SUBSTITUTION PLAN

PUBLIC VERSION

Legal name of applicant(s):	*Abbott Laboratories Limited*
Submitted by:	*Abbott Laboratories Limited*
Substance:	*4-(1,1,3,3-tetramethylbutyl) phenol, ethoxylated*
Use Number:	*1*
Use Titles:	*Professional use as a surfactant in the final use of In-Vitro Diagnostic Devices (IVDs) for clinical testing using ARCHITECT, Alinity and ABBOTT PRISM automated analyser systems.*

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LIST OF ABBREVIATIONS

4-tert-OPnEO	4-(1,1,3,3-tetramethylbutyl) phenol, ethoxylated
AfA	Application for Authorisation
AoA	Analysis of Alternatives
DV	Design Verification
EU	European Union
ISO	International Organisation for Standardisation
IVD	*In-Vitro* Diagnostic Devices
IVDD	*In-Vitro* Diagnostic Directive
IVDR	*In-Vitro* Diagnostic Regulation
N/A	Not applicable
R&D	Research & Development
REACH	Regulation (EC) 1907/2006 on Registration, Evaluation, Authorisation and Restriction of Chemicals
SDS	Safety Data Sheet
TPM	Third Party Manufacturer
UK	United Kingdom, made up of England, Scotland, Wales and Northern Ireland

DECLARATION

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

Also, we, Abbott Laboratories Limited, request that the information blanked out in the "public version' of the Substitution Plan is not disclosed. We hereby declare that, to the best of our knowledge as of today, **30th September 2021**, the information is not publicly available, and in accordance with the due measures of protection that we have implemented, a member of the public should not be able to obtain access to this information without our consent or that of the third party whose commercial interests are at stake.

Signature: Date, Place:

Colleen O'Donnell 30 Sep 21, Sligo Ireland

Colleen O'Donnell

Program Director, Global Technical Operations

Abbott Ireland

Finisklin Business Park,

Sligo,

Ireland

INTRODUCTION

Abbott is a worldwide healthcare company that has a broad range of branded generic pharmaceuticals, medical devices, diagnostics, and nutrition products. The Company's diagnostics division provides immunoassays, including blood screening products, and clinical chemistry tests. Its medical tests and diagnostic instrument systems are used worldwide by hospitals, laboratories and blood banks for clinical diagnosis and monitoring diseases.

The uses in the context of this Substitution Plan are for the downstream use of IVDs containing 4-tert-OPnEO by the Applicant's UK based customers:

> *Use No.1. Professional use as a surfactant in the final use of In-Vitro Diagnostic Devices (IVDs) for clinical testing using ARCHITECT, Alinity and ABBOTT PRISM automated analyser systems.*

For Use 1, 4-tert-OPnEO is used in the end use of IVD reagents and test kits and.

- acts as an effective surfactant and wetting agent that reduces nonspecific interactions, prevents protein binding on surfaces and aggregation of proteins or microparticles. Furthermore, it promotes solubility and stabilises proteins, allowing for their detection.

The Applicant's EU REACH Application for Authorisation, for the use of 4-tert-OPnEO in the formulation of IVDs and the subsequent end use of these reagents by its EU customers, has received final opinions from the ECHA Committees recommending a seven-year review period. As a result, the Applicant is requesting a 5.5-year review period (until 4-Jan-2028) under UK REACH to coincide with the substitution plan established under EU REACH.

The Applicant has identified a potentially suitable alternative. The Applicant is in the process of verifying the technical feasibility of the selected alternative, before they proceed with the subsequent phases of substitution. As a result, the Applicant cannot conclude that a suitable and available alternative has been definitively identified. Further information on potential alternatives and on the suitability and availability can be found in Sections 4, 5, and 6 of the Analysis of Alternatives (AoA).

1. FACTORS AFFECTING SUBSTITUTION

As detailed in the AoA, the factors affecting the substitution are as follows.

