEA market would depend on their OPE content and the granting or not of an Authorisation for the continued use of OPE by Siemens Marburg customers (Uses #4 and #5 applied for separately). If these downstream uses are authorised, imports of non-EEA-made IVD kits and washing solutions might increase.

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

As per the discussion above, it is not possible to express an informed view as to whether changes to international trade would be significant. This will depend on the outcome of several AfAs (the present one, the separate one for Uses #4 and #5 as well as those of competitors) and the availability of OPE-free technologies on the Sunset Date.

5.4.3 Changes in EU and MS/regional taxes

A reduction in the scale of operations in Marburg and the concomitant reduction in profits made would likely result in a reduction of taxes paid by Siemens Marburg to the German tax authorities. This is a distributional impact which is difficult to scope and as such no attempt has been made to quantify it.

5.4.4 Changes to the local economy

Siemens Marburg is located at Behringwerke Marburg Industrial park, a biotechnology centre hosting innovative pharmaceutical companies with approximately 5,500[22] employees in total. A key

[22] https://www.behringwerke.com/

advantage for innovative pharmaceutical companies on Behringwerke Industrial Park is that both established companies and start-up companies can take advantage of its existing infrastructure for research, production and sales or start work on the planning and construction of buildings and facilities together with the site operator.

Siemens Marburg accounts for D# % (range: 10-50%) of the staff at this industrial park, and is considered an integral part of maintaining the efficiency and economy of scale at the site.

On the other hand, Marburg is a university town in the German federal state (Bundesland) of Hessen, capital of the Marburg-Biedenkopf district (Landkreis). The town has a population of approximately 81,000. Siemens is one of the largest employers in the area.

Under the main assumption of the "Non-use" Scenario, the number of jobs lost would be modest and therefore, impacts on the wider community would probably be limited. Even if the worst-case scenario materialised and Siemens Marburg's operations collapsed, it would be unlikely that there would be repercussions on the functioning of the industrial park.

5.5 Distributional impacts

The following three tables summarise the envisaged distributional impacts from the granting of an Authorisation.

Table 5–12: Distributional impacts from the continued use of OPE in the Applied for Use #1		
Affected group	**Economic (and social) impact**	**Human health and environmental impact**
Economic operator		
Applicant: Siemens Marburg	Continued manufacture and sales of IVD kits – profits made from Triton™ X-100-dependent IVD kits: Use #1: € #D (PV, 2021-2029, 4%)	Low local releases of 4-tert-OP to the aquatic environment after treatment of wastewater at municipal STP. Overall aquatic release of 4-tert-OP in the period 2021-2029 is estimated at #H, J (range: 0.1-1) kg, while environmental stocks peak at #H, J kg prior over the requested review period
Siemens Llanberis	Continued manufacture of the #D protein in Marburg would allow the continued manufacture of the OPE-free #D kit in Llanberis. Overall profit of Siemens Llanberis from sales of the (OPE-free) #D kit: #E (PV, 2021-2029, 4%)	Low local releases of OPE to the environment after treatment of wastewater at industrial and municipal STPs associated with the manufacture of OPE-dependent IVD kits for the #D platform
EEA suppliers to Siemens Marburg	Continued sales of raw and other materials to Siemens Marburg – profits made are uncertain	None
Non-EEA suppliers to Siemens Marburg		None
Non-EEA Siemens Healthineers operations	Marburg-made #D® and #D IVD kits remain available on the market and thus future sales of analysers can continue without obstacle; in the period 2021-2029 #D (range: 1,000-10,000) analysers are envisaged to be sold in the EEA and a further #D (range: 1,000-10,000) in non-EEA countries in relation to Use #1 kits	None
Third-party diagnostic test and analyser providers	No access to potential new customers (hospitals, labs) who are currently operating Siemens Healthineers analysers and who would be able to make full use of their analysers	No
EEA-based customers of Siemens Marburg	Access to #D IVD kits (excluding the #D kit sold via Siemens Llanberis) allowing important assays to be run on up to #D analysers (2017 stock) and several more analysers to be sold in the period 2018-2020 (#D relevant to all three Applied for Uses); ability to offer full range of assays required by healthcare providers; avoidance of premature replacement of Siemens Healthineers analysers, cost estimated at € (PV, 4%)	None (NB. OPE is not present in the affected IVD kits)

Table 5–12: Distributional impacts from the continued use of OPE in the Applied for Use #1		
Affected group	**Economic (and social) impact**	**Human health and environmental impact**
Non-EEA-based customers of Siemens Marburg	Access to #D® IVD kits (excluding the #D kit sold via Siemens Llanberis) important assays to be run on existing and 2018-2020 stock of analysers. Benefits not quantified	None (NB. OPE is not present in the affected IVD kits and these customers are outside the EEA)
EEA-based customers of Siemens Llanberis	Access to the #D kit allowing the continued performance of the assay on up to #D #D analysers (2017 stock) and another #D sold in the years 2018-2020; ability to offer full range of assays required by healthcare providers; avoidance of premature replacement of #D analysers (cost included in estimate for Siemens Marburg customers above)	None (NB. OPE is not present in the affected IVD kit)
Non-EEA-based customers of Siemens Llanberis	Access to the #D kit allowing the continued performance of the assay on up to #D analysers (2017 stock) and another #D sold in the years 2018-2020; ability to offer full range of assays required by healthcare providers; avoidance of premature replacement of #D analysers	None (NB. OPE is not present in the affected IVD kit 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 abnormalities. Ca. #C, D (range: 10-100 million) tests were sold by Siemens Healthineers in 2017
Geographical scope		
Marburg, Hesse, Germany	Local economy is supported by retaining #D, E jobs at Siemens Marburg	None
River Lahn, Germany	Limited volumes of OPEs will still be released in the period 2021-2029 (albeit gradually declining), thus monitoring of Siemens Marburg's use and associated releases need to continue	Low releases of 4-tert-OP to the aquatic environment after treatment of wastewater at municipal STP. Overall aquatic release of 4-tert-OP in the period 2021-2029 is estimated at #H, J (range: 0.1-1) kg, while environmental stocks peak at #H, J 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 affected IVD kits)

Table 5–12: Distributional impacts from the continued use of OPE in the Applied for Use #1		
Affected group	**Economic (and social) impact**	**Human health and environmental impact**
Within the applicant's business		
Employers/Owners	Profit-generating activities continue unhindered (see details above)	None
Exposed workers	Jobs in Marburg will be retained (see above)	None
Non-exposed employees		

Table 5–13: Distributional impacts from the continued use of OPE in the Applied for Use #2		
Affected group	**Economic (and social) impact**	**Human health and environmental impact**
Economic operator		
Applicant: Siemens Marburg	Continued manufacture and sales of IVD kits– profits made from Triton™ X-100/Triton™ X-405-dependent IVD kits: Use #2: € #D, E (PV, 2021-2032, 4%)	Low local releases of 4-tert-OP to the aquatic environment after treatment of wastewater at municipal STP. Overall aquatic release of 4-tert-OP in the period 2021-2032 is estimated at #H, J (range: 0.001-0.01) kg, while environmental stocks peak at #H, J kg prior over the requested review period
Siemens Llanberis	No direct benefit other than it maintains Siemens Marburg's financial health and this would ensure that the #D protein and the #D wash solution would continue to be manufactured in Marburg	Low local releases of OPE to the environment after treatment of wastewater at industrial and municipal STPs
EEA suppliers to Siemens Marburg	Continued sales of raw and other materials to Siemens Marburg – profits made are uncertain	None
Non-EEA suppliers to Siemens Marburg		None
Non-EEA Siemens Healthineers operations	#D Marburg-made IVD kits remain available on the market and thus future sales of analysers can continue without obstacle; in the period 2021-2032 #D (range: 1,000-10,000) analysers are envisaged to be sold in the EEA and a further #D (range: 1,000-10,000) in non-EEA countries in relation to Use #2 kits	None
Third-party diagnostic test and analyser providers	No access to potential new customers (hospitals, labs) who are currently operating Siemens Healthineers analysers and who would be able to make full use of their analysers	No
EEA-based customers of Siemens Marburg	Access to #D IVD kits allowing important assays to be run on up to #D analysers (2017 stock) and several more analysers to be sold in the period 2018-2020 (#D relevant to all three Applied for Uses); ability to offer full range of assays required by healthcare providers; avoidance of premature replacement of Siemens Healthineers analysers, cost estimated at € #D, E (PV, 4%)	Low local releases of OPE to the environment arising from the use of OPE-containing IVD kits
Non-EEA-based customers of Siemens Marburg	Access to #D IVD kits allowing important assays to be run on existing and 2018-2020 stock of analysers. Benefits not quantified	Low local releases of OPE to the environment outside the EEA arising from the use of OPE-containing IVD kits

Table 5–13: Distributional impacts from the continued use of OPE in the Applied for Use #2		
Affected group	**Economic (and social) impact**	**Human health and environmental impact**
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 abnormalities. Ca. #C, D (range: 1-10 million) tests were sold by Siemens Healthineers in 2017
Geographical scope		
Marburg, Hesse, Germany	Local economy is supported by retaining #D, E jobs at Siemens Marburg	None
River Lahn, Germany	Limited volumes of OPEs will still be released in the period 2021-2032 (albeit gradually declining), thus monitoring of Siemens Marburg's use and associated releases need to continue	Low releases of 4-tert-OP to the aquatic environment after treatment of wastewater at municipal STP. Overall aquatic release of 4-tert-OP in the period 2021-2032 is estimated at #H, J (range: 0.001-0.01) kg, while environmental stocks peak at #H, J 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	Low releases of OPE to the environment arising from the use of OPE-containing IVD kits
Within the applicant's business		
Employers/Owners	Profit-generating activities continue unhindered (see details above)	None
Exposed workers	Jobs in Marburg will be retained (see above)	None
Non-exposed employees		

