ANALYSIS OF ALTERNATIVES

Legal name of applicant(s):	Roche Diagnostics Limited
Submitted by:	Roche Diagnostics Limited
Substances:	1) 4-(1,1,3,3-Tetramethylbutyl)phenol, ethoxylated (covering well-defined substances and UVCB substances, polymers and homologues); (Octylphenolethoxylates, OPnEO). 2) 4-Nonylphenol, branched and linear, ethoxylated (substances with a linear and / or branched alkyl chain with a carbon number of 9 covalently bound in position 4 to phenol, ethoxylated covering UVCB- and well-defined substances, polymers and homologues, which include any of the individual isomers and / or combinations thereof); (Nonylphenolethoxylates, NPnEO).
Use titles:	Use 3: Use of Octyl- and Nonylphenolethoxylates in *in vitro* diagnostic (IVD) assays specified in Appendix 1 to the AoA.
Use number:	3

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GLOSSARY

Term	Explanation
AA-EQS	Annual average environmental quality standard
ACS	American Chemical Society
AfA	Application for Authorisation
AIDS	Acquired Immunodeficiency Syndrome
AoA	Analysis of Alternatives
BILT3	Bilirubin Total Gen 3
BIVDA	The British In Vitro Diagnostics Association
CAGR	Compound Annual Growth Rate - the mean annual growth rate of an investment over a specified period of time longer than one year.
CC	Clinical chemistry is a diagnostic method which tests for various components of blood and urine and enables healthcare professionals to overview significance of abnormal values. CC portfolio are part of the Serum Work Area.
CE mark	CE marking proves that your product has been assessed and meets EU safety, health and environmental protection requirements
CEC	Corporate Executive Committee
CESIO	Comité Européen des Agents de Surface et de leurs Intermédiaires Organiques - European Committee of organic surfactants and their organic intermediates
CFDA	China Food and Drug Administration
CH	Switzerland
CHF	Swiss francs
CLIA Waver	CLIA waiver means that this product is waived from Clinical Laboratory Improvement Amendments (CLIA) regulations that regulates laboratory testing and therefore do not require clinical laboratories certification by a state as well as the Centre for Medicare and Medicaid Services (CMS) before they can accept human samples for diagnostic testing.

Term	Explanation
CLP	European Union regulation, which aligns the EU system of classification, labelling and packaging of chemical substances and mixtures. The EU CLP Regulation as amended is retained in the UK law under the SI 720 of 2019.
CMC	Critical micelle concentration
cobas®	Trade name of Roche diagnostic instrument
CPS	Centralised & Point of Care (CPS) is the largest business area of Roche Diagnostics. It is a leading supplier of solutions, instruments, tests, software and services for small- to mid-size and large-size commercial and hospital labs and laboratory networks.
CSF	CerebroSpinal Fluid is a clear, colourless body fluid found in the brain and spinal cord.
CSR	Chemical Safety Report
DIG	Digoxigenin
DJSI	Dow Jones Sustainability Indices. Indices evaluating the sustainability performance of thousands of companies trading publicly and a strategic partner. This is based on an analysis of economic, social and environmental performance of the company. The DJSI family of indices serves as a benchmark for investors who integrate sustainability considerations into their portfolios
DM	Drug Monitoring, that is included in clinical chemistry, specializes in the measurements of levels of therapeutic drugs or narcotic drugs.
DNA	Deoxyribonucleic acid (contains the genetic code of organisms)
DNP	Dinitrophenyl
EBITA	Earnings Before Interest, Taxes, Depreciation, and Amortization It is an accounting measure calculated using a company's net earnings, before interest expenses, taxes, depreciation, and amortization are subtracted, as a proxy for a company's current operating profitability (i.e., how much profit it makes with its present assets and its operations on the products it produces and sells, as well as providing a proxy for cash flow).