1.1 Suitability

1.1.1 Technical Feasibility

For Use 1, the Applicant's AoA has concluded through the screening process that Alternative No.1, secondary alcohol ethoxylates (1a & b), has properties that most closely match those of 4-tert-OPnEO and therefore, is considered to be the best choice for substitution. The physicochemical properties of Alternative No. 1 are closely aligned with those of the surfactant currently in use therefore it is not anticipated that any changes will be required to be made to the manufacturing process or to the use conditions at customer locations to allow for the substitution. Studies performed so far indicate that Alternative No. 1, secondary alcohol ethoxylate, shows promise as a technically feasible alternative to 4-tert-OPnEO in many of the Applicant's IVD products. However, a final determination of technical feasibility cannot yet be established for all products as determination still requires

completion of design verification testing, and external clinical evaluation in the case of transfusion products.

1.1.2 Constraints of laboratory and manufacturing facilities

The process of establishing technical feasibility for any given product involves a complex multi-step IVD manufacturing process. Due to physical capacity constraints within the laboratories and manufacturing facilities it is not possible to run technical feasibility studies on the approximately 200 IVD products in parallel. Moreover, studies have shown that the primary alternative is not technically feasible in some product applications, thus additional studies with secondary alternatives are required on a case by case basis. Considering the need for the completion of substitution within a broad range of approximately 200 IVD products, the substitution plan timing was expected to run through 2027.

1.1.3 Economic feasibility

Overall investments and resources needed to develop and implement the substitution of 4-tert-OPnEO have been identified. In this context, the Applicant has designed its substitution and phase out plan through the end of 2027. More information on economic feasibility can be found within Section 5.3 of the AoA. The substitution of 4-tert-OPnEO by the current primary alternatives are considered economically feasible for the Applicant over the course of the requested review period.

1.2 Availability

1.2.1 Availability for Implementation

The identified alternatives are already in use by the Applicant in a number of their current marketed products. Therefore, the Applicant has already qualified a supplier for the surfactants, and it has been confirmed that the increased demand for use in its approximately 200 assays can be met within the updated substitution timeframe. Although the identified alternatives are considered commercially available to the Applicant, availability for implementation as a substitute is dependent on regulatory approvals of the change. Marketing approval applications must be prepared, submitted, and granted by the regulatory authorities in all of the countries where the IVDs are marketed. It is therefore concluded that the identified alternatives are not yet available for substitution to the Applicant.

1.2.2 In-Vitro Diagnostic Directive (98/79/EC) IVDD) (in the process of being replaced by the In-Vitro Diagnostic Regulation (EU 2017/746) (IVDR)

The manufacture of IVD reagents and test kits is regulated within the EU under the scope of the *In-Vitro* Diagnostic Directive (98/79/EC) IVDD [1] (which is in the process of being replaced by the *In-Vitro* Diagnostic Regulation (EU 2017/746) (IVDR)) [2] and compliance is fulfilled through a set of complimentary ISO Quality Standards [3]. Stringent requirements for research and development and design verification activities to support regulatory approval of IVD product changes do not allow for swift substitution of 4-tert-OPnEO from the manufacturing processes.

The IVDR outlines a set of guidelines and quality standards. Compliance with the quality standards is mandatory for all manufacturers and the EU Regulation specifically addresses the safety, quality and performance of IVDs. The introduction of any change to the formulation of an IVD, reagent and test kit is subject to rigorous and lengthy internal quality procedures and external regulatory approval

processes required to safeguard the health and safety of patients, users and other persons. Thus, the introduction of an alternative surfactant in the impacted IVDs requires a multitude of R&D and revalidation activities as well as global regulatory re-approvals.

The IVD Directive (98/79/EC) will be repealed and replaced with the IVD Regulation (Regulation (EU) 2017/746) in May 2022. Thus, leading up to the 2022 date, products being substituted have been evaluated to determine if additional activities, i.e. performance studies, documentation, etc. are required for resubmission for adherence to the IVDR. The IVD classification system is being modified and it is expected that approximately 80% of the Applicant's IVD products will need to receive notified body review, where previously, approximately 20% required the review. Not only will this be required for products undergoing substitution to remove 4-tert-OPnEO, but any product distributed in the EU will also need to be submitted. The EU IVDR did not take effect during the transition period and will not be transposed into law in Great Britain. Therefore, registrations are required for IVDs being placed on the market and any changes to products will meet the requirements for law in Great Britain.

