SUBSTITUTION PLAN

Public version

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

Note

This complete version of this document includes some text and figures that are highlighted in grey. These parts of text have been blanked out in the public version of this document. Justification for confidentiality claims is provided in the Annex (Section 5) of the present document.

Table of contents

List of tables

List of figures

List of abbreviations

4-tert-OP	4-tert-Octylphenol / 4-(1,1,3,3-tetramethylbutyl)phenol
AfA	Application for Authorisation
AoA	Analysis of Alternatives
CAI	Chemistry, Automation & Informatics
CMC	Critical Micelle Concentration
[redacted]	#D, F (table)
CRB	Change Review Board
DCP	Design Change Process
DfE	Design for the Environment
DU	Downstream Users
EEA	European Economic Area
EFTA	European Free Trade Association
EOL	End of Life
EPA	Environmental Protection Agency (US)
EU	European Union
FDA	Food and Drug Administration (US)
GmbH	Gesellschaft mit beschränkter Haftung
HLB	Hydrophile-lipophile balance
IFU	Instruction for Use
IVD	In-Vitro Diagnostic
IVDR	In-vitro diagnostic medical device regulation
OEM	Original Equipment manufacturer
OP	Octylphenol
OPE, OP/E, OPnEO	Octylphenol ethoxylate
PDP	Product Development Process
PHT	Product Health Team
PMA	Premarket Approval Application
PTR	Product Technical Requirements
R&D	Research and development
RA	Regulatory Affairs
REACH	Registration, Evaluation, Authorisation and Restriction of Chemicals
SCM	Supply Chain Management
SEA	Socio Economic Analysis
SEAC	Committee for socio-economic analysis

[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
USA	United States of America

DECLARATION

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

Also, we request that the information blanked out in the "public version" of the Substitution Plan is not disclosed. We hereby declare that, to the best of our knowledge as of today (15/10/2019) the information is not publicly available, and in accordance with the due measures of protection that we have implemented, a member of the public should not be able to obtain access to this information without our consent or that of the third party whose commercial interests are at stake.

Signature:

Fraser Logue, Managing Director

Date, Place: 15/10/19
Siemens, Llanberis

Signature:

Gill Hughes, Finance Director

Date, Place: 15/10/19
Siemens, Llanberis.

Summary

Background to the substance and the Applied for Uses

This Application for Authorisation and Substitution Plan are relevant to Entry #42 in the Authorisation list; the specific OPE that is of relevance to this analysis is commercially known as Triton™ X-100.

This OPE is used as a processing aid in the manufacture of beads which are an essential component of the IVD kits for a specific immunoassay platform, #D . The platform also uses an OPE-containing #D which is manufactured by Siemens Marburg (the use of OPE in the manufacture of this #D is covered in a separate AfA submitted by Siemens Healthcare Diagnostics Products GmbH).

OPE is used in the production of #D (range: 10-100) analyte bead components, which are bespoke to specific target analytes for certain diseases and conditions. The #D beads are used as a component in #D (range: 10-100) #D IVD kits.

The function of OPE in these IVD analyte beads can be grouped into the following two categories:

- Acting as a cleaning agent for the removal of impurities from the #B surface of the beads (#D IVD analyte beads); and
- Acting as a stabiliser in the coating of the #D bead and the #D bead.

OPE is used as a processing aid in the bead production and is not present in the final product.

To give some background to IVD technology, it is core to the practice of modern medicine. IVD Kit Reagents and associated IVD Wash Solutions are used to perform qualitative and quantitative tests to diagnose a broad range of diseases and health conditions. They are used by downstream users within the healthcare sector, typically hospitals and commercial laboratories, for diagnosis of certain diseases and conditions in patient samples. Immunoassays are analytical tests which measure the concentration or presence of an analyte through the exploitation of a highly specific antibody-antigen interaction. Section 5.2.2 of the AoA-SEA document estimates that ca. #D (range: 10-100 million) tests have been performed on EEA patients using the OPE-dependent #D IVD kits in 2017.

The Substitution Plan

Siemens Llanberis will not actively aim to substitute OPE in the preparation of the beads but will rather substitute the #D that relies on the use of OPE with #C, D . of the requested 9-year review period. In addition, the applicant will aim to further minimise releases of OPEs from the use of Triton™ X-100 as a process chemical in Llanberis by 99% prior to the sunset date.

It is important to note that the #D is one part of the global portfolio of Siemens Healthineers products which are impacted by the addition of OPE to Annex XIV. The rest of the global portfolio is subject to another AfA submitted by Siemens Healthcare Diagnostics Products GmbH.

Substituting OPE in an IVD product of any kind is a lengthy and challenging process, and therefore Siemens Healthineers has focused its Substitution efforts #D [redacted]. The challenges of substitution and the rationale for the global strategy are presented in more detail in the following text.

1 Factors affecting substitution

1.1 Availability of the Alternative

1.1.1 Introduction

As noted, Siemens Llanberis will gradually phase out the use of OPE's at Llanberis #D [redacted]. As described in the separate AfA submitted by Siemens Healthcare Diagnostics Products GmbH, many of the #D [redacted] IVD Reagents currently contain OPE and there is significant focus on re-designing these products to substitute OPE at present.

Given that the substitution of the #D [redacted] relies on the substitution of OPE with an alternative substance #D [redacted], the factors affecting substitution of OPE with an alternative substance are a main focus of this document.

Also, as the strategy described above is just one part of a larger Substitution Plan to substitute OPE or phase out products containing OPE in the wider Siemens Healthineers portfolio this document presents the Siemens Llanberis Substitution Plan within that larger context.

Section 4.1.1 of the AoA-SEA document provides a detailed analysis of the challenges faced by IVD kit manufacturers in their efforts to substitute OPEs in their formulations. Some of this information is replicated below for convenience.

1.1.2 Steps and complexity of design change processes

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 1–1**, 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.