Table 5–14: Distributional impacts from the continued use of OPE in the Applied for Use #3		
Affected group	**Economic (and social) impact**	**Human health and environmental impact**
Economic operator		
Applicant: Siemens Marburg	Continued manufacture and sales of IVD wash solutions – profits made from Triton™ X-100-dependent wash solutions: Use #3: € #D, E (PV, 2021-2032, 4%)	Low local releases of 4-tert-OP to the aquatic environment after treatment of wastewater at municipal STP. Overall aquatic release of 4-tert-OP in the period 2021-2032 is estimated at #H, J (range: 1-10) kg, while environmental stocks peak at #H, J kg prior over the requested review period
	Continued sales of all #D wash solution-dependent kits for #D affected analysers – profits made will be € #D, E (PV, 2021-2032, 4%)	
Siemens Llanberis	Continued manufacture of the #D #D in Marburg would allow all #D IVD kits to remain usable on the #D platform thus ensuring the continued operation of Siemens Llanberis which manufactures #D IVD kits. Overall profit of Siemens Llanberis operations: #D, E (PV, 2021-2029, 4%)	Low local releases of OPE to the environment after treatment of wastewater at industrial and municipal STPs. Overall aquatic release of 4-tert-OP in the period 2021-2029 is estimated at #H, J (range: 0.1-1) kg, while environmental stocks peak at #H, J kg prior over the requested review period
EEA suppliers to Siemens Marburg and Siemens Llanberis	Continued sales of raw and other materials to Siemens Marburg and Siemens Llanberis – profits made are uncertain	None
Non-EEA suppliers to Siemens Marburg and Siemens Llanberis		None
Non-EEA Siemens Healthineers operations	#D Marburg-made OPE-containing wash solution products remain available on the market thus future sales of analysers can continue without obstacle; in the period 2021-2032 (#D (range: 1,000-10,000) analysers are envisaged to be sold in the EEA and a further #D (range: 100-1,000) in non-EEA countries)	None
	Continued sales of all #D wash solution-dependent kits for #D affected analysers – profits made will be € #D, E (PV, 2021-2032, 4%)	
Third-party diagnostic test and analyser providers	No access to potential new customers (hospitals, labs) who are currently operating Siemens Healthineers analysers and who would be able to make full use of their analysers	No

Table 5–14: Distributional impacts from the continued use of OPE in the Applied for Use #3		
Affected group	**Economic (and social) impact**	**Human health and environmental impact**
EEA-based customers of Siemens Marburg	Access to #D IVD wash solution products allowing important assays to be run up on to #D analysers (2017 stock) and several more analysers to be sold in the period 2018-2020 (#D ; ability to offer full range of assays required by healthcare providers; avoidance of premature replacement of Siemens Healthineers analysers, estimated cost of € #D, E (PV, 4%)	Low local releases of OPE to the environment arising from the use of OPE-containing IVD wash solutions
Non-EEA-based customers of Siemens Marburg	Access to #D IVD wash solutions allowing important assays to be run on existing and 2018-2020 stock of analysers. Benefits not quantified	Low local releases of OPE to the environment outside the EEA arising from the use of OPE-containing IVD wash solutions
EEA-based customers of Siemens Llanberis	Access to the #D wash solution allowing the continued performance of #D #D analysers (2017 stock) and another #D sold in years 2018-2020; avoidance of premature replacement of #D analysers (cost included in estimate for Siemens Marburg customers above)	Low releases of OPE to the environment arising from the use of OPE-containing IVD wash solution
Non-EEA-based customers of Siemens Llanberis	Access to the #D wash solution allowing the continued performance of #D #D analysers (2017 stock) and another sold in years 2018-2020; avoidance of premature replacement of #D analysers	Low releases of OPE to the environment outside the EEA arising from the use of OPE-containing IVD wash solution
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 abnormalities. Several millions of tests were sold by Siemens Healthineers in 2017 for use alongside the Use #3 wash solutions
Geographical scope		
Marburg, Hesse, Germany	Local economy is supported by retaining #D, E jobs at Siemens Marburg	None
North-west Wales, UK	Local economy is supported by retaining #D, E jobs at Siemens Llanberis	None
River Lahn, Germany	Limited volumes of OPEs will still be released in the period 2021-2032 (albeit gradually declining), thus monitoring of Siemens Marburg's use and associated releases need to continue	Low releases of 4-tert-OP to the aquatic environment after treatment of wastewater at municipal STP. Overall aquatic release of 4-tert-OP in the period 2021-2032 is estimated at #H, J (range: 1-10) kg, while environmental stocks peak at #H, J kg prior over the requested review period

Table 5–14: Distributional impacts from the continued use of OPE in the Applied for Use #3		
Affected group	**Economic (and social) impact**	**Human health and environmental impact**
Mersey estuary, North-east England, UK	Industrial STP that receives wastewater from Siemens Llanberis will continue to earn revenue #D, E from the continued business relationship with the applicant.	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 #H, J (range: 0.1-1) kg, while environmental stocks peak at #H, J kg prior over the requested review period
	Limited volumes of OPEs will still be released in the period 2021-2029 (albeit gradually declining), thus monitoring of Siemens Llanberis's use and associated releases need to continue*	
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	Low releases of OPE to the environment arising from the use of OPE-containing IVD wash solutions
Within the applicant's business		
Employers/Owners	Profit-generating activities continue unhindered (see details above)	None
Exposed workers	Jobs in Marburg (and Llanberis) will be retained (see above)	None
Non-exposed employees		
* the situation in the UK after Brexit may or not differ to the current one		

5.6 Uncertainty analysis

Table 5–15 explains the influence of key uncertainties over the conclusions of the analysis of socio-economic impacts.

Table 5–15: 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. For subsequent years, it is assumed that no change to sales/profits occurs year-on-year	More reliable estimates are not available. The product portfolio is in the midst of transition due to a major product launch with the potential to impact the regional composition of the supply chain. However, the overall impact would result in a need to increase manufacturing capacity. Due to this transition, it is difficult to precisely forecast which manufacturing sites will support the incremental capacity needed. However, the overall business plan suggests that individual plant volumes should at least remain consistent with current trends, and incremental capacity has been assumed as US-based for the purposes of this exercise
Number of jobs to be lost	The assumed number of jobs to be lost is based on the share (#D of the IVD kits and wash solutions falling within Applied for Uses #1, #2 and #3 within the sales of all IVD products made in Marburg	It cannot be certain what the actual number of job losses might be. However, the loss of the sales of the impacted IVD kits and wash solutions could have a strongly undermining impact on the marketability of OPE-independent IVD kits made in Marburg and thus the losses incurred by Siemens Marburg could be far greater than this factor (#D would imply. For Siemens Llanberis, without the #D #D that is manufactured in Marburg, the entire Welsh operations would come to a halt
Availability of OPE-independent kits/analysers on the market	Siemens Marburg cannot be certain whether competitors in the #D IVD kits are similarly or more or less dependent on the use of OPEs. It is known that competitors are concerned about OPE but the extent of their current use, reformulation efforts and Authorisation of their continued use are unknown	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)

Table 5–15: Uncertainty analysis		
Area of uncertainty	**Basic assumption**	**Alternative assumptions – Sensitivity analysis**
Authorisation of downstream uses of Marburg-made IVD kits and wash solutions	It is generally assumed that Siemens Marburg will be granted an Authorisation for Uses #4 and #5 that are separately being applied for	The discussion in this document aims to reflect this uncertainty without being in a position to categorically state whether an Authorisation for Uses #4 and #5 will be granted, as this is up to the European Commission to decide
Ability of Siemens Marburg's customers to outsourcing their diagnostic activities	Siemens Marburg 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, 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 and Triton™ X-405 in Marburg that were presented in Section 5. Overall, a benefit of ca. #E (range: €0.1-10 billion, Present Value, 4% discount) can be estimated for each of the Applied for Uses.

It should be appreciated that the cost of non-Authorisation could be much greater than what these figures indicate, due to a likely 'domino 'effect on Siemens Healthineers' sales for both #D IVD products:

If Siemens Marburg is not granted an Authorisation that would allow the sales of certain IVD products, sales of these products would be lost

⇩

Customers using the impacted kits would probably abandon their Siemens Healthineers analysers as these could not deliver the full functionality they had been purchased for

⇩

Fewer active analysers would mean that sales of OPE-independent kits would be heavily impacted

⇩

General acceptance of Siemens Healthineers analysers is reduced as their functionality would become known to be impaired

⇩

Sales of new analysers would suffer, affecting profit margins and future viability of analyser lines

⇩

Sales of analysers could be seriously impacted or cease thus leading to loss of sales of IVD products, irrespective of their dependence on OPEs

⇩

Siemens Healthineers analysers could end up in early retirement

⇩

Manufacture of IVD products for the retired analysers would stop

⇩

Customers operating existing analysers would be unable to source required consumables

Table 6–1: Summary of socio-economic benefits from the continued use of OPE under the "Applied for Use" Scenario					
Stakeholder affected/impacted	**Description of impact**	**Quantification of impact**			**Considered in the total monetised benefit calculated below**
		Use #1 (2021-2029)	**Use #2 (2021-2032)**	**Use #3 (2021-2032)**	
Benefits to the applicant and/or their supply chain					
Siemens Marburg	Uninterrupted/unaffected manufacture and sale of OPE-dependent kits and wash solutions – Gross profit to be made	#D, E (table) (PV, 4%)	[redacted] (PV, 4%)	[redacted] (PV, 4%)	Yes
	Uninterrupted/unaffected manufacture and sale of IVD kits the use of which depends on the continued availability of OPE-containing wash solutions – Gross profit to be made	N/A	N/A	[redacted] (PV, 4%) sales of all impacted [redacted] IVD kits	Partially – to err on conservative side, only sales to EEA-based customers are considered → [redacted] (PV, 4%)
	Avoidance of contractual penalties	Not quantified	Not quantified	Not quantified	No
Siemens Llanberis	Continued manufacture of the [redacted] kit for the [redacted] analysers – Gross profit to be made	[redacted] (PV, 4%)	N/A	Included below	Yes
	Continued manufacture of all [redacted] kits – Gross profit to be made	N/A	N/A	[redacted] (PV, 4%)	Partially – to err on conservative side, only sales to EEA-based customers are considered → [redacted] (PV, 4%)
EEA-based manufacturers of Siemens Healthineers analysers	Continued manufacture and sale of certain analysers on behalf of Siemens Healthineers	N/A – no sales of analysers from external vendors after Sunset Date	Unknown profit margin; [redacted] (included below)	N/A – no sales of analysers from external vendors after Sunset Date	No – quantification not possible