2. LIST OF ACTIONS AND TIMETABLE WITH MILESTONES

2.1 Key Progress Markers for Substitution

The phases for the establishment of suitability and availability of alternatives have been identified and are described below:

Suitability

- Identification of Alternatives - *Complete*
- Completion of Technical Feasibility (Preliminary and Design Verification) Studies - *In Process through 2025*
- Completion of External Clinical Performance Evaluation (where required) - *Scheduled 2021 - 2025*

Availability

- Regulatory Approval - *Scheduled 2020 - 2026*
- Implementation - *Scheduled 2020 - 2026*
- Customer Conversion - *Scheduled 2021 - 2027*

2.2 Milestones & Actions

The substitution process involves a number of individual steps that mirror the Applicant's IVD design process, taking account of regulatory and technical performance requirements. The steps involved in the substitution project are given below.

1. Identification of Alternatives - ***Complete***

As described in the AoA, Section 4.2, possible alternatives were identified via a literature search, consultation with suppliers and with internal departments. Further characterisation was performed to determine surfactants that were likely to be technically feasible as an alternative to 4-tert-OPnEO, based on their chemical structure and physical-chemical properties. Once the primary alternative was identified, the evaluation moved to the next phase. Identification of potential alternatives was completed in 2014.

2. Technical Feasibility Studies – ***In Progress through 2025***

(a) Preliminary Feasibility: During this phase, each product impacted by substitution is manufactured at a small scale with side-by-side batches containing either 4-tert-OPnEO or the primary alternative. The assay performance of the manufactured product is then evaluated using studies described in the AoA Section 5.2. Comparative performance studies are conducted between the product manufactured with 4-tert-OPnEO and the product manufactured with the identified alternative. Where results are favourable, the product moves to the next phase for additional and more thorough evaluation. Where results are not favourable, the product requires additional characterisation to determine whether an alternative concentration or alternative substance will provide the required assay performance. Preliminary technical feasibility activities began in 2015 and are now complete.

(b) Design Verification: Completion of preliminary technical feasibility studies for some products in 2017 and 2018 allowed the Applicant to shift resources to begin the Design Verification Phase in

2018. At this stage, full scale production lots of the product are manufactured with the alternative substance. This requires drafting the production documents to manufacture the required number of verification lots. In addition, subject matter experts with in-depth knowledge of individual products are needed to draft and approve protocols required to complete the design verification product requirement testing outlined in the Analysis of Alternatives Section 5.2. Design verification testing is completed to verify that product manufactured with the alternative substance meets all product requirements and continues to perform in an equivalent manner to product manufactured with 4-tert-OPnEO. Highly skilled technical resources are also needed for verification and report creation, as well as review and approval of the design verification reports. The entire activity is carried out under a strictly controlled design planning process dictated by regulatory requirements for IVDs. The Applicant's experience with similar product changes indicates that this design process requires a minimum of 18 months for a single product to complete. At this stage, if a product shows unacceptable performance, it will return to the preliminary feasibility phase to determine changes required to produce a product meeting the product specifications. As discussed further below, it is not technically nor economically feasible to run all products through the design verification phase in parallel. Products made by third party manufacturers will be substituted in the same time period. Design verification activities are scheduled through 2025.

3. External Clinical Performance Evaluation – ***Scheduled 2021 - 2025***

For some products, depending on the regulatory classification, it may be necessary to perform external studies in a clinical setting. This entails the instruments for the impacted products are either installed or are present in a customer laboratory. The number of specimens requiring testing can exceed 5,000 for many of the impacted products. External studies are scheduled from 2021 through 2025.

4. Regulatory Approval – ***Scheduled 2020 - 2026***

Once the product has completed design verification studies, and, if required, external clinical performance evaluation and is thereby shown to meet the product requirements, the regulatory documentation is drafted. As these products are *in-vitro* medical devices, they require approval from regulatory bodies to ensure the conformity of the product with the relevant quality, safety and efficacy regulations. Extensive documentation is required to be compiled on each product and submitted to multiple regulatory agencies across the world. This includes compliance with the EU *In-Vitro* Diagnostic Regulation as described in section 1.2.2. Review times in the various countries can be extensive, with some countries requiring up to 18 months to review a package. Once approval is obtained from all the impacted countries, the alternative substance can be implemented into the manufacturing process for commercial use.