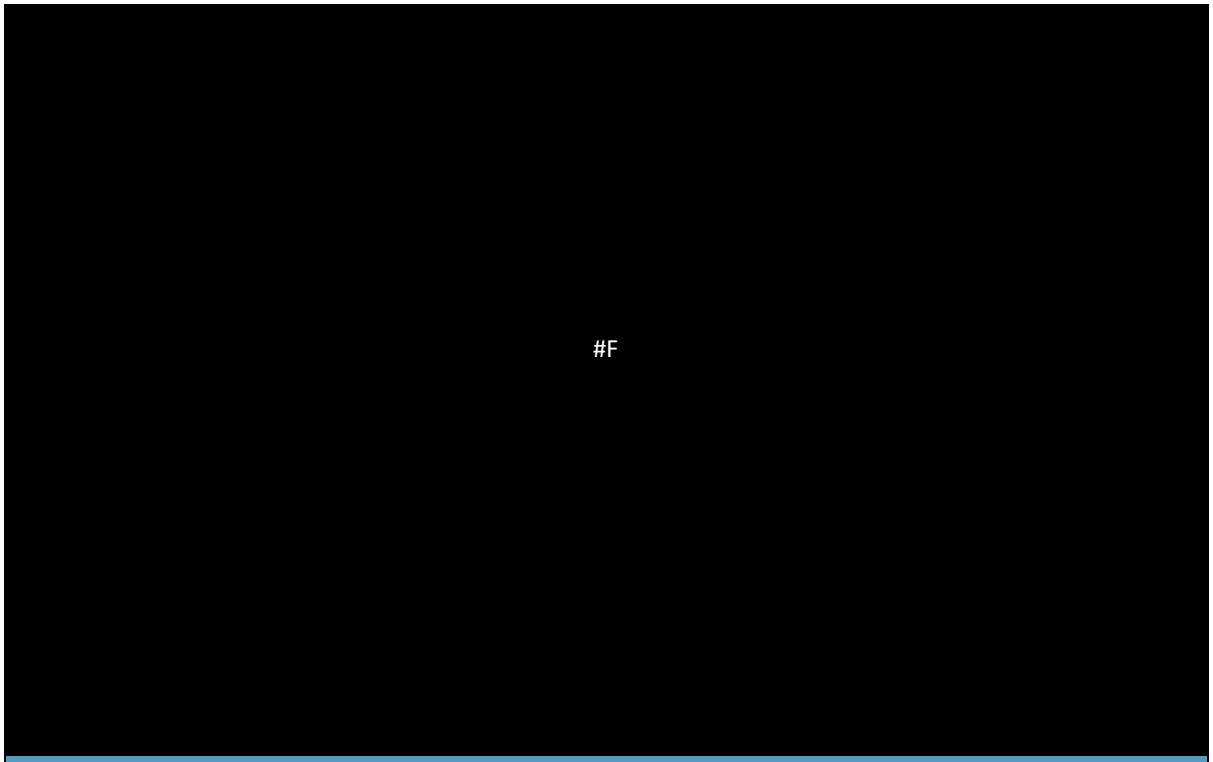

Figure 1–1: Product Design and Design Change Process Steps

The different activities involved in each phase of the process are shown in **Figure 1–2**.