Table 6–1: Summary of socio-economic benefits from the continued use of OPE under the "Applied for Use" Scenario					
Stakeholder affected/impacted	**Description of impact**	**Quantification of impact**			**Considered in the total monetised benefit calculated below**
		Use #1 (2021-2029)	**Use #2 (2021-2032)**	**Use #3 (2021-2032)**	
Siemens Healthineers non-EEA operations	Continued sales of analysers – Gross profit to be made	[redacted] analysers to be sold in EEA. [redacted] analysers to be sold outside EEA. [redacted] (PV, 4%, est.)	[redacted] analysers to be sold in EEA. [redacted] analysers to be sold outside EEA. [redacted] (PV, 4%, est.)	[redacted] analysers to be sold in EEA. [redacted] analysers to be sold outside EEA. [redacted] (PV, 4%, est.)	Yes
	Continued sales of non-EEA-made IVD kits – Gross profit to be made	Potentially significant but not quantified	Potentially significant but not quantified	[redacted] (PV, 2021-2029, 4%) – [redacted] IVD kits	Partially – to err on conservative side, only sales to EEA-based customers are considered → [redacted] (PV, 4%)
OEM	Continued sales of IVD kit components to Siemens Marburg	N/A	Unknown profit margin of [redacted] – to be presented by the OEM in their individual AfA	N/A	No
Siemens Marburg customers	Continued operation of existing (and future) Siemens Healthineers analysers that use the affected IVD kits and wash solutions – Avoided cost of premature replacement of analysers	[redacted] (PV, 4%)	[redacted] (PV, 4%)	[redacted] (PV, 4%)	Yes – if all Uses are considered together, the total cost is [redacted]
	Avoidance of cost increases from outsourcing diagnostic tests	Not quantified	Not quantified	Not quantified	No
Customers of Siemens Llanberis	Continued operation of existing (and future) [redacted] analysers that use the affected [redacted] IVD kit and/or the [redacted]	Uncertain but important – [redacted] is an esoteric assay and not widely available on other automated immunoassay systems	N/A	Avoided cost of premature replacement of analysers: [redacted] (PV, 4%)	No – these impacts are already included above under Siemens Marburg customers

Table 6–1: Summary of socio-economic benefits from the continued use of OPE under the "Applied for Use" Scenario					
Stakeholder affected/impacted	**Description of impact**	**Quantification of impact**			**Considered in the total monetised benefit calculated below**
		Use #1 (2021-2029)	**Use #2 (2021-2032)**	**Use #3 (2021-2032)**	
Benefits to other actors					
Healthcare providers/patients	Continued access to tests needed for the diagnosis and treatment of a range of diseases/conditions	Cost increases for healthcare systems to be avoided: unknown			No – no quantified data
		Treatment/health outcome impacts from delayed testing or loss of diagnostic capability to be avoided: unknown			No – no quantified data
Workers at Marburg	Preservation of jobs in Marburg – Benefits to society from retaining jobs	€ [redacted] (PV, 4%) [redacted] jobs	€ [redacted] (PV, 4%) [redacted] jobs	[redacted] (PV, 4%) [redacted] jobs	Yes
Workers at Llanberis	Preservation of jobs in North-west Wales – Benefits to society from retaining jobs	N/A	N/A	€ [redacted] (PV, 4%) [redacted] jobs	Yes
City of Marburg	Prevention of increased unemployment around Marburg	Benefits to local economy: not quantified			No – benefits are included above
Village of Llanberis/ North-west Wales	Prevention of increased unemployment around Llanberis	Benefits to local economy: not quantified			No – benefits are included above
Overall Aggregated socio-economic benefit of continued use of OPE		[redacted] **(range: €0.1-1 billion)**	[redacted] **(range: €10-100 million**	[redacted] **(range: €1-10 billion)**	

On the other hand, the total emissions of OPE to the environment under the "Applied for Use" Scenarios were shown in **Table 3–34**, **Table 3–35** and **Table 3–36**. As sludge is not applied to agricultural soil, only releases to the aquatic environment are of relevance to the present analysis. The benefits and releases per Applied for Use over the requested review period are shown in **Table 6-2**.

Table 6-2: Cost of non-use per kg and year		
Use #1		
Parameter	**Present Value, 2021-2029**	**Annualised value (worst-case release)**
Total cost of non-use	#E	#E
Total emissions	#H	#H
Ratio	**€ #E, H per kg (range: €1-10 billion per kg)**	**€ #E, H per kg (range: €0.1-1 billion per kg)**
Use #2		
Parameter	**Present Value, 2021-2032**	**Annualised value (worst-case release)**
Total cost of non-use	#E	#E
Total emissions	#H	#H
Ratio	**€ #E, H per kg (range: €10-100 billion per kg)**	**€ #E, H per kg (range: €10-100 billion per kg)**
Use #3		
Parameter	**Present Value, 2021-2032**	**Annualised value (worst-case release)**
Total cost of non-use	#E	#E
Total emissions	#H	#H
Ratio	**€ #E, H per kg (range: €0.1-1 billion per kg)**	**€ #E, H per kg (range: €10-100 million per kg)**

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, H to € #E, H per kg of 4-tert-OP released per individual Applied for Use**. A more conservative calculation can be performed if the total benefit (cost of non-use) per Use is annualised and the highest annual release of 4-tert-OP (is considered. Then the ratio becomes **€ #E, H to € #E, H r kg of 4-tert-OP released**.

These figures are certainly underestimates because whilst socio-economic benefits have been discounted, the physical releases of 4-tert-OP have not.

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 periods for the continued use of OPE at Siemens Marburg are:

- Use #1 – Isolation of protein: 9 years;
- Use #2 – Formulation of IVD kit reagents: 12 years; and
- Use #3 – Formulation of IVD wash solutions: 12 years.

6.2.2 Criterion 1: Siemens Marburg's investment cycle

Use #1

The full Siemens Healthineers product portfolio #D the inclusion of OPEs on the REACH Authorisation list, with over #D (range: 50-500) individual IVD products falling within the scope of REACH Authorisation which requires significant investment in resources and funds #C . It is important to note that the successful substitution of Triton™ X-100/Triton™ X-405 in one product by a 'safer' alternative substance will not necessarily mean that this alternative will be appropriate as a substitute for the next product, even within the same product line. The properties which make OPEs effective in one product may be completely different to what makes it effective in another, and this is 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' (described in Section 6.3). As part of this plan, all products which are connected to the #D analysers e.g. #D products) or which are expected to have a longer life-cycle (#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-span (e.g. #D) will not be subject to Design Change so the company can focus its re-design efforts on products which will continue to be used into the future.

The key driver behind the request for a 9-year review period for Use #1 at Marburg hinges upon the need for a period of continued use of OPE of 9 years before a Process Change project for the elimination of OPE from the cell extraction processes involved in this Use. In this context, it is important to note the following issues which highlight the interconnection between the present AfA and the separate AfA that is submitted by Siemens Llanberis:

- The quantity of OPE used in Marburg under Use #1 will reduce as Process Change projects come to fruition. As discussed in Section 6.3, a Process Change Project for #D, G IVD products and a separate one covering #D, G for #D, G products #D, G are planned to be completed by the end of #D, G . A third Process Change Project which

focuses on the #D for the newly launched #D is given priority and is planned to be completed by the end of #D, G; and

- A separate Process Change Project for the #D specifically aimed at the #D kit manufactured in Llanberis for the #D analyser is not envisaged. As described in the separate Siemens Llanberis AfA, #D. This would not allow the #D process to be changed and then the new protein extract to be validated and re-registered for use on the #D analysers in time for such an investment to produce a return. In other words, the #D process for the respective #D kit that is manufactured in Llanberis must be allowed to continue #D. It is important to note that the #D assay is an esoteric test and very unlikely to be available on other platforms. It is further critical to point out that as #D, the consumption of OPE in Marburg for #D #A.

Therefore, a 9-year review period will allow the roll-out of the significant investment in R&D that Siemens Healthineers is planning for the Process Changes to be implemented and would also allow the orderly winding down of the #D business line. The latter is planned to be replaced by the #D analysers the IVD kits and wash solutions of which are given utmost priority in Siemens Healthineers' quest to eliminate the use of OPE.

Use #2

The argumentation presented above for Use #1 would also be relevant here. Section 6.3 presents two Design Change projects for the relevant IVD kits that fall under Applied for Use #2. One of these projects is of high priority (Priority 1), will cover #D, G products and is expected to finish in #D, G, meaning that the use of OPE for the formulation of the corresponding IVD kit reagents will be eliminated by #D, G, i.e. #D years before the end of the requested review period of 12 years. In addition, a second project of lower priority (Priority 2) which will cover an additional #D products is planned to start in early #D, G and will finish by the end of 2032. The reason for this is because the 2nd project must start after the project for the wash solutions (Use #3) is near completion as the new wash solution will need to be tested against the reagents.

The first project is envisaged to consume #G FTEs while the second will be allocated #G FTEs. For this investment in resources and time to come to fruition without disrupting the supply of IVD kits used in the #D analysers, a sufficiently long review period of 12 years will be required. Again, it is worth noting that the #D are Siemens Healthineers' #D on the market. If the availability of IVD kits on those platforms are impacted, this would have a very negative impact on the marketing success of these #D.