Term	Explanation
ECHA	European Chemicals Agency
ECLIA	Electrochemiluminescence immunoassay
ECS	Environmental Contributing Scenario
ED	Emergency department or Endocrine disrupting
EEA	European Economic Area is the area in which the Agreement on the EEA provides for the free movement of persons, goods, services and capital within the European Single Market.
EMEA	Europe, the Middle East and Africa
Enzyme	A substance produced by a living organism which acts as a catalyst to bring about a specific biochemical reaction. Most enzymes are proteins with large complex molecules whose action depends on their particular molecular shape. Some enzymes control reactions within cells and some, such as the enzymes involved in digestion, outside them
EO	EO degree of ethoxylation
EQS	Environment Quality Standard from the EU Water Frame Directive 2013/39/EU
ERC	Environmental Release Category
EU	European Union
EUR	Euros
FDA	US Food and Drug Administration
FTE	Full-Time Equivalents is a unit that indicates the workload of an employed person in a way that makes workloads or class loads comparable across various contexts.
GDP	Gross domestic product
GJ	Gigajoule, unit of energy
Hb	Haemoglobin
HDL	High Density Lipoproteins, commonly referred to as “good cholesterol”

Term	Explanation
HIV	HIV Assay or Human Immunodeficiency Virus
HIV Duo	Newer generation HIV assay which is OPnEO / NPnEO-free
HIVcPT	HIV combi PT assay
HPLC	High Performance Liquid Chromatography
ICU	Intensive care units
IHC	Immunohistochemistry
Ig	Immunoglobulin
IPC	In-Process Control
ISH	*In situ* hybridization which is a technique for identifying specific DNA or RNA sequence or portion within individual cells in tissue sections, providing insights into physiological processes and disease pathogenesis
IT	Information technology
IVD	*In vitro* diagnostic medical devices. IVD products are regulated and defined by the UK Medical Devices Regulations 2002 (as amended) (S.I. 618 of 2002) as a medical device which is a reagent, reagent product, calibrator, control material, kit, instrument, apparatus, equipment, or system, whether used alone or in combination, and intended by the manufacturer to be used in-vitro for the examination of specimens, including blood and tissue donations derived from the human body, solely or principally for the purpose of providing information: ▪ concerning a physiological or pathological state, or ▪ concerning a congenital abnormality, or ▪ to determine the safety and compatibility of donations, including blood and tissue donations with potential recipients, or ▪ to monitor therapeutic measures; and includes a specimen receptacle but not a product for general laboratory use, unless that product, in view of its characteristics, is specifically intended by its manufacturer to be used for in vitro diagnostic examination.

Term	Explanation
IW	Industrial worker
LAD	Latest Application Date
LDLC	Low density lipoprotein cholesterol, commonly referred to as 'bad cholesterol'
log Koc	Organic Carbon-Water Partitioning Coefficient
MAC-EQS	Maximum allowable concentration environmental quality standard
Mgmt	Management
MLS	Managed Laboratory Services
MD	Molecular Diagnostic
MDR	Medical Device Regulations
MDROs	Multidrug-resistant organisms
MHRA	Medicines and Healthcare products Regulatory Agency in UK which regulates medicines, medical devices and blood components for transfusion. It is an executive agency, sponsored by the Department of Health and Social Care
MLS	Managed Laboratory Services
NAD	Nicotinamide Adenine Dinucleotide
NHS	National Health Service
NICE	National Institute of Health and Care Excellence
NOEC	No Observed Effect Concentration
Non-EEA	All countries outside the European Economic Area (EEA).
NP	4-nonylphenol, branched and linear
NP1EC	4-nonylphenoxyacetic acid
NP1EO	Nonylphenolmonoethoxylate
NP2EC	4-nonylphenoxyethoxyacetic acid
NP2EO	Nonylphenoldiethoxylate

Term	Explanation
$NP_{equiv.}$	4-nonylphenol Equivalent
NPnEO	4-nonylphenol, branched and linear, ethoxylated (substances with a linear and / or branched alkyl chain with a carbon number of 9 covalently bound in position 4 to phenol, ethoxylated covering UVCB- and well-defined substances, polymers and homologues, which include any of the individual isomers and / or combinations thereof), 4-NPnEO [Corresponding to entry 43 of Annex XIV of the REACH regulation as defined in regulation 2017/999/EU and entry 43 of Annex 14 of the UK REACH regulation]
NPV	Net Present Value It is a measurement of profit calculated by subtracting the present values (PV) of cash outflows (including initial cost) from the present values of cash inflows over a period of time. Incoming and outgoing cash flows can also be described as benefit and cost cash flows, respectively.
OC	Operational conditions
OEM	Original Equipment Manufacturer
OP	4-(1,1,3,3-tetramethylbutyl)phenol (4-tert-OP)
OP1EC	4-octylphenoxyacetic acid (4-tert-OP1EC)
OP2EC	4-octylphenoxyethoxyacetic acid (4-tert-OP2EC)
$OP_{equiv.}$	4-(1,1,3,3-tetramethylbutyl)phenol Equivalent
OPnEO	4-(1,1,3,3-tetramethylbutyl) phenol, ethoxylated (Covering well-defined substances and UVCB substances, polymers and homologues), 4-tert OPnEO [Corresponding to entry 42 of Annex XIV of the REACH regulation as defined in regulation 2017/999/EU and entry 42 of Annex 14 of the UK REACH regulation]
OSH	Occupational safety and health
PBT	Persistent, Bioaccumulative and Toxic