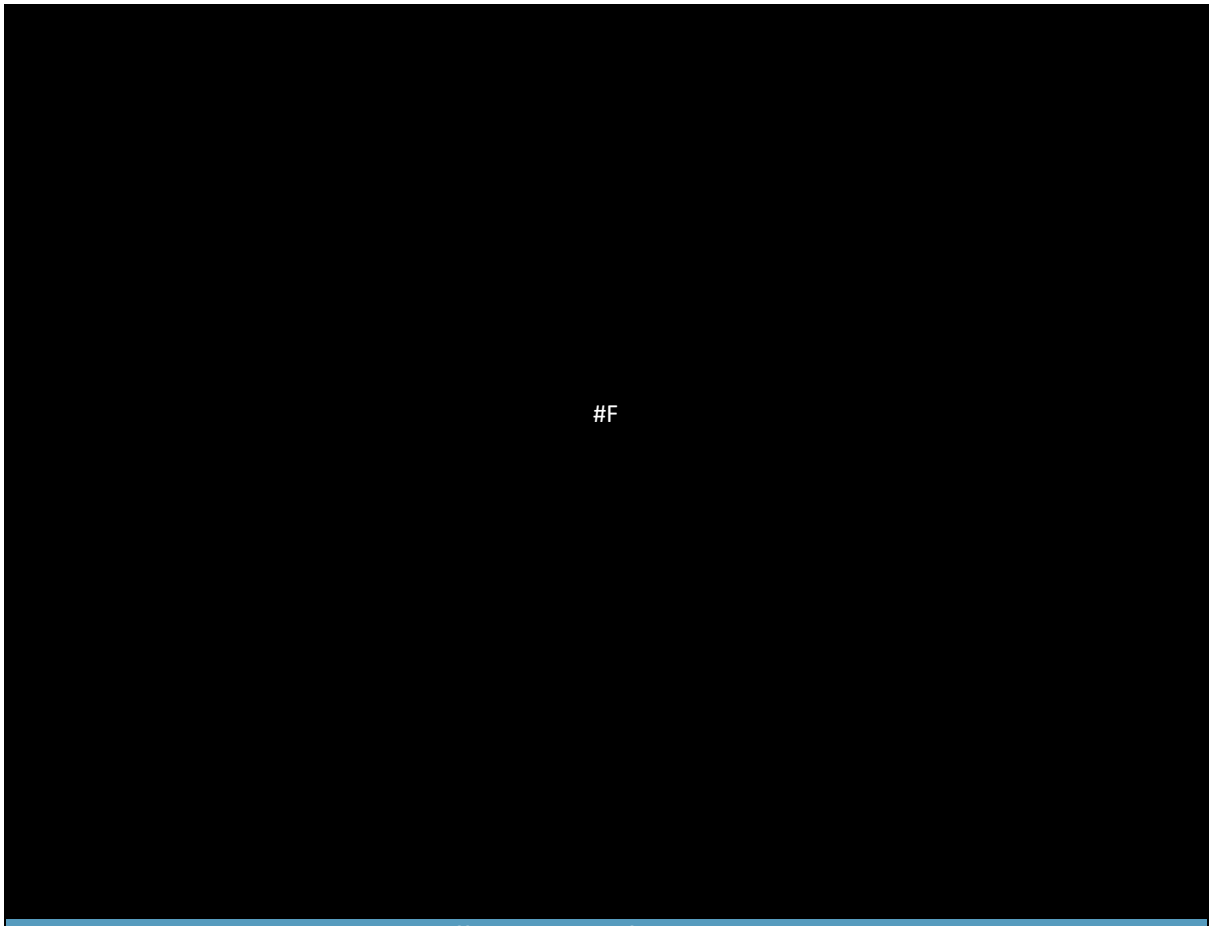

Figure 1–2: Activities involved in the different stages of a Design Change Project
Acronyms are –
DMR – Device Master Record
CRB – Change Review Board
CIA – Change Impact Assessment
DHF – Design History File

Each of the activities listed in **Figure 1–2** are specifically set out in the Siemens Healthineers extensive governing procedure for Design Change (#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.

1.1.3 Requirements and complexity of regulatory approvals

As noted in **Figure 1–2**, 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.

Siemens Healthineers typically allows #B months for submission preparation in each country. There are approximately 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 2-1 gives a non-exhaustive overview of the periods it takes (on average) to be issued a 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.

Table 1-1: 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

Overall, the entire re-registration process can take up to #B, or ca. 4 years[1].

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 significantly dependent upon the particular challenges which arise in relation to each project.

1.1.4 The technical challenge when identifying an alternative substance to OPEs

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

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

  As an analogy – It is like manufacturing many different jigsaw designs, except the pieces are microscopic and there are dynamic biochemical reactions happening between the pieces 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;

- 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 portfolio formulations (analyte beads) use OPE (and #D (bullet point)) and within the wider Siemens Healthineers portfolio formulations use OPE (representing products), the scale of the project-work and resources required to phase out OPEs is a

[1] 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).

significant undertaking and requires skilled coordination across functions, countries and [redacted] analyser platforms and extensive collaboration in terms of technological knowledge in R&D.

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

Each design is different and subject to biological variability

A significant technical challenge in substituting 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 1–3** for the description of a typical immunoassay 'Sandwich ELISA' reaction.

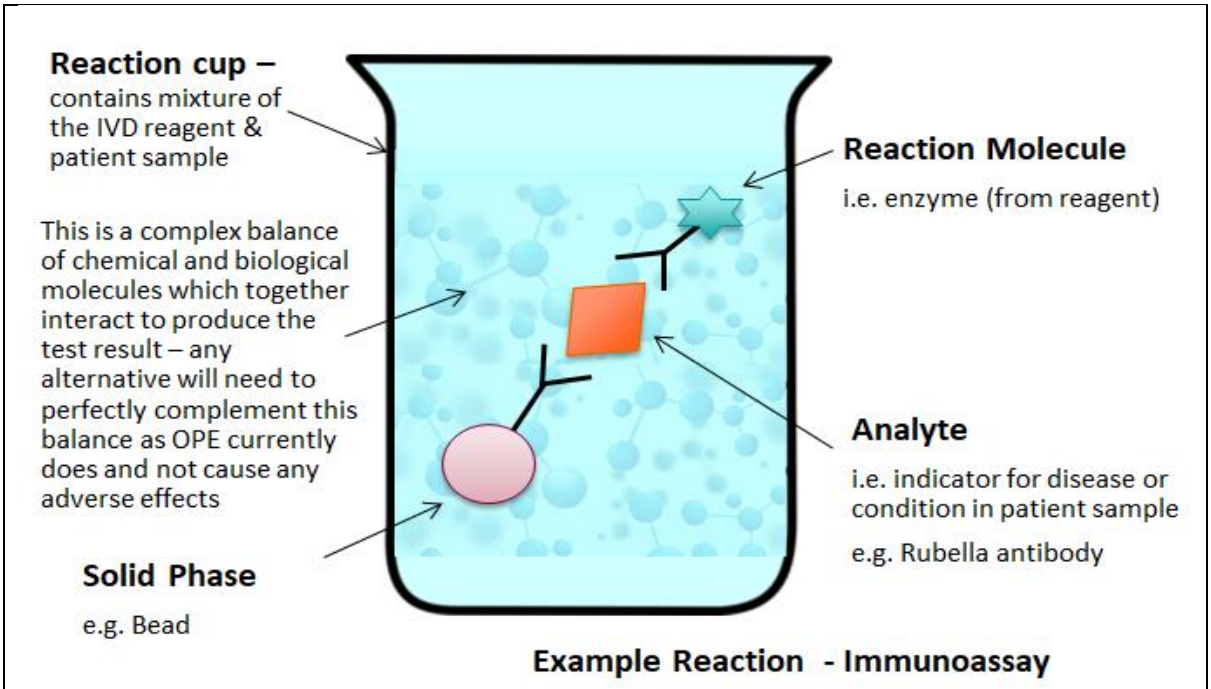

Figure 1–3: Example of the reaction in an immunoassay test
NB. When referring to many IVD products within the scope of this AfA, OPE is typically found in the IVD reagent itself

In addition to the immunoassay example, there are several ways to perform such measurements. Additional IVD kit reagent technologies utilise enzymes as the reporter system while other IVD kit reagent technologies utilise light-emitting molecules such as #D [redacted] as the reporter system.