Use #3

For the wash solutions falling within the scope of Applied for Use #3, a Design Change project for #D product is planned. This is envisaged to start in #D, G and be completed by the end of 2032. The investment envisaged amounts to #G FTE. This project will cover the wash solution employed on the #D analyser which #D has a long future ahead. The wash solution for the #D analysers will not be reformulated. The IVD wash solution to be reformulated will have to be tested against #D assays to ensure that it remains compatible with those and that allows accurate and reproducible diagnostic results to be obtained. For this reason, its reformulation needs to wait until the relevant IVD kits are reformulated first, before the wash solution itself is

reformulated. If the opposite were to occur, the wash solution would first be reformulated and tested against the existing IVD kits and then re-tested again against the reformulated IVD kits.

6.2.3 Criterion 2: Cost of using alternatives

The cost of using alternatives has been discussed in Section 4.3.1 there are inherent uncertainties as the identity of the alternatives cannot be known and can only be established on a reagent-by-reagent basis. In any case, the most critical cost element would be the loss of profit associated with the period of downtime that would accompany any effort made by Siemens Marburg to implement process changes and reagent/wash solution reformulations. The basis for assumptions on the length of Siemens Marburg's absence from the market is the Siemens Healthineers' OPE Substitution plan which is presented in Section 6.3.

As discussed in the Section 4.3.1, the implementation of any alternative might attract the following costs:

- Internal R&D (reformulation) cost;
- Internal re-registration submission preparation cost;
- Re-registration fees; and
- Downtime losses for Siemens Marburg.

As summary of all costs per Applied for Use was presented in **Table 4–5** and is reproduced below for convenience. These costs are also compared to the Siemens Marburg profits from sales of the relevant IVD products in the year 2017.

Table 6–3: Summary of costs associated with the implementation of alternative substances per Applied for Use

Cost element	Use #1	Use #2	Use #3
Internal R&D (reformulation) cost	#D, E, G (table)	[redacted]	[redacted]
Internal re-registration submission preparation cost	[redacted]	[redacted]	[redacted]
Downtime losses for Siemens Marburg	[redacted]	[redacted]	[redacted]
Indirect losses for Siemens Healthineers	[redacted]	[redacted]	[redacted]
Total cost (PV, 4%)	[redacted]	[redacted]	[redacted]
Comparison to Siemens Marburg profits from sales of corresponding IVD products in 2017	[redacted]	[redacted]	[redacted]

The table confirms the significant costs that would be associated with the implementation of yet unknown alternatives as substitutes for OPE in each of the three Applied for Uses, if an Authorisation for these uses had not been granted. Moreover, the figures shown above are higher than the costs of the selected "Non-use" Scenario, shown in **Table 4-8** as the implementation of alternatives under conditions of non-Authorisation would ultimately result in the loss of profit equivalent to the shutdown of the relevant Marburg operations on top of the costs of researching and implementing the alternatives and re-registering the reformulated products with IVD authorities across the globe.

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

of OPEs on the Annex XIV list. This investment in OPE substitution activities diverts significant funds and efforts away from other areas of the Siemens Healthineers business and delays the development of innovative assay projects.

6.2.4 Criterion 3: Results of R&D on alternatives

Siemens Healthineers has been undertaking R&D on potential alternatives and Section 4.1.1 describes relevant experiments that have been conducted. To establish the most appropriate alternative substances for all the impacted IVD kits and wash solutions would require resources and time. For commercial OPE-containing products or those that have obtained final design status, only select feasibility testing has been conducted by Siemens Healthineers. The strategy has been to determine the efforts required to identify potential alternatives to Triton™ X-100/Triton™ X-405 in several critical assays spanning several different technologies. While there are examples of this being completed successfully using #F, there are also examples where it has been demonstrated that #F is not an acceptable replacement.

Each IVD product design is unique and each one must be fully tested to confirm that the selected 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 only 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 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 appears to be based on molecular interactions between the chemicals and the proteins involved, but the exact mechanisms are not fully understood. Each product is therefore produced by following a unique and product-specific protocol.

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

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/Triton™ X-405, the performance of the products would have to be verified and any performance changes will require a re-registration in most countries, at least for Uses #2 and #3.

Generally, the process of preparing an application for re-registration of an IVD kit and submitting it to the relevant authorities would include the following steps:

1. Change Project initiated by the Siemens Healthineers change team;
2. Initial Regulatory Assessment prepared by RA;
3. A Product Change Notification 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 would be consolidated and provided back to change team to incorporate requirements into project planning;

5. RA would review the change verification plans and reports and would prepare and collect the requested documentation to support country re-registrations. The Regulatory Assessment would be updated based on the verification results and the Country RA feedback; and

6. Country RA would prepare the applications to be submitted to their regulatory Authority. Q&A between Country RA and Business line RA would follow as needed to generate the required submission content.

Siemens Healthineers would typically allow #C, D months for submission preparation in each country. There are about 80 countries with re-registration requirements and submission requirements to each country vary. Siemens Healthineers estimates that re-registrations would generally be required in ca. 50 countries. This estimate is based on the fact that about 80 countries have regulatory requirements and 31 are under the EU + EFTA. The review time in the different countries vary between a few months to three-and-a-half years, with China taking the longest (42 months). The actual number will vary because it is dependent on the number of countries where each IVD product is placed on the market.

Siemens Healthineers' REACH Response Plan presented in Section 6.3 takes into account the regulatory activities that would be required after the completion of the reformulation activities.

The OPE Authorisation/Sunset Date coincides largely with the timeline for implementation of the new IVD Regulation 2017/746. Under the current legislation (IVD Directive 98/79/EC), the vast majority of the products are self-declared and can be brought into the market without involvement of a notified body. This will change dramatically under the new IVD Regulation when about 80% of the products will fall under the responsibility of a notified body. Prior to the date of application of the IVDR (May 2022) most IVD companies will be working to full capacity in nearly all departments implementing the new IVD regulation and preparing dossiers for the IVDR registration. Likewise, the notified bodies in each country will be dealing with large numbers of IVDR registrations. Working on the OPE replacement in parallel to the IVD Regulation re-registration could jeopardise the latter, and thereby the placing on the market in the EU (and in many other countries requiring a CE-mark).

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

Benefit-cost ratios for Applied for Uses

The benefit-cost ratios for the continued use of OPE under Applied for Uses #1, #2 and #3 are shown in **Table 6-4**. This table also shows the consumption of OPE in Marburg for each Use in 2021. The amounts shown will gradually decline as OPEs are substituted in the different processes and IVD products manufactured and the estimates of releases take into account the declining consumption of OPE and the associated releases of 4-tert-OP over time. The table shows that the benefit-cost ratio for each Applied for Use is substantial, ranging from € #E, H per kg of 4-tert-OP released to € #E, H per kg 4-tert-OP released.

Table 6-4: Benefit-cost ratios for Applied for Uses					
Applied for Use	**Requested review period**	**Consumption of OPE in Marburg in 2021 (kg)**	**Benefit to society over review period (€, PV, 4%)**	**Estimated 4-tert-OP aquatic releases over review period (kg)**	**Benefit-cost ratio (€/kg)**
Use #1	9 years	#A	#D, E	#H, J	#E, H
Use #2	12 years				
Use #3	12 years				

The above estimates do not encompass significant impacts that would arise under the "Non-use" Scenario and which could not be quantified/monetised. Under the "Non-use" Scenario, access of EEA patients to key assay tests run on a wide range of Siemens Healthineers analysers would be impacted, thus affecting 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 IVD kits falling within the scope of Uses #1 and #2 and many more were performed alongside the IVD wash solutions of Use #3. Moreover, it cannot be certain that there will be capacity for such tests to be undertaken in the EEA in the event of a non-Authorisation, as it is expected that IVD kits of other manufacturers which may also perform these tests could also rely on OPEs or the capacity to perform the impacted tests could be limited. Finally, these benefit-cost values are certainly underestimates because whilst benefits have been discounted, physical amounts of 4-tert-OP released over time have not been discounted.

In 2015, 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 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 of 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 Uses #1-3 above #E, H per kg 4-tert-OP released) are significantly higher than the higher end of the WTP values established by the IVM researchers.

Potential actions for further minimisation of the remaining risks

As described in Appendix 3 (Section 11), Siemens Marburg has considered the practicality and cost of implementing a range of different RMMs for the three Applied for Uses with the air of further reducing the releases of OPE/4-tert-OP to the environment. As is explained in the Appendix, the cost of introducing additional RMMs could potentially be very high. Nevertheless, for Use #1 and Use #2 Siemens Marburg has reached the decision to take measures beyond what is currently in place. Therefore, the following measures are planned to be implemented before the Sunset Date:

- Use #1: implementation of a system to collect fraction of OPE-containing buffer, classify as hazardous waste and send for incineration; and
- Use #2: implementation of disposable bulk containers, classification of empty containers as hazardous waste and disposal by incineration.

It is estimated that emission rates for these two Uses will decline by a factor of 95% compared to current (2019) levels.

On the other hand, the most appropriate additional RMM for Use #3 (implementation of a segregation system to collect the fraction of wastewater from OPE-containing buffers, classify as hazardous waste and send for incineration) could not be implemented before the Sunset Date and would have a very high cost estimated at ca. € #E, H (range: €1-10 million) per kg of 4-tert-OP release avoided, without taking into account the loss of profit from downtime during the implementation of the additional RMM. This cost is considered disproportionate and as such further measures to control releases from that use cannot be justified on either practical or cost-effectiveness grounds.