Products that began design verification studies in 2018 entered the Regulatory Approval Phase in 2020. The last regulatory approvals for products completing design verification and external clinical Performance Evaluation activities at later dates are expected to be received in 2026.

5. Implementation – ***Scheduled 2020 - 2026***

In this phase, the documents drafted in the Design Verification Phase replace the current documents for manufacturing the product with new product labelling ordered if required. The first lots to stock utilising the alternative surfactant will be manufactured and readied for distribution. Final lots using 4-tert-OPnEO will be manufactured to allow time for customers to convert to the new formulation. Changes are then made to the impacted recipes, so that products are manufactured using the identified alternative. Once the production documents have been updated, any new lots of a product will no

longer contain 4-tert-OPnEO. The Implementation Phase began in 2020 and is scheduled to run into 2026.

6. Customer Conversion – ***Scheduled 2021 - 2027***

In the final phase, the product is distributed to customers for use in laboratories generating patient results. The current distributed products have expiration dates up to 18 months. A period of time is needed to convert all customers from the products containing 4-tert-OPnEO to those containing the substituted substance. Based on evaluation of customer ordering patterns, it has been identified that the conversion is expected to occur in approximately 6 months, once the product begins shipping to downstream users (customers). In rare cases, additional time may be required for customers to perform cross-over testing studies, as required by individual laboratory procedures. Cross-over testing studies are performed by downstream users to demonstrate equivalency of results obtained before and after the product change. Such studies may be warranted if internal design verification and/or validation studies identify a higher than expected bias with the new formulation. An example would be studies performed as required, to confirm and/or establish the laboratory's quality control ranges, or normal ranges for patient results. Once a customer has begun utilising the product containing the alternative, they will no longer be able to source the product containing 4-tert-OPnEO. The Applicant has a formal process for customer communication consisting of Technical Bulletins and Customer Letters that will be used during Customer Conversion to inform the downstream users of the substitution and any actions required for implementation. Customer conversion for products that began design verification activities in 2018, is expected to be completed in 2021; the last customer conversions for products completing Implementation at later dates are expected to occur by 2027.

Table 1: Summary of Actions & Milestones for Substitution

Phase	Description		Actions	Status	Timeframe	Resource	Milestone
1.	**Identification of Alternatives**		• Literature search • Consultation with suppliers • Internal Consultation • Screening based on physicochemical properties	Complete	2014	Internal/Consultants /Literature search	**N/A**
2.	**Technical Feasibility**	Preliminary Studies	• Small scale manufacture • Comparative performance studies	Complete	2015-2021	Technical Personnel	**1.Data Review**
		Design Verification Studies	• Full scale production lots • Drafting production documentation • Complete design verification product requirement testing • Report creation & review and approval of the design • Ensure IVD regulatory requirements for testing are met • Verification for each product change	In progress a Products completed Milestone 2 Design Plan Pre-Approval and Milestone 3 – Complete DV Manufacturing a products complete Milestone 4- Complete DV Testing a products completed Milestone 5. DV Team Review	2018-2025	Technical Personnel	**2.Design Plan Pre-Approval** **3.Complete DV Manufacturing** **4.Complete DV Testing** **5.DV Team Review**
3.	**External Studies**		• Possible clinical setting testing (for some products, the number of specimens requiring testing can exceed 5,000)	Pending a [redacted]	2021 - 2025	Clinical Affairs	**6.Clinical Data Review**

4.	**Regulatory Approvals**	• Documentation delivery (Extensive documentation is required to be compiled on each product) • Strategy delivery • Await results from regulatory approvals (can be extensive- up to 24 months to review a package)	In progress a products completed Milestone 7. Issue Notification of Change a products completed Milestone 8. Receipt of Approvals from Required Countries	2020-2026	Regulatory	**7.Issue Notification of Change** **8.Receipt of Approvals from Required Countries**
5.	**Implementation**	• Change Control • Change of Labelling of inserts/operational manuals/SDSs' • Manufacturing documentation updates	In progress a products completed Milestone 9. Pre-Market Review products completed Milestone 10. First Lot to Stock in Distribution	Scheduled 2020-2026	Technical Operations Labeling Environmental Health & Safety	**9.Pre-Market Review** **10.First Lot to Stock in Distribution**
6.	**Customer Conversion**	• Inform customers (communication plan) • Expire Stock (up to 18 months), per ordering patterns, occurs in ~6 months • Validation Procedures (Cross-over testing studies may be required)	In progress	Scheduled 2021 - 2027 (completion)	Commercial	**11.Last 4-tert-OPnEO lot expires**