Reaction at the molecular level is important

To describe the reaction shown in **Figure 1–3** 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 is critical

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 in the #D bead washing buffer solutions act as a cleaning agent for the removal of impurities from the #B surface of the beads, while OPEs in the bead coating buffer solutions act as a stabiliser for specific biological materials coated on to the surface of the bead. If reformulation work was undertaken with these products, any alternative substance would have to be proven to fulfil these functions while not having any adverse effect on the physical and biological functions of other constituents. Performance must be proven beyond a doubt through 'trial and error' testing in the feasibility stage, followed by validation and verification activities which normally involve real-time stability testing matching the shelf-life of the product, before any commercialisation activities can commence. The timelines associated with this are extensive and described in Section 2.

No 'one size fits all' alternative

Given the wide range of functionalities that OPEs mediate in IVD products, it is certain that there would be no 'one size fits all' alternative which could be successfully substituted in every IVD Product in scope of this AfA (#D #D analyte bead formulations), and certainly not across the wider impacted Siemens Healthineers portfolio. An adequate substitute for one functionality can result in poorer performance for another key functionality, as demonstrated in the alternative testing activities already conducted by Siemens Healthineers and further described in Section 2.

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

The development of an IVD product involves a high degree of empirical observations and '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.

1.1.5 Technical resource challenges for the 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 Section 2 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 next section.

2 List of actions and timetable with milestones

2.1 Actions and timeline for Substitution #D [redacted]

As explained in Section 4.3.1 of the AoA-SEA document, the #D [redacted]

When production of the #D [redacted]

The rationale for this approach to phasing out OPE's is due to the complexity and challenges of design change described in the previous section. Substitution to alternatives can take 5-12 years at considerable cost and these products manufactured at Siemens Llanberis are only one part of the wider Siemens Healthineers Substitution Plan to phase out OPE's across its impacted portfolio. #D [redacted]

2.2 Actions and timeline for overall Siemens Healthineers Substitution Plan

Action to phase out OPE's in the wider Siemens Healthineers portfolio has been ongoing for some time, these extensive efforts towards the identification of alternatives are hereby presented. Some of this information is replicated from Section 4.1.1 of the AoA-SEA document for the reader's convenience as follows.

2.2.1 Framework of research on alternatives for OPEs

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.

2.2.2 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 #D saleable products, representing #D formulations of IVD kit reagents and IVD wash solutions.

2.2.3 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.

2.2.4 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 2-1**.

Figure 2-1: 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 (rest of section 2.2)[2]. The challenge presented by OPEs in terms of the widely impacted Siemens Healthineers product portfolio, and the strong interest in identifying alternatives and potential partners in managing chemicals of concern was presented to a technical team at . The institute presented the and groups of interest ( ) who could potentially support on this topic. While these links did not initially prove fruitful, dialogue with continued, and in May 2015 Siemens Healthineers presented its case at the on May 19, 2015. Further discussion was held with to discuss work he and his students had already conducted around OPE substitution in other applications.

[2]

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 2-2**.

#F

Figure 2-2: **#F**

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

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

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

  The result of this work was a list of potential surfactant alternatives which Siemens Healthineers R&D were able to use to inform their ongoing work to develop and design new products without the use of OPEs, and to initiate work to reformulate existing products containing OPEs. The list of potential alternatives generated from this work is included in the long-list of potential alternatives established by Siemens Healthineers for consideration in new and existing product design in **Table 2-1** below. [redacted] 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 2-3** 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 2-3: Example of substance profiling to identify alternatives with a lower hazard category

From the consultation work carried out above with chemical suppliers, the [redacted], and known experts in the field of OPE study, combined with the professional knowledge of Siemens Healthineers Method Chemists and their understanding of the performance of other surfactants in other IVD products, the list in **Table 2-1** 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 2-1: List of OPE alternatives which could be suitable for IVD Products based on the various branches of work conducted by Siemens Healthineers to identify suitable alternative surfactants		
Name	**CAS Number**	**Tested in Siemens Healthineers IVD product?**
Triton™ X-100	9002-93-1	Reference
1-Oleoyl-rac-glycerol	111-03-5	
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 7607	-	
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 AoA-SEA document provides detailed 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.

2.3 Developing and Implementing a Substitution Strategy – Siemens Healthineers 'REACH Response Plan'

2.3.1 Background and overview of the plan

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

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

Section 6.3.2 of the AoA-SEA documents explain that 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;

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 DCP and PDP projects is shown in **Figure 2–4**. These durations apply per group of IVD kits/wash solutions and as shown in the REACH Response Plan timetable in Figure 2-5, several of these projects will be required. The terms used in this figure are explained in **Table 2-2**. An overview of the full Siemens Healthineers 'REACH Response Plan' is shown in **Figure 2–5**, with references to Uses #4&#5 which are downstream uses applied for under the separate Application for Authorisation submitted by Siemens Healthcare Diagnostics Products GmbH. Project 6 referred to in **Figure 2–5** is therefore representative of #D.

Table 2-2: Terms used in the description of activities encompassed in Siemens Healthineers' REACH Response Plan	
Terms	**Description**
[redacted]	#F, G (table) [redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