6.2.7 Overall conclusion

Siemens Marburg's use of OPEs meets the criteria set out by the ECHA Committees for the granting of long review periods:

- With regular maintenance, the Siemens Marburg unit can continue operating at a profit for decades to come, while Siemens Healthineers is making significant financial commitments in the active substitution of OPEs in a wider range of IVD products through its REACH Response Plan which aims to eliminate OPEs from the Applied for Uses by the end of 2032. The estimated cost of the entire REACH Response Plan is estimated at € #G (range: €10-100 million); within this, for Uses #2 and #3 for which resource demands can be estimated, a combined R&D cost of € #E, G (range: €1-10 million) is envisaged;

- The cost of using yet to be identified alternatives is very high and estimated to lie in the range of #D Euros. For Applied Use #3 in particular, significant costs would arise for Siemens Llanberis too;

- Ongoing and past R&D has not been successful in identifying a single feasible alternative; alternatives need to be investigated and selected on a product-by-product basis. Alternatives would require a long implementation period of several years, however absence from the market for more than 6 months would drive customers away from Siemens Healthineers analysers. Once customers invest (typically tens of thousands or Euros and often through a long tendering process) in a new analyser, they would be extremely unlikely to return to Siemens Healthineers products after the latter completes its reformulation activities and eliminates the use of OPEs;

- Substitution of OPE in attracts specific regulatory requirements in jurisdictions across the world. Re-registration of reformulated IVD products will take up to ca. 4 years in some cases. This time-consuming process prolongs the duration of substitution efforts and consequently the absence of the impacted IVD products from the market (if an Authorisation was not granted), thus causing significant market losses to Siemens Marburg; and

- The benefit:cost ratio for the continued use of OPEs is very high at between € #E, H and € #E, H per kilogram of 4-tert-OP released. The driver behind these values is the economic and social benefits for Marburg and Llanberis from the continued use of Triton™ X-100/Triton™ X-405. Significant, indeed critical, impacts on EEA patients are not reflected in these ratios because it has not been possible to quantify them. It should be understood that the number of tests run each year on the impacted Siemens Healthineers analysers is very large (in the range of millions per year) and they cover a wide range of diseases and conditions, both acute and long-term. There is a clear and substantial benefit to the EEA society from the continued use of OPEs in Marburg which allows the uninterrupted operation of #D analysers across the EEA.

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

6.3.1 Introduction to the process of substituting OPEs

There are three types of processes to be considered and described here when changing reagents, accessories (i.e. wash solutions) and processes (i.e. where OPE is a processing aid):

1. **Design Change Process (DCP)**: this is the type of project that will be initiated when it is planned to change the design of an existing product, or a formulation used in the manufacturing process needs to be changed.

2. **Product Development Process (PDP)**: this relates to the development and commercialisation of a new product; however, this also includes existing products where the reagent will be used on a new platform.

3. **Process Change**: this type of project will be initiated where an existing manufacturing process needs to be adapted, e.g. for the Cell Extraction process at Marburg, removing OPE would be considered a Process Change as the OPE is not present in the final product.

The typical duration of these projects is shown in **Figure 6–1**. These durations apply per group of IVD kits/wash solutions and it should be clear that for Siemens Marburg several such projects would be required.

The terms used in these two figures are explained in **Table 6-5**.

Table 6-5: Terms used in the description of activities encompassed in Siemens Healthineers' REACH Response Plan

Terms	Description
#F, G (table)	

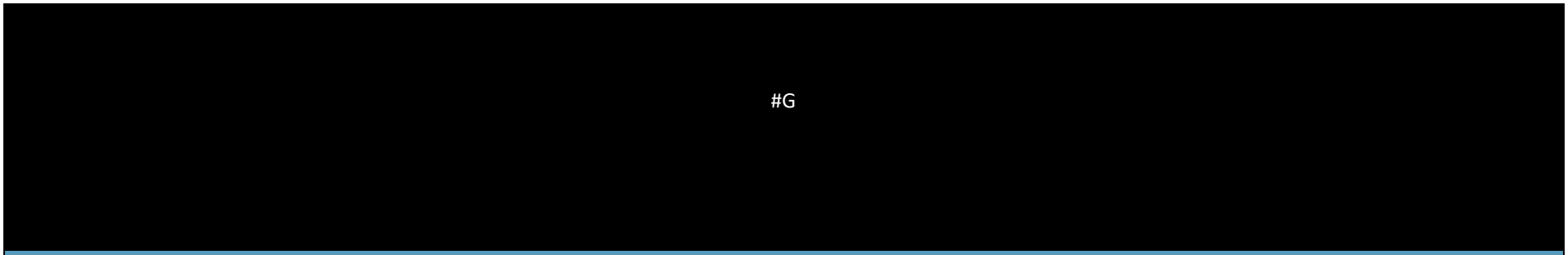


Figure 6–1: Overview of the duration of different types of substitution projects

6.3.2 OPE substitution strategy for Applied for Uses #1, #2 and #3

A further figure, **Figure 6–2**, summarises the steps and durations involved in all projects involved in the substitution of OPEs in the two Applied for Uses. The key parameters of the projects involved are outlined for clarity in the following table.

Table 6–6: Summary of costs associated with the implementation of alternative substances per Applied for Use

Applied for Use	No. of projects	Project	IVD formulations involved		Estimated date of completion (end of)
			#	IDs	
[redacted]	[redacted]	[redacted]	[redacted]	#D, G (table)	Q1 2028
					Q4 2029 – End of Life
					Q1 2028
					Q4 2032
					Q3 2027
					Q4 2029 – End of Life
					Q1 2033
					Q4 2029 – End of Life

Figure 6–2: OPE Substitution Programme for Siemens Marburg's Applied for Uses #1, #2 and #3 - Overview

The plan behind this table is described further below:

- **Use #1**: for Protein Cell Extraction, the volume of OPE used for this process is ca. #A (range: 1-10) kg per year (projected for 2021), it is used in a controlled manufacturing environment (as set out in the CSR), with solid waste collected as hazardous and incinerated and liquid waste discharged to a municipal water treatment facility and there is no OPE in the final product sent to customers. Of the ca. #A kg consumed, #A (range: 0.1-1) kg is used to manufacture the #D, so a reduction in use is expected year on year as the #D. A Process Change is planned for #D which could be completed within #G years, and therefore a reduction in the consumption of OPEs will occur throughout the 9 years of the requested review period;

- **Use #2**: it is planned to reformulate #D, G of the impacted products and it is expected to take 12 years to complete this task. This is due to the Design Change process, the high number of reformulations and the required resources, also the concomitant re-registration activities. For these products, real-time stability data will be required (this period matches the shelf-life of the product). The first step is a selection of alternative candidates, buffer conditions and validation of concentrations, next step is real-time stability (normally 2 years), then performance evaluation and any subsequent regulatory activity - and this must be performed for each individual product. It is the Siemens Healthineers' strategy to initially perform feasibility testing with alternatives which may not affect/change the product performance, and in which case will reduce the regulatory activity necessary (could result in 'Note to File') and the expected reduction in OPE volume will happen sooner. It is not known whether this strategy will be successful until feasibility testing has been completed. Therefore, the current review period requested reflects >3 years 'Agency Submission Review'; and

- **Use #3**: it is planned to reformulate the #D wash solution, however this is expected to take 12 years to complete this work due to the Design Change process and resources required at Marburg. The reformulation of the #D wash solution must be done sequentially (as indicated in the REACH Response Plan) following the reformulation of the #D reagents. The reason for this is because the reformulated wash will need to be tested with all #D assays used on the same platform (at the feasibility stage).

There are a further five IVD products #D which will come to the end of their lives by the end of the requested review period and therefore reformulation will not be undertaken for them. Also, for reasons explained earlier, reformulation of the #D #D (Applied for Use #3) will not be performed, as the #D business line is . Finally, the plan does not include details of any substitution activities planned by #D, the OEM that supplies #D of the IVD kit reagents that Siemens Marburg sells to certain of its customers. Details are supplied in #D's separate AfA.

Siemens Healthineers' focus on this extensive REACH Response Plan does mean that significant funding and effort is diverted from other areas of the business and this will result in a reduction in the number of innovative assay projects that the company can focus on developing in the next decade or so.

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 Llanberis is separately applying for its own continued use of OPE in the formulation and use of bead coating/washing solutions which are used in the manufacture of OPE-free #D IVD kits. One of the solutions used is based on the #D protein that Siemens Marburg generates under the present Applied for Use #1. Also, Siemens Marburg manufactures the #D #D which must be used alongside all #D IVD kits manufactured in Llanberis whether these depend on the use of OPE of not. The following dependencies are therefore noted:

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

  - 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 #D to remain available or else the entire #D business line would collapse after the Sunset Date as no #D analyser user could continue operating their analysers without the irreplaceable #D.

- 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 noted:

  - **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;

  - **Siemens Llanberis** relies on Use #5 being granted an Authorisation in order for EEA demand for #D IVD kits (whether they depend on the use of OPE) to be maintained after the Sunset Date. Without the #D, no #D IVD kit can be used;

  - **Siemens Healthineers in the USA** relies on Uses #4 and #5 being granted an Authorisation in order for (a) EEA demand for the OPE-containing IVD kits manufactured in the USA and sold in the EEA market via the EDC to be maintained after the Sunset Date, (b) EEA demand for the OPE-containing IVD wash solutions manufactured in the USA and sold in the EEA market via the EDC to be maintained after the Sunset Date;

  - **OEMs** manufacturing OPE-containing IVD kits and wash solutions which are subsequently sold by Siemens Marburg to EEA customers via the EDC rely on Uses #4 and #5 being granted an Authorisation in order for EEA demand for their OPE-containing IVD kits and wash solutions 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 IVD kits and wash solutions made in Marburg with the use of OPEs 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 #D OPE-dependent #D kits to be maintained after the Sunset Date.

7 REFERENCES

Ardisson, L., Iafrate, A. J. and Lewandrowski, K. (2007) 'An Analysis of Reference Laboratory Testing in a Large Urban Academic Medical Center: The Impact of New Molecular Diagnostic Technologies', *Lab Medicine*, 38(8), pp. 472–485. doi: 10.1309/G2MM69T9C4C97W0W.

BAuA (2011) *ANNEX XV REPORT-IDENTIFICATION OF SVHC Annex XV Dossier PROPOSAL FOR IDENTIFICATION OF A SUBSTANCE AS A CMR CAT 1A OR 1B, PBT, vPvB OR A SUBSTANCE OF AN EQUIVALENT LEVEL OF CONCERN*. Available at: https://echa.europa.eu/documents/10162/397abe32-ecb8-451c-87d2-33af413687dd (Accessed: 18 January 2019).