2.3 Uncertainties that May Affect the Actions or the Timing of Actions

Use 1

- The Applicant has approximately 200 IVD products with individual chemistry and formulation impacted by this substitution and each product must undergo the entire process outlined above in Section 2.2. The high number of impacted products leads to uncertainties around the exact timing of actions as the products will overlap as they progress through the various phases depending on their performance. However, the Applicant has prepared mitigation measures to effectively deal with any arising issues by developing a substitution plan. One measure includes that if the primary alternative does not pass preliminary technical feasibility for an IVD product, the IVD will be subject to follow further optimization processes and repeat feasibility studies with other alternatives for 4-tert-OPnEO (already identified) and then will continue through the substitution process. The requested review period accounts for any such technical feasibility issues that may be encountered.

- The IVD Directive (98/79/EC) (IVDD) will be repealed and replaced with the IVD Regulation (Regulation (EU) 2017/746) (IVDR) in May 2022, which causes uncertainties within the Applicant's timing of the substitution plan. The IVD classification system is being modified and will require a majority of the Applicant's IVD products to receive notified body review, where previously, approximately 20% required this review. Not only will this be required for products undergoing substitution to remove 4-tert-OPnEO, but any product distributed in the EU will also need to be submitted. With the implementation date of the IVDR coinciding with the substitution timing, it is expected that delays for some products could be experienced. With the current understanding of the impact of the IVDR, the Applicant has been able to combine the country submissions for the IVDR with those covering the 4-tert-OPnEO substitution, thus mitigating potential delays due to IVDR. Since the EU IVDR did not take effect during the transition period and will not be transposed into law in Great Britain, registrations will be required for IVDs being placed on the market with any changes to products meeting the requirements for law in GB.

- As these products are *in-vitro* medical devices, they require approval from regulatory bodies to ensure the conformity of the product with the relevant quality, safety and efficacy regulations of countries worldwide. Extensive documentation is required to be compiled on each product and submitted to multiple regulatory agencies across the world. Review times in the various countries can be extensive, with some countries requiring up to 18 months to review a package. The approval times obtained will be variable, based on the number of submissions from all sources for each regulatory body. Once approval is obtained from all the impacted countries, the alternative substance can be implemented into the manufacturing process for commercial use. The Applicant's mitigation method for this uncertainty is management reviews for strategy changes and/or increased resource allocation. The Applicant has anticipated such delays and has incorporated a contingency in the expected timeline and the requested review period.

  Figure 1 below shows the projected timeline for substitution of 4-tert-OPnEO from the Applicant's products within 5.5 years of the Sunset Date.

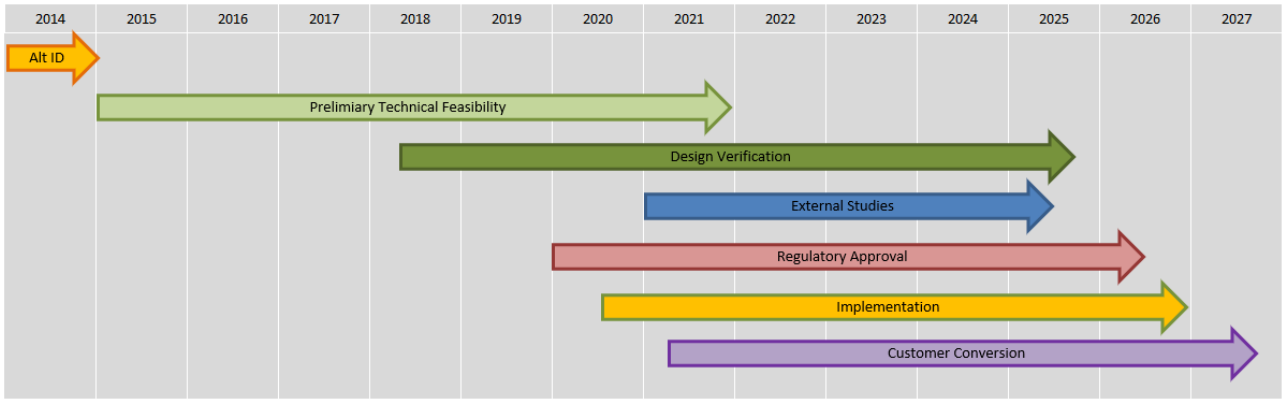

Figure 1: Updated timeline for substitution of 4-tert-OPnEO from the Applicant's IVD reagents