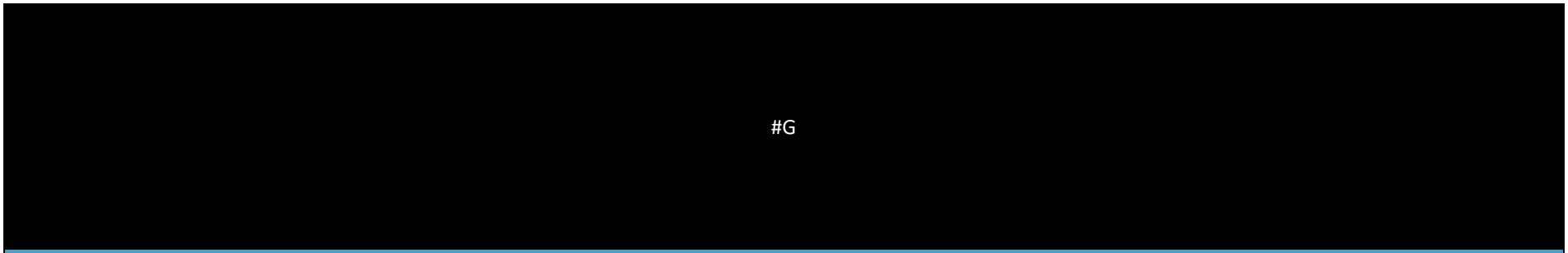

Figure 2–4: Overview of the duration of different types of substitution projects

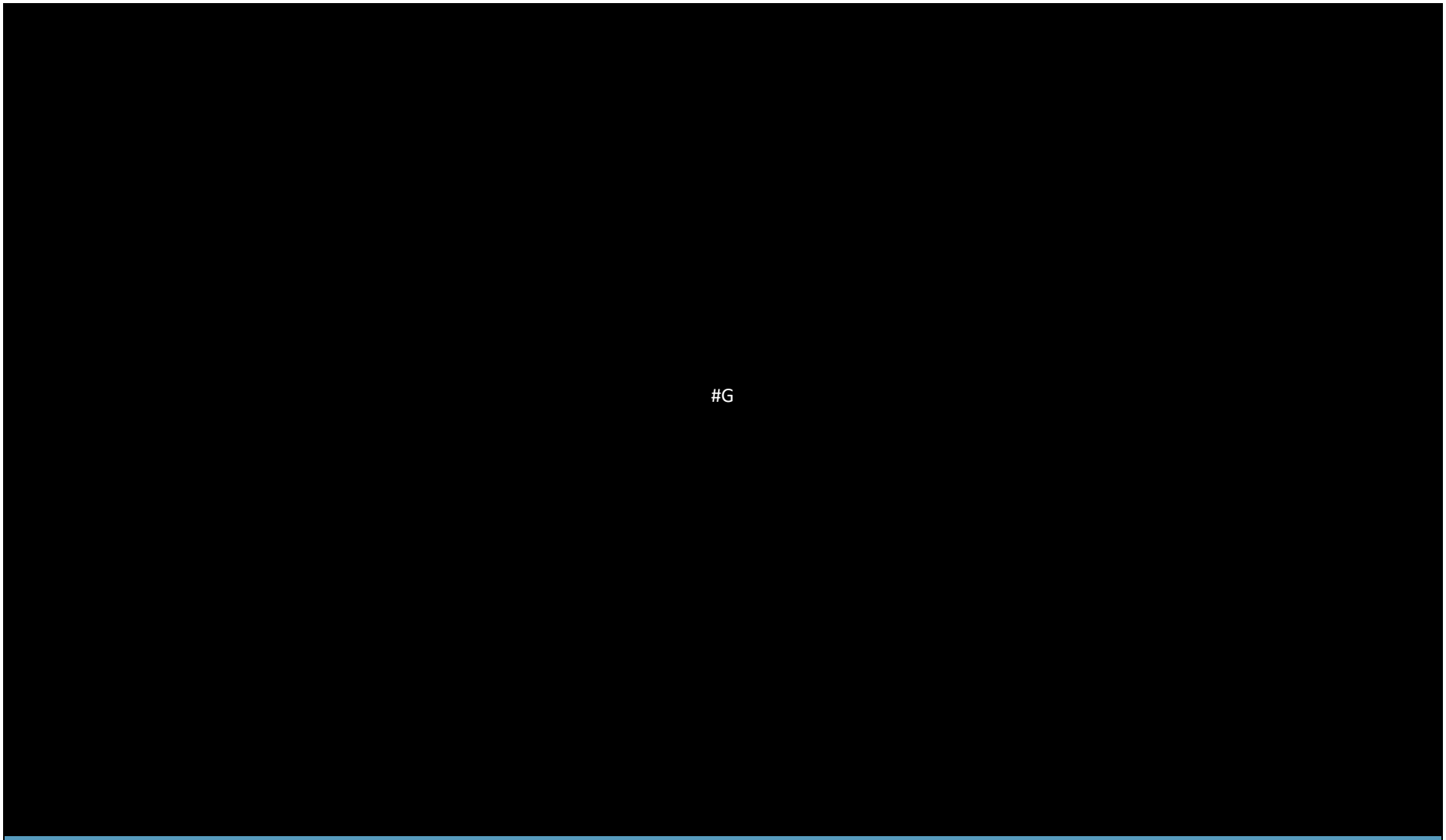

Figure 2–5: Siemens Healthineers REACH Response Plan overview

2.3.2 Rationale for the Substitution Plan Strategy

Siemens Llanberis has demonstrated in this AfA that the "Applied for Use" Scenario will be to allow the #D [redacted]. Importantly, the Triton™ X-100 used as a processing aid at Siemens Llanberis is not found in IVD kits used by customers who operate #D analysers.

It was described in the previous section how challenging it would be to identify feasible alternatives for #D different formulations that use OPE which are relevant to #D IVD kits. In addition, the #D associated with the use of these kits (manufactured by Siemens Healthcare Diagnostic Products GmbH and subject a separate AfA) would also need to be reformulated and this is used alongside more than #D kits which are not relevant to the use of OPE by Siemens Llanberis. Whilst the impacted IVD kits need to remain on the market for a period of 9 years after the Sunset Date, the substitution to alternatives could take 5-12 years at considerable cost including the cost of Siemens Healthineers resources diverted from R&D on alternatives for long lifecycle and high-volume products.

The full Siemens Healthineers product portfolio #D by the inclusion of OPEs on Annex XIV, with over #D individual IVD products falling within the scope of REACH Authorisation. This requires significant investment and is currently underway as can be seen from Figure 2-5. It is important to note that the successful substitution of Triton™ X-100 in one product by an unrestricted alternative substance will not necessarily mean that this alternative will be successful as a substitute for the next IVD product, even within the same product line. The properties which make Triton™ X-100 effective in one product may be completely different to what makes it effective in another, and the suitability of alternatives can only be proven through 'trial and error' feasibility testing.