Dubourg, R. (2016) *Valuing the social costs of job losses in applications for authorisation*. Available at: https://echa.europa.eu/documents/10162/13555/unemployment_report_en.pdf/e0e5b4c2-66e9-4bb8-b125-29a460720554 (Accessed: 28 December 2017).

ECHA (2013) *SETTING THE REVIEW PERIOD WHEN RAC AND SEAC GIVE OPINIONS ON AN APPLICATION FOR AUTHORISATION*.

ECHA (2016) *The social cost of unemployment*. Available at: https://echa.europa.eu/documents/10162/13555/seac_unemployment_evaluation_en.pdf/af3a487e-65e5-49bb-84a3-2c1bcbc35d25 (Accessed: 28 December 2017).

Environment Agency (2016) *Catchment Data Explorer - Mersey*. Available at: https://environment.data.gov.uk/catchment-planning/WaterBody/GB531206908100 (Accessed: 7 March 2019).

EU (2010) *Directive 2010/75/EU of the European Parliament and of the Council of 24 November 2010 on industrial emissions (integrated pollution prevention and control)*. Available at: https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=celex:32010L0075 (Accessed: 21 February 2019).

European Commission (2016) *Priority Substances and Certain Other Pollutants according to Annex II of Directive 2008/105/EC - Environment - European Commission*. Available at: http://ec.europa.eu/environment/water/water-framework/priority_substances.htm (Accessed: 21 February 2019).

Kalorama Information (2016) *The Worldwide Market for IVD Tests, 10th Edition*.

Oosterhuis, F. and Brouwer, R. (2015) *Benchmark development for the proportionality assessment of PBT and vPvB substances*. Available at: https://echa.europa.eu/documents/10162/13647/R15_11_pbt_benchmark_report_en.pdf (Accessed: 13 December 2018).

OSPAR Commission (2014) *Background Document - Establishment of a list of Predicted No Effect Concentrations (PNECs) for naturally occurring substances in produced water (OSPAR Agreement 2014-05)*. Available at: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/361476/OSPAR_RBA_Predicted_No_Effect_Concentrations__PNECs__Background_Document.pdf (Accessed: 7 March 2019).

Porter, K. L. *et al.* (2011) 'Effects of 4-tert-octylphenol on Xenopus tropicalis in a long term exposure', *Aquatic Toxicology*. Elsevier, 103(3–4), pp. 159–169. doi: 10.1016/J.AQUATOX.2011.02.019.

StatsWales (2017) *Average (median) gross weekly earnings by Welsh local areas and year (£)*. Available at: https://statswales.gov.wales/Catalogue/Business-Economy-and-Labour-Market/People-and-Work/Earnings/medianweeklyearnings-by-welshlocalareas-year (Accessed: 9 October 2018).

UK Government (2015) *The Water Framework Directive (Classification, Priority Substances and Shellfish Waters) Regulations (Northern Ireland) 2015*. Available at: http://www.legislation.gov.uk/nisr/2015/351/pdfs/nisr_20150351_en.pdf (Accessed: 21 February 2019).

WRRL (2017) *WRRL-Viewer*. Available at: http://wrrl.hessen.de/mapapps/resources/apps/wrrl/index.html?lang=en (Accessed: 12 April 2019).

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]

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

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]
[redacted]	[redacted]	[redacted]	[redacted]

9 Appendix 1: Consultations

To support the Siemens Marburg's AfAs (and primarily the one for the downstream uses #4 and #5), a limited number of interviews and a more extensive customer survey were undertaken with the aim of identifying potential impacts on customers as a result of authorisation. The survey in particulat was aimed at Siemens Healthineers (Marburg) customers that use OPE-containing products, in other words, at a pre-selection of the total set of Siemens Healthineers customers. The objective of the survey was to investigate the ways in which customers deal with analyser waste water and the potential impacts of additional RMMs intended to change their current approach.

A digital, web-based survey was launched in 6 languages (English, French, German, Italian, Spanish and Greek). Siemens sent letters by post to their selected customer contacts inviting them to participate, and this invitation was followed by a reminder letter. Approximately #D (range: 1,000-10,000) relevant EEA customers were invited to participate. The survey ran from week 3 of March 2019 for a period of 5 weeks.

The survey included 21 questions, 6 on demographic information and 15 content questions. In particular, detail was sought on numbers and types of Siemens Healthineers analyser used, especially #D analyser models. Questions also covered analyser wastewater management: treatment, volumes, costs; impacts of change.

The highlight results of the survey can be summarised as follows:

- In total, there were #D, I (range: 50-200) respondents. All responses to each language survey came from the associated country (e.g. English survey respondents are located in the UK, etc.). Respondents were mostly (#D, I % (range: 50-75%)) hospitals, with a fairly even split between town and city locations;

- In terms of types of analysers owned (Siemens Healthineers vs other suppliers' analysers), in total just over 25% #D, I (range: 100-1,000) of analysers used by respondents are Siemens Healthineers analysers, with #D, I % (range: 1-10%) of these being #D analyser models;

- #D, I (range: 10-100) respondents provided input on how they deal with Siemens Healthineers analyser wastewater, with some reporting more than one of the possible approaches. Most (just under #D, I % of Siemens Healthineers analysers) goes down the drain (just over #D, I % via direct connection from the analyser to the drain; the rest being collected in a sump and emptied manually). Most #D, I % (range: 60-90%) indicated that more than 80% of total Siemens Healthineers analyser wastewater volume is disposed of in this way;

- Respondents typically (67%) do not have access to a central waste system; and

- Some participants (19% of responses received to these questions were "unknown") provided input on the impacts of changing wastewater management processes. Most frequently mentioned (though low in absolute number) were concerns regarding the need for structural changes that would be required for the implementation of additional RMMs.

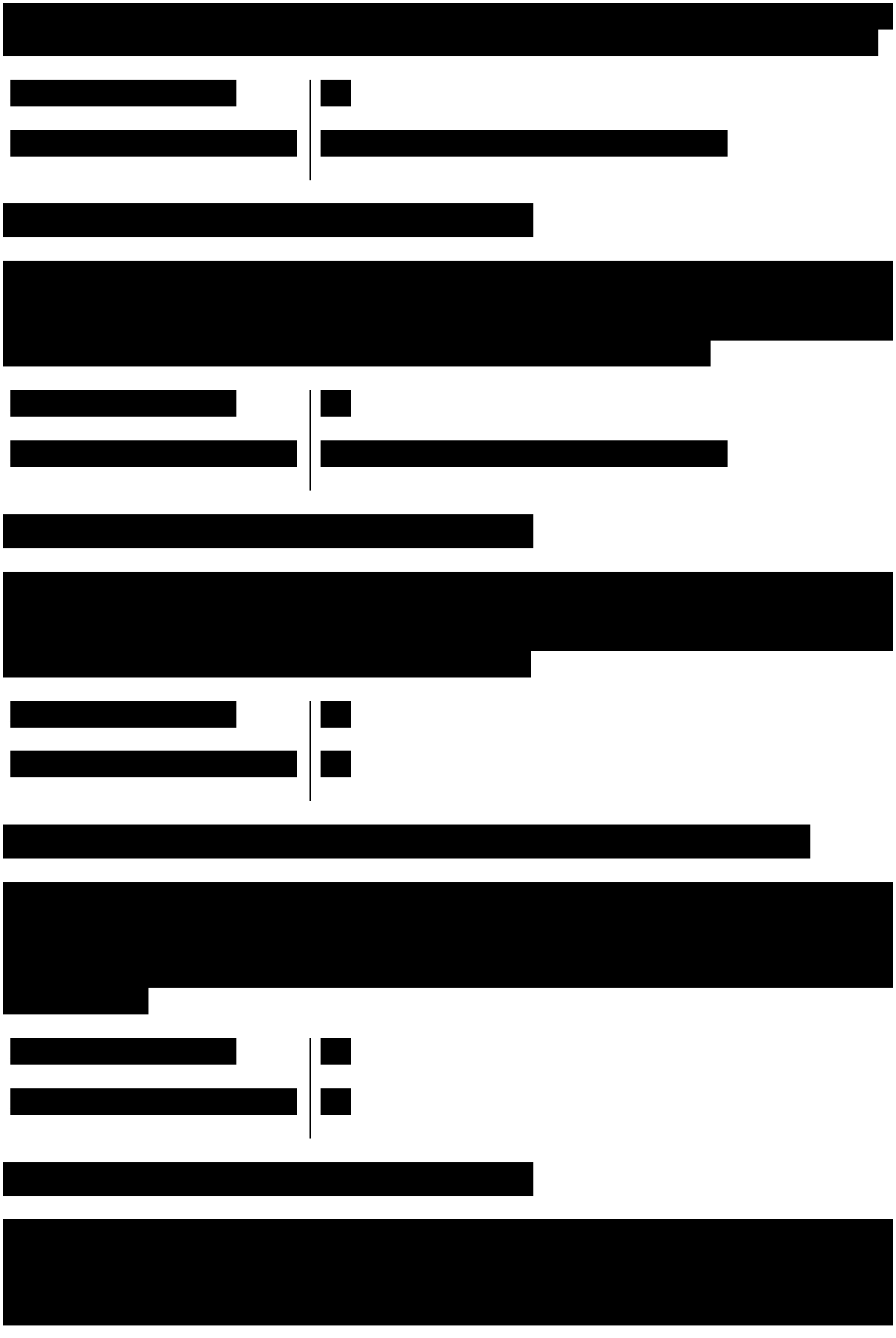
The reader is referred to Appendix 1 to the Siemens Marburg AoA-SEA for Uses #4 and #5 (separate document) for further details of the survey, including analyses per country.