3. MONITORING OF THE IMPLEMENTATION OF THE SUBSTITUTION PLAN

The Applicant has established a program level organization dedicated to identifying and implementing alternatives for 4-tert-OPnEO in the Applicant's entire range of IVD products. Individual project managers are in place at each manufacturing site with responsibility for tracking and reporting progress on a weekly basis. A program management office is in place to provide overall monitoring of the implementation of the substitution plan with monthly reporting to executive management.

Table 2: Monitoring Plan Summary

Phase	Phase Description	Actions	Resource	Timeframe	Monitoring Progress	Identified risks/factors impacting substitution	Mitigation / Escalation
1.	**Identification of Alternatives**	• Literature search • Consultation with suppliers • Internal Consultation • Screening based on physicochemical properties	Internal/Consultants/ Literature search	Complete 2014	N/A	N/A	N/A
2.	**Technical Feasibility** a) Preliminary Studies	• Small scale manufacture • Comparative performance studies	Technical Personnel	Complete 2021	Ongoing Review of Study Results Weekly Team meeting to review substitution progress	Preliminary studies indicate that primary alternative is not suitable /results do not meet specifications or are not equivalent to on-market product	Follow further optimization process, Repeat feasibility studies with alternate substitute for 4-tert-OPnEO

					Monthly management reviews		
	Technical Feasibility b) Design Verification Studies	• Full scale production lots • Drafting production documentation • Complete design verification product requirement testing • Report creation & review and approval of the design • Ensure IVD regulatory requirements for testing are meet • Verification for each product change	Technical Personnel	*In progress* *2018-2025*		Product requirements not met, or results are not equivalent to on-market product	Follow failure investigation process, determine root cause, implement corrective and preventive actions, repeat studies or return to preliminary feasibility phase and evaluate additional alternatives
3.	**External Studies**	• Possible clinical setting testing (for some products, the number of specimens requiring testing can exceed 5,000)	Clinical Affairs	*Scheduled* *2021 - 2025*	Clinical monitoring status	Resources not available to conduct studies	Management review to assess need for strategy changes and/or increased resource
4.	**Regulatory Approvals**	• Documentation delivery (Extensive documentation is required to be compiled on each product) • Await results from regulatory approvals (can be extensive- up to 24 months to review a package)	Medical Writing Regulatory	*Scheduled* *2020 - 2026*	N/A	Resources or design data needed to support regulatory submissions insufficient; approval cycle times too long	Management review to assess need for strategy changes and/or increased resource allocation

						(can be 2-3 years).	
5.	**Implementation**	• Change Control (creation of new documents) • Change of Labelling of inserts/operational manuals/SDSs • Manufacturing documentation updates	Technical Operations Labeling Environmental Health & Safety	*Scheduled 2020 - 2026*	Weekly Team meeting to review. implementation progress. Monthly management reviews	Resources insufficient to complete necessary document updates	Management review to assess need for strategy changes and/or increased resource allocation
6.	**Customer Conversion**	• Inform customers (communication plan) • Expire Stock (up to 18 months) • Validation Procedures (Cross-over testing studies may be required)	Commercial	*Scheduled* *2021 - 2027*	Perform periodic reviews of customer service tickets and complaints	Customer acceptance and/or assay validation progress inconsistent with timeline	Consider additional customer communication and/or training activities

4. CONCLUSIONS

Suitability

The Applicant's Analysis of Alternatives has concluded through the screening process that secondary alcohol ethoxylates have properties that most closely match those of 4-tert-OPnEO, and therefore is considered to be the best choice for substitution.