As described in the previous section, Siemens Healthineers has conducted a full analysis of the impacted product portfolio and launched a 'REACH Response Plan'. As part of this plan, certain priorities have been set for allocating resources to the significant reformulation task that Siemens Healthineers is undertaking:

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

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

2.3.3 Impact of the Substitution Plan

Taking all this into account, Siemens Llanberis will not actively aim to substitute OPE in the preparation of beads and as such it has not developed a typical Substitution Plan for the specific Applied for Use which would aim to substitute OPE with another substance. Instead, the applicant will aim to

substitute the #D . The following figure illustrates the projected decline in the consumption of OPEs in the Applied for Use.

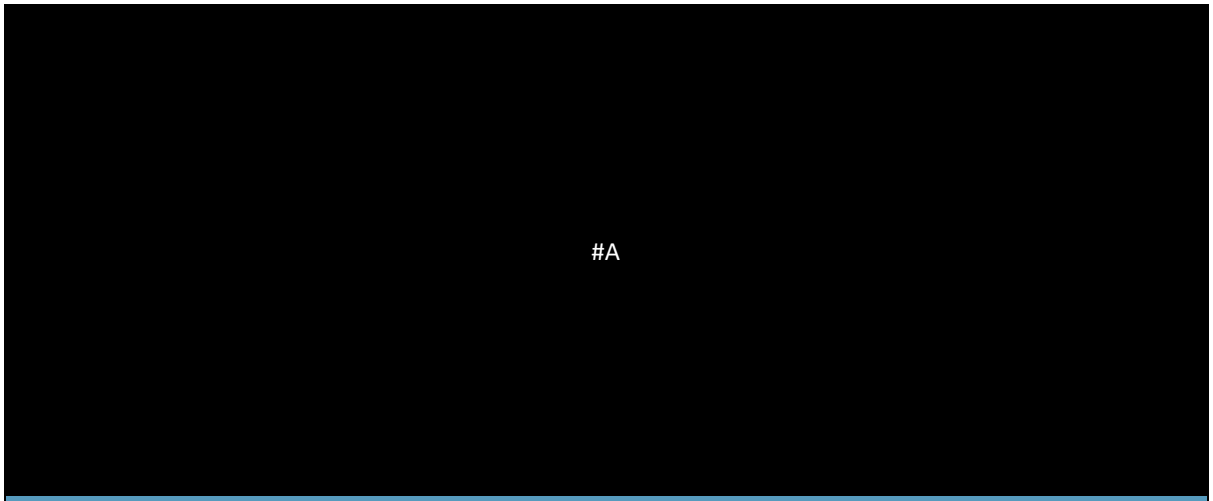

Figure 2-6: Projected consumption of OPEs in the Applied for Use – kilograms per year

At the same time, Siemens Llanberis will further minimise releases of OPEs from the use of Triton™ X-100 as a process chemical in Llanberis with the implementation of further Risk Management Measures before the sunset date, thus reducing any potential emission from the downstream Wastewater Treatment Plant by 99%.

Siemens Healthineers' overall REACH Response Plan will ensure that OPE consumption (and any associated releases to the environment) is reduced across the portfolio while avoiding shortages of important IVD products on the market or business disruption and impacts on the applicant's competitiveness.

3 Monitoring of the implementation of the substitution plan

3.1 Description of the organisational structure

3.1.1 Introduction

Siemens Healthineers have in place a multi-layer organisational structure aimed at the timely and successful implementation of the Siemens Healthineers REACH Response Plan. This is presented in **Figure 3-1** and is elaborated below, starting from the body that engages more frequently in monitoring and strategy activities and ending with the highest-level board team that ultimately is responsible for the strategic guidance of the company.