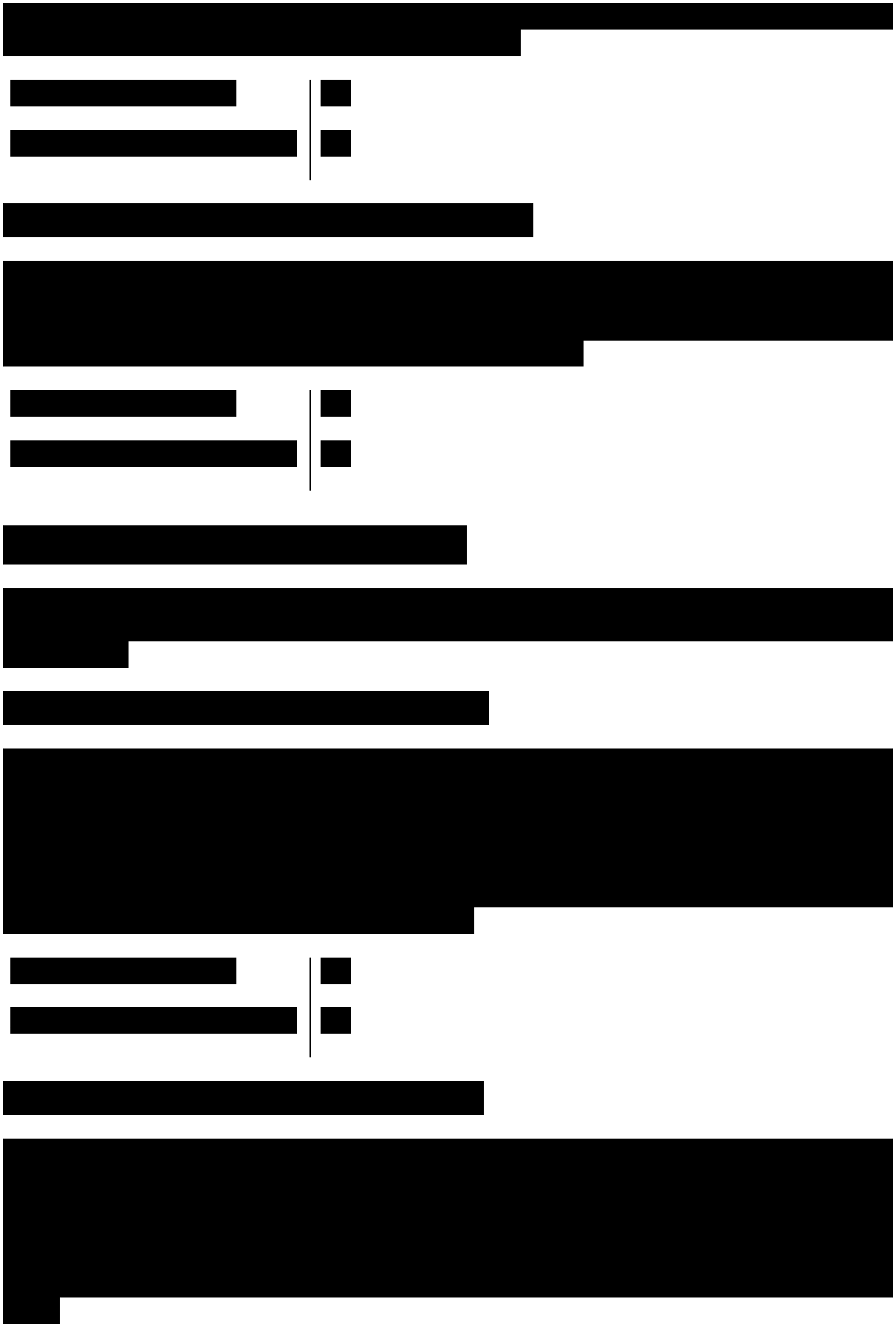
10 Appendix 2: Overview of relevant analysers

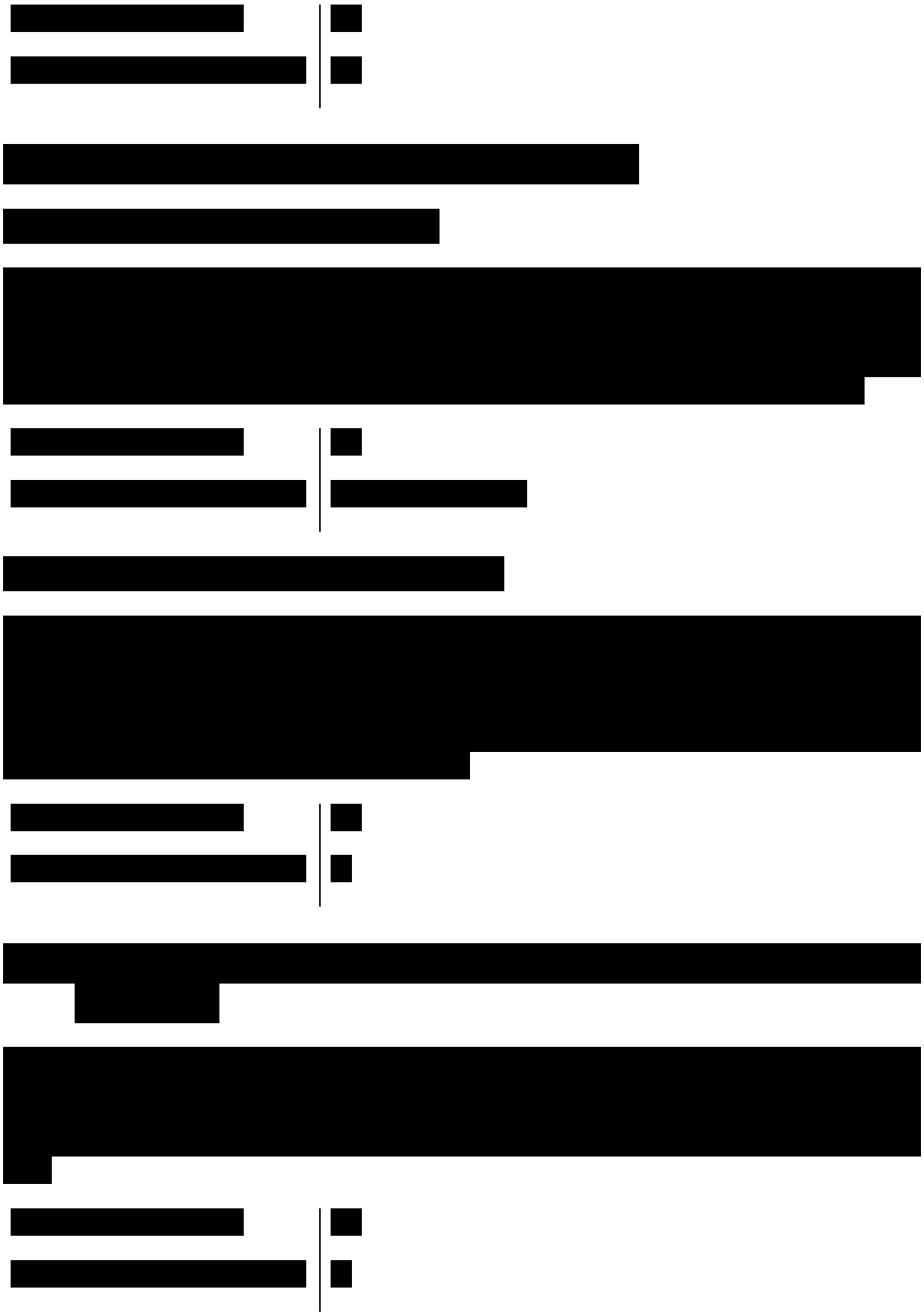
10.1 Introduction

Siemens Healthineers currently have #D (entire Appendix) different analyser models that that rely on OPE-dependent IVD kits. Additionally, Siemens Healthineers supplies OPE-dependent IVD kits to be used with [redacted] third party analysers (these are given only a cursory reference due to the lack of substantial volumes of information on them). In many cases, the analysers can only work with Siemens Marburg-made IVD kits. The different analysers using IVD products (reagents and wash solutions) manufactured by Siemens Marburg are presented below. Third party analysers use only a very small proportion of Marburg-made IVD products and are not discussed.

[redacted]







[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 wastewater for the Use #1, Use #2 and Use #3 in Marburg, 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 uses of OPE in Marburg are:

- Amount of OPE consumed:
  - **Use #1**: #A kg;
  - **Use #2**: #A kg; and
  - **Use #3**: #A kg.
- Amount of OPE in Marburg wastewater:
  - **Use #1**: #A kg;
  - **Use #2**: #A kg; and
  - **Use #3**: #A kg.
- Volume of wastewater generated at Marburg:
  - **Use #1:** ca. #H t/y wastewater is generated from discharge of buffers containing OPE; and
  - **Use #2 and Use #3:** ca. #B t/y wastewater is generated from cleaning of stainless steel containers for storage of buffer containing OPEs, but also from cleaning of numerous stainless-steel containers for storage of buffer containing which do not contain OPE as well as cooling water, etc.
- Current wastewater disposal arrangements:
  - Siemens Marburg (Siemens Healthcare Diagnostics Products GmbH) is located at the Behringwerke business park in Marburg Görzhausen. At the business park Behringwerke, there is no segregation between wastewater and rainwater. The wastewater comes together into the same drainage-system.
  - At each building-outlet, samples for analysis can be taken. The entire wastewater of the plant comes into the main sewer pipe which leads into the STP in Marburg-Cappel (approximately 12km far away from the business park).
  - A retention basin is at the business park located in front of the transfer point into the public sewer pipe. Samples for analysis can be taken at this retention basin as well.
  - The Pharmaserv company (site operator of the business park Behringwerke) has the required discharge permit from the city of Marburg.

11.2 Possible scenarios for further reduction of OPE release

11.2.1Use #1

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.

Table 11-1: Alternative scenarios for the implementation of additional Risk Management Measures for the minimisation of OPE releases to the environment – Applied for Use #1	
	Alternative Scenario
Description	Implement system to collect fraction of OPE-containing buffer, classify as hazardous waste and send for incineration
Key technical parameters	- The volume of wastewater would be ca. #B t/year
Key cost parameters	- **Investment cost - Initial set-up**: ca. € #D - **Ongoing cost – additional work load and incineration cost**: ca. € #D /y
Anticipated reduction in OPE emissions	- Assumed 95%
Benefits	- Nearly complete elimination of OPE emissions at acceptable cost
Risks/Drawbacks	- Change in practices to ensure correct disposal (update of procedures, training, etc.) - Initial investment and ongoing costs - Environmental impact of incinerating of wastewater

11.2.2Use #2

Alternative scenarios have been developed for the theoretical implementation of additional RMMs beyond what is currently in place. These are set out in **Table 11-2** and assessed for feasibility.