Studies performed so far indicate that Alternative No. 1, secondary alcohol ethoxylate, shows promise as a technically feasible alternative to 4-tert-OPnEO in many of the Applicant's IVD products. However, a final determination of technical feasibility cannot yet be established for all products as determination still requires completion of design verification testing, and external clinical evaluation as required.

If secondary alcohol ethoxylates are not technically feasible in certain products, those products would require further R&D efforts to ensure performance is at the level obtained with 4-tert-OPnEO. The Applicant continues to evaluate technical feasibility through a combination of optimisation of concentrations and evaluation of additional potential alternatives identified through screening.

Availability

Although the Alternatives are considered commercially available to the Applicant, availability for implementation as a substitute is dependent on regulatory approvals of the change. Marketing approval applications must be prepared, submitted and granted by the regulatory authorities in all of the countries where the IVDs are marketed. It is therefore concluded that the identified alternatives are not yet available for substitution to the Applicant. The substitution of 4-tert-OPnEO by the current primary alternatives are considered economically feasible for the Applicant over the course of the requested review period.

Substitution Phases & Corresponding Milestones

Suitability

- Identification of Alternatives – (*Complete)*

- Completion of Technical Feasibility

  Preliminary Verification Studies (*Complete)*
  - **Data Review**

  Design Verification Studies (*In Process through 2025)*
  - **Design Plan Pre-Approval**
  - **Complete DV testing**
  - **Complete DV Manufacturing**
  - **DV Team Review**

- Completion of External Clinical Performance Evaluation (where required) (*Scheduled 2021 – 2025)*
  - **Clinical Data Review**

Availability

- Regulatory Approval (*Scheduled 2020 – 2026**)***
  - **Issue Notification of Change**
  - **Receipt of Approvals from Required Countries**

- Implementation (*Scheduled 2020 – 2026*)
  - **Pre-Market Review**
  - **First Lot to Stock in Distribution**

- Customer Conversion (*Scheduled 2021 – 2027)*
  - **Last 4-tert-OPnEO lot expires**

Critical Factors Affecting the Substitution

Suitability of Alternatives: The successful demonstration of technical feasibility for the six immunoassays for Use 1 in which Alternative 1 was not suitable is a critical factor for progression of these products through the substitution plan. Studies performed so far indicate that Alternative No. 1, secondary alcohol ethoxylate, shows promise as a technically feasible alternative to 4-tert-OPnEO in many of the Applicant's IVD products. Successful completion of design verification testing for the remaining products is a critical factor for establishing suitability of alternatives and therefore further progress through the substitution plan.

Constraints of Laboratory and Manufacturing Facilities: Due to physical capacity constraints within the laboratories and manufacturing facilities it is not possible to run technical feasibility studies on the approximately 200 IVD products in parallel. Products manufactured by TPMs will have design verification activities occur in the TPM facilities.

Regulatory Approvals / IVDR: Timely regulatory approval is a critical factor for establishing availability of alternatives and therefore adherence to the substitution plan. With the implementation date of the IVDR coinciding with the substitution timing, synergies have been identified between the EU IVDR submissions and the 4-tert-OPnEO substitution, allowing the regulatory submissions to be performed together.

Overall timelines

Results to date indicate that the secondary alcohol ethoxylates have the potential to act as suitable alternatives to 4-tert-OPnEO in Use 1 and that conclusions on technical feasibility in the final products cannot be made until completion of both preliminary feasibility and design verification studies. Furthermore, the Applicant's substitution schedule entails several phases that are mandated by both internal quality procedures and regulatory requirements that must be completed in a phased manner. Given the remaining technical feasibility studies to be completed, the external clinical performance evaluation, and the regulatory approval and phase-out processes required, substitution was expected to complete 5.5 years beyond the Sunset Date in the submitted AfA. This requested review period includes the mitigation measures for the above uncertainties that may arise during the substitution process of 4-tert-OPnEO from the Applicant's impacted products.

REFERENCES

[1] Directive 98/79/EC of the European Parliament and of the Council of 27 October 1998 on in vitro diagnostic medical devices. Available from Official Journal online OJ L 331, 07/12/1998 P. 0001 – 003

[2] 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. Available from Official Journal online L 117/176

[3] International Organisation for Standardization Quality & Environmental Management Systems. Available from: https://www.iso.org/home.html