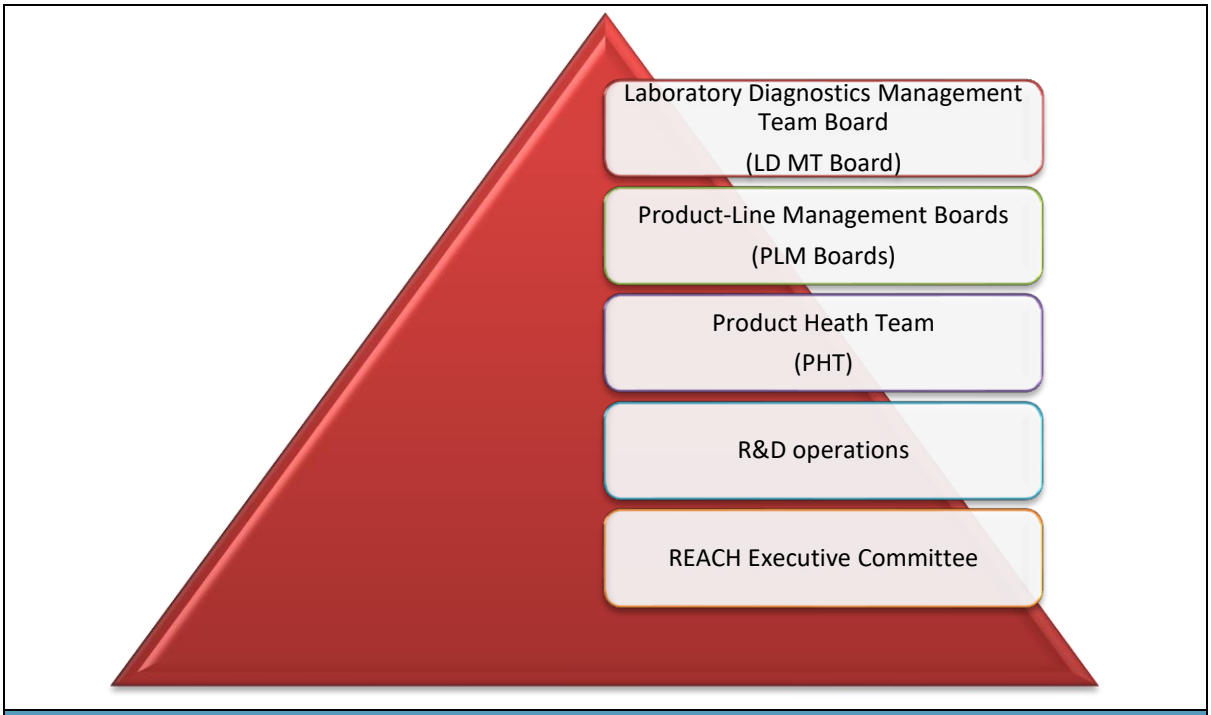

Figure 3-1: Internal organisational structure of Siemens Healthineers relevant to

3.1.2 Organisation, tasks and reporting/meeting frequency

REACH Executive Committee

The REACH Executive Committee has had hands-on involvement in the preparation of the AfAs that Siemens Healthineers legal entities submitted in May 2019. Within the Executive Committee several functions are represented, Legal, EHS, Marketing, R&D.

General Role: the general role of the Committee is to review REACH topics as they arise, while the REACH Response Plan dashboard (more on this later) is not reviewed here. In the Committee's monthly meetings, general progress is discussed to ensure a link back to the AfAs submitted

Research & Development operations

This group includes all scientific personnel that is actively involved in researching alternatives, testing new formulations, developing new products and preparing regulatory submissions for the approval of new IVD kits.

General Role: in the context of the Siemens Healthineers REACH Response Plan, R&D operations are responsible for the specific projects (DCP, PDP, etc.) related to the formulations/products which are subject to reformulation. The work of R&D operations is continuous and representatives participate in meetings with other function representatives on a regular basis, as needed, to report on progress and discuss horizon scanning.

Product Health Team (PHT)

Within each of the business areas, #D , there can be multiple PHTs, depending on the homogeneity of the product lines managed in each area. Typical membership can include Product and Portfolio Management (PPM), Marketing, R&D, Manufacturing, Procurement, Commercial Product Quality (CPQ), Commercial Product Support (CQSCPS), Customer Service and Medical Affairs (i.e. does not include Finance representatives). The team meets monthly, or more frequently if needed, and also reviews progress with the REACH Regulation on a monthly basis.

General Role: the PHT tends to be focused on tactical management of projects and risks, closer to the work being undertaken, task-focused, e.g. putting response plans together that may need approval at the PLM (higher) level.

With particular regard to the Siemens Healthineers REACH Response Plan, the R&D/CPS/Manufacturing members of the PHT will present to the group an update on project progress, any challenges or successes highlighted. Challenges are escalated via the PLM (see below); successes such as the identification of a technically feasible alternative would be highlighted here but shared at the functional level to ensure timely dissemination of data.

Product-Line Management (PLM) Boards

Similar to the PHT, PLM Boards (#D) meet monthly and review REACH-related matters quarterly. Each one has typical membership of senior PPM, Marketing, Finance, R&D, Manufacturing, Procurement, CPQ, Regulatory, Customer Service and Medical Affairs.

General Role: the boards oversee specific sets of product-lines to monitor performance, product development and make top level decisions on strategy, responding to any issues

With particular regard to the Siemens Healthineers REACH Response Plan, there are various PLM groups which oversee progress within their business area. The Boards reviews REACH-related matters every quarter.

Laboratory Diagnostics (LD) Management Team (MT) Board

This board represents several functions, Legal, HR, Quality, PPM, Marketing, Engineering, R&D, Finance, Manufacturing.

General Role: the Management Board oversees all Laboratory Diagnostics Business Area activities

With particular regard to the Siemens Healthineers REACH Response Plan, updates are provided to the Management Board on a monthly basis via an internal reporting process and 6-monthly in-person meetings to monitor progress of plan and discuss any significant issues, impacts which require top-level decision-making.

3.2 Processes for documenting progress of implementation of the Substitution Plan

Discussions at the LD MT, PLM and PHT are minuted so that progress with the implementation of the REACH Response Plan is documented and follow up with on a regular basis. Typically, every meeting may include presentations of progress made and generally the information and reports are escalated to the level above, i.e. the REACH Executive Committee presents findings to the PHT, the PHT reports to the PLM Boards and the ultimate decision-making is performed by the LD MT.

A key tool in the monitoring of progress are the PLM Dashboards. These are visual presentations of progress with the implementation of the REACH Response Plan which cover Design Change Projects (DCP), Product Development Projects (PDP) and Process Change Projects (PCP) in the different business areas – an example is provided in **Figure 3–2**. The dashboards show the progress that has been made for the individual projects within the REACH Response Plan and highlight key issues arising.

Overall, Siemens Healthineers has set up a system that will allow the continuous monitoring of progress and multi-layer oversight with frequent meetings and reporting. Siemens Llanberis will be prepared to provide updates to the regulator on demand, if this were to be required.