On the basis of the analysis presented in the table, **Alternative Scenario 3** has been concluded to be the most feasible for the following reasons:

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

11.2.3Use #3

Alternative scenarios have been developed for the theoretical implementation of additional RMMs beyond what is currently in place. These are set out in **Table 11-3** and assessed for feasibility.

Table 11-2: Alternative scenarios for the implementation of additional Risk Management Measures for the minimisation of OPE releases to the environment – Applied for Use #2					
	Alternative Scenario 1	**Alternative Scenario 2**	**Alternative Scenario 3**	**Alternative Scenario 4**	**Alternative Scenario 5**
Description	Classify all wastewater of this manufacturing area as hazardous waste and send all wastewater for incineration	Implement segregation system to collect fraction of wastewater from OPE-containing buffers, classify as hazardous waste and send for incineration	Implement disposable bulk containers, classify empty containers as hazardous waste and send for incineration	All wastewater 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. Incinerator
Key technical parameters	The volume of wastewater would be ca. #B t/year	The volume of wastewater would be ca. #B t/year	Single use containers: Sizes from 5 to 1000 litres	At present no known filter technology on the market designed for OPEs	Area on site would need to be identified for installation
Key cost parameters	- **Investment cost**: ca. € #E for new installation and storage tanks of wastewater - **Ongoing cost - incineration cost**: € #D /t, or € #D, E /y	- **Investment cost - Initial set-up**: ca. € #E for new installation and storage tanks of wastewater - **Ongoing cost – incineration cost**: € #D /t, or € #D, E /y	- **Investment cost - Initial set-up**: ca. € #E - **Ongoing cost:** Comparable to actual cost	Not possible to calculate at present	**Investment cost**: ca. € #E
Anticipated reduction in OPE emissions	Assumed 100%	Assumed 100%	Assumed 95%	Unknown until filter was designed and efficacy tested	Assumed 100%
Benefits	Complete elimination of OPE emissions	Complete elimination of OPE emissions	Nearly complete elimination of OPE emissions	If filter was available, volume of hazardous waste generated would be low	- Complete elimination of OPE emissions - Wastewater does not need to be transported off-site, once treated, assume wastewater could go into public sewer system

Table 11-2: Alternative scenarios for the implementation of additional Risk Management Measures for the minimisation of OPE releases to the environment – Applied for Use #2					
	Alternative Scenario 1	**Alternative Scenario 2**	**Alternative Scenario 3**	**Alternative Scenario 4**	**Alternative Scenario 5**
Risks/Drawbacks	- Significant overall costs due to low calorific value of wastewater - Environmental impact of incinerating high volumes of wastewater	- Change in practices to ensure correct disposal (update of procedures, training etc) - Initial investment and ongoing costs - Environmental impact of incinerating of wastewater	- Material change of primary containers (from stainless steel to single use) needs intensive validation work - Risk of leaking of plasticisers into reagent - Risk of undefined absorption of reactive components to single-use container	At present no known filter on the market designed to deal with OPEs, developing one (if technically feasible) could take significant time	Incinerator: community concern over installation of an incinerator very likely (based on similar initiatives in region). Likelihood of receiving planning permission considered low.

Table 11-3: Alternative scenarios for the implementation of additional Risk Management Measures for the minimisation of OPE releases to the environment – Applied for Use #3					
	Alternative Scenario 1	**Alternative Scenario 2**	**Alternative Scenario 3**	**Alternative Scenario 4**	**Alternative Scenario 5**
Description	Classify all waste water of this manufacturing area as hazardous waste and send all wastewater for incineration	Implement segregation system to collect fraction of wastewater from OPE-containing buffers, classify as hazardous waste and send for incineration	Implement disposable bulk containers, classify empty containers as hazardous waste and send for incineration	All wastewater 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. Incinerator
Key technical parameters	The volume of wastewater would be ca. #B t/year	The volume of wastewater would be ca. #B t/year	At present disposable bulk containers for 2000+ litres are not manageable	At present no known filter technology on the market designed for OPEs	Area on site would need to be identified for installation
Key cost parameters	- **Investment cost**: ca. € #E for new installation and storage tanks of waste water - **Ongoing cost - incineration cost**: € #D /t, or € #D, E /y	- **Investment cost - Initial set-up**: ca. € #E for new installation and storage tanks of waste water - **Ongoing cost – incineration cost**: € #D /t, or € #D, E /y	Not possible to calculate at present	Not possible to calculate at present	- **Investment cost**: ca. € #E
Anticipated reduction in OPE emissions	Assumed 100%	Assumed 100%	Assumed 95%	Unknown until filter was designed and efficacy tested	Assumed 100%
Benefits	Complete elimination of OPE emissions	Complete elimination of OPE emissions	Nearly complete elimination of OPE emissions	If filter was available, volume of hazardous waste generated would be low	- Complete elimination of OPE emissions - Wastewater does not need to be transported off-site, once treated assume wastewater could go to public sewer system

Table 11-3: Alternative scenarios for the implementation of additional Risk Management Measures for the minimisation of OPE releases to the environment – Applied for Use #3					
	Alternative Scenario 1	**Alternative Scenario 2**	**Alternative Scenario 3**	**Alternative Scenario 4**	**Alternative Scenario 5**
Risks/Drawbacks	- Significant overall costs due to low calorific value of wastewater - Environmental impact of incinerating high volumes of wastewater	- Change in practices to ensure correct disposal (update of procedures, training, etc.) - Initial investment and ongoing costs - Environmental impact of incinerating of wastewater	- Material change of primary containers (from stainless- steel to single-use containers) needs intensive validation work - Risk of leaking of plasticisers into wash solution - Risk of undefined absorption of reactive components to single-use container surface	At present no known filter on the market designed to deal with OPEs, developing one (if technically feasible) could take significant time	Incinerator: community concern over installation of an incinerator very likely (based on similar initiatives in region). Likelihood of receiving planning permission considered low.

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 OPE 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 OPE releases to the environment at a cost lower than other Scenarios.

11.3 Proportionality of the additional RMMs

Table 11-4 summarises the steps that would be required for the practical implementation of the shortlisted additional RMMs for each of the Applied for Uses. This table suggests that following costs for implementing the shortlisted RMMs for each of the Applied for Uses:

- Use #1: ca. € #E, H (range: €1,000-10,000) per kg 4-tert-OP release prevented;
- Use #2: ca. € #E, H (range: €1-10 million) per kg 4-tert-OP release prevented; and
- Use #3: ca. € #E, H (range: €1-10 million) per kg 4-tert-OP release prevented.

It can be seen that only for Use #1 the envisaged cost for additional RMMs can be deemed proportionate. For this Applied for Use, Siemens Marburg has formally decided to implement the shortlisted RMMs which will reduce emissions by an estimated 95% and implementation is to be completed before the Sunset Date.

For the other two Applied for Uses, the envisaged costs of additional RMMs are significantly higher when compared to the amount of 4-tert-OP releases that could be prevented. However, for Use #2 the total cost (in Euros) for implementing the shortlisted additional RMM is considered modest and as such Siemens Marburg has formally decided to implement it and by that reduce emissions by an estimated 95%. Implementation of the additional RMM is to be completed before the Sunset Date.

On the other hand, the implementation of the shortlisted RMM for Applied for Use #3 cannot be justified for several reasons:

- Its implementation has a high cost. Moreover, manufacturing activities during installation of the waste stream pipe systems would be disrupted. This would come at a cost that has not been taken into account in the calculations of **Table 11-4**; and

- The additional RMM cannot be implemented before the Sunset Date.

Thus, the cost of the additional RMM for Use #3 is deemed disproportionate. As a result, Siemens Marburg cannot justify any RMM beyond what is currently in place for that Applied for Use.

Table 11-4: Alternative scenarios for the implementation of additional Risk Management Measures for the minimisation of OPE releases to the environment			
	Use #1	**Use #2 / Scenario 3**	**Use #3 / Scenario 2**
Implementation steps			
Description	Implement system to collect fraction of OPE-containing buffer, classify as hazardous waste and send for incineration	Implement disposable bulk containers, classify empty containers as hazardous waste and send for incineration	Implement segregation system to collect fraction of wastewater from OPE-containing buffers, classify as hazardous waste and send for incineration
Implementation steps	Change in practices to ensure correct disposal (update of standard operating procedures, training, etc.)	- Validate use of disposable bulk containers for OPE containing reagent bulks - Implement (update of standard operating procedures, training, etc.)	Implement segregation system Implement transportation to incineration
Economic impact			
Implementation cost / Set-up costs	ca. € #E	ca. € #E	ca. € #E
Implementation cost / Ongoing costs	Additional work load and incineration cost: ca. € #D /y	Nil	Additional work load and incineration cost: ca. € #E /y
Total present value cost over requested review period	**ca. € #D, E (range: €10,000-100,000)**	**€ #D, E (range: €10,000-100,000)**	**ca. € #D, E (range: €10-100 million)**
Envisaged OPE release reduction			
Assumed OPE release reduction achieved compared to current status	95%	95%	100%
Assumed OPE release reduction achieved over requested review period	#H kg (aquatic + sludge)	#H kg (aquatic + sludge)	#H kg (aquatic + sludge)
Benefit:cost ratio			
Ratio costs [€] per kg of OPE release avoided	ca. #E, H (range: 1,000-10,000)	ca. #E, H (range: 1-10 million)	ca. #E, H (range: 10-100 million)
Implementation before OPE sunset date	Yes	Yes	No

12 Appendix 4: Past research on alternative for OPEs

13 Appendix 5: Confidential information submitted in support of Application for Authorisation by #D [redacted]