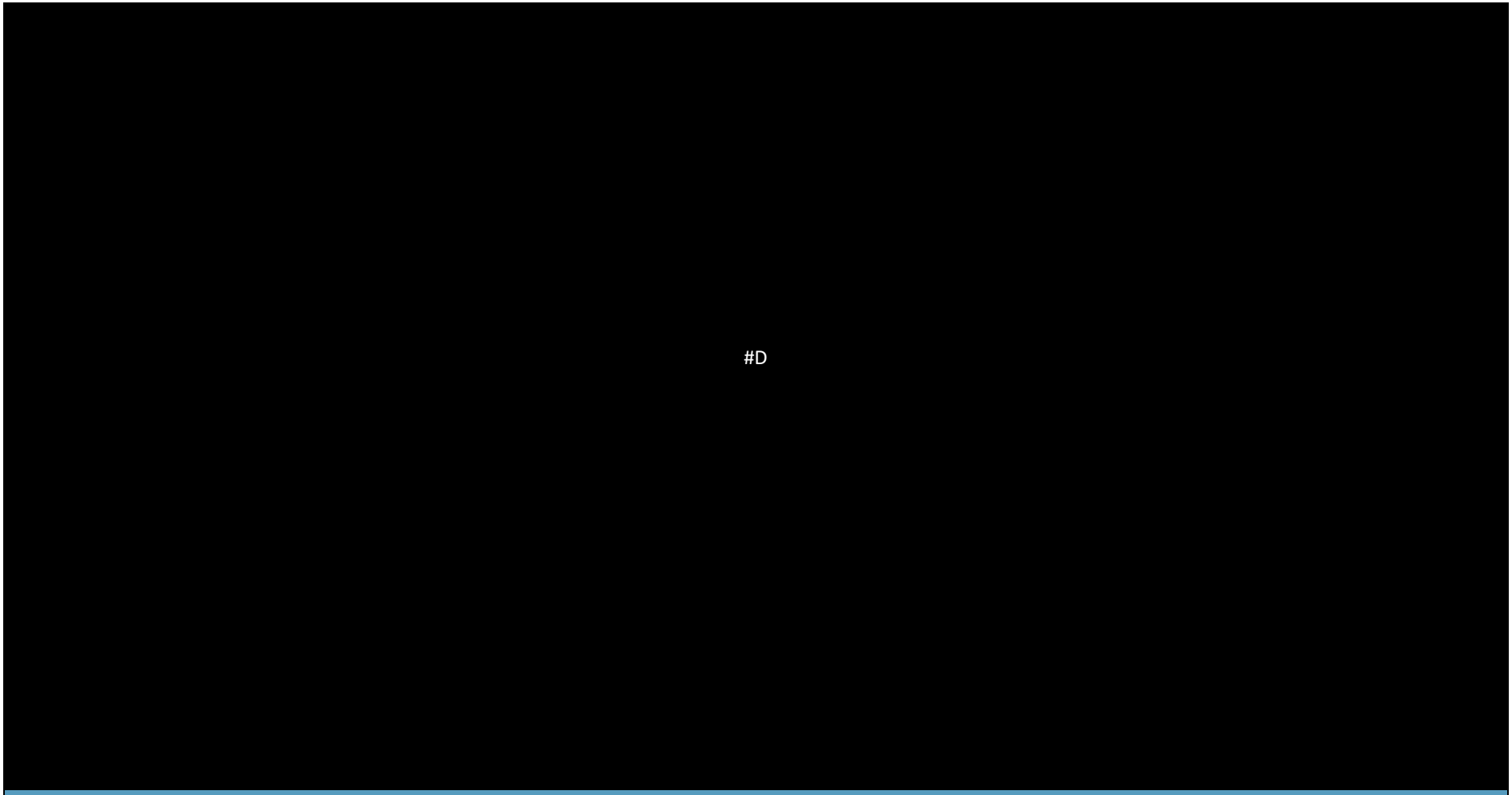

Figure 3–2: Visual representation of a PLM Dashboard used for the monitoring of the Siemens Healthineers REACH Response Plan

4 Conclusions

4.1 Siemens Healthineers' commitment towards the substitution of OPEs

Following the inclusion of OPEs on the SVHC list in 2012, Siemens Healthineers have 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 'REACH 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.

Siemens Healthineers is committed to eliminating OPEs from its wide-ranging portfolio and wishes to achieve this as quickly as possible. In the case of the specific Applied for Use, Siemens Healthineers plans to #D , this is due to the significant process of identifying feasible alternatives for all #D impacted formulations and the length of the regulatory process of re-registering these across all jurisdictions. As such, the gradual reduction of the use of OPE in Llanberis is considered the most appropriate approach to the elimination of their use over a period of 9 years from the Sunset Date.

4.2 Selection of a suitable alternative for OPEs

The AoA-SEA document explains in detail that the OPE-containing products #D the work to identify alternatives is focused on these. The technical challenges in doing so include -

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

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

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. Due to the different functions OPEs mediate across the impacted portfolio it is certain that there will be no 'one size fits all' alternative – Design Change work already undertaken has also proven this. Testing of different alternatives must be undertaken on a per IVD kit solution/product basis and in the case of wash solutions (Use #3) testing would need to involve all IVD products used alongside a re-formulated wash solution, irrespective if those kits contain or depend on OPEs or not.

4.3 Complexity of substitution

This Substitution Plan documents the complexities of identifying, approving and implementing an alternative chemical agent in IVD products. The key factors can be summarised as follows:

- Re-design/re-formulation processes are 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;

- Each stage of a Design Change Project will typically involve resources from a wide range of business functions within the applicant's organisation;

- The regulatory re-registration of an IVD kit includes several steps and the entire re-registration process can take up to ca. 4 years. When taking into account the time for re-registration of product, the full Design Change process can take 5-12 years. The impacted Siemens Healthineers IVD products are sold across the world;

- With over #D IVD products affected in the wider Siemens Healthineers portfolio the technical challenge in terms of initiating multiple Design Change Projects with only a certain availability of technical resources significantly increases.

4.4 The Substitution Plan

Siemens Llanberis will not actively aim to substitute OPE in the preparation of B| beads but will rather substitute the #B that relies on the use of OPE #D . In addition, the applicant will significantly minimise releases of OPEs from the use of Triton™ X-100 as a process chemical in Llanberis #D of the requested 9-year review period.

5 Annex – Justifications for confidentiality claims

[redacted]

Table 5-1: Justifications for confidentiality claims			
Reference type	Commercial Interest	Potential Harm	Limitation to Validity of Claim
[redacted]	[redacted]	[redacted]	[redacted]

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Reference type	Commercial Interest	Potential Harm	Limitation to Validity of Claim
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

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[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]