Term	Explanation
PC	Article categories
PCR	Polymerase Chain Reaction It is a technique used in molecular biology to amplify a single copy or a few copies of a segment of DNA across several orders of magnitude, generating thousands to millions of copies of a particular DNA sequence.
PEC	Predicted environmental concentration
PMA	Pre-Market Approval
PNEC	Predicted no-effect concentrations
PP	Protein production processes
PPE	Professional protective equipment
PRO	Test-strips containing one field
PROC	Process category
PVDF	Polyvinylidene fluoride
PW	Professional worker
Q1, Q2, etc.	Quartal 1, Quartal 2, etc.
QALY	Quality adjusted life year
QC	Quality Control
QSAR	Quantitative structure activity relationship
R&D	Research and Development
RAC	Committee for Risk Assessment
RDG - Roche Diagnostics GmbH	Part of the Diagnostic Division of F. Hoffmann-La Roche Ltd. Roche Diagnostics GmbH (RDG) has an extensive portfolio, one aspect of which is the manufacturing of instrument platforms and reagents for the different Roche affiliates worldwide. It is located in Germany (Mannheim and Penzberg).
RDL	Roche Diagnostics Limited (RDL) is the Roche affiliate in the UK selling Roche's IVDs in the UK.

Term	Explanation
RDUK	All Roche affiliates in the UK.
REACH	Regulation on Registration Evaluation, Authorisation and Restriction of Chemicals European Regulation (EC) No 1907/2006 The EU regulation as amended is reflected in the UK REACH under the SI 758 of 2019. UK REACH is a regulation that applies to the majority of chemical substances that are manufactured in or imported into Great Britain (GB) (England, Scotland, Wales).
RMMs	Risk Management measures
RNA	Ribonucleic acid (contains the genetic code of some viruses, for example HIV)
Roche	F. Hoffmann-La Roche Ltd. and its affiliates are collectively referred to as 'Roche'
RTD	Roche Tissue Diagnostics is a business area of Roche Diagnostics. It is the world's leading supplier of tissue-based cancer diagnostics. Its instruments and reagent systems are used in histology, cytology and drug discovery laboratories worldwide.
RT-PCR	Reverse transcription polymerase chain reaction is a variant of polymerase chain reaction (PCR), is a technique commonly used in molecular biology to detect RNA expression
SDG	Sustainable Development Goals
SDS	Safety data sheet
SEA	Socio-Economic Analysis
SEAC	Socio-economic Analysis Committee
SIN list	The SIN (Substitute It Now!) List is a comprehensive database of chemicals likely to be restricted or banned in the EU.
SOP	Standard operating procedure
spERC	Specific Environmental Release Category
STP	Sewage treatment plant

Term	Explanation
SVHC	Substances of Very High Concern A SVHC is a chemical substance (or part of a group of chemical substances) which meets the criteria of art.57 UK REACH
SWA	Serum work area is a segment of Centralized & Point of Care (CPS), which is characterised by modular instruments. This includes immunoassays, clinical chemistry, and drug monitoring.
TMPA	Total Mycophenolic Acid
TPA	Tripropylamine
UK RP	UK Responsible Person
UN	United Nations
UVCB	Substance of Unknown or Variable composition, Complex reaction products or Biological materials
US	United States
VLDL	very low-density lipoproteins
VOLY	Value of a Life Year Lost
vPvB	very Persistent very Bioaccumulative
VSCC	Value of a Statistical Case of Cancer
VSL	Value of a Statistical Life
WCS	Worker Contributing Scenario
WHO	World Health Organisation
£	British pound sterling

DECLARATION

We, the Applicant Roche Diagnostics Limited, are aware of the fact that further evidence might be requested by HSE to support the information provided in this document.

Also, we request that the information blanked out in the 'public version' of the Analysis of Alternatives is not disclosed. We hereby declare that, to the best of our knowledge as of today (8th of July 2022) the information is not publicly available, and in accordance with the due measures of protection that we have implemented, a member of the public should not be able to obtain access to this information without our consent or that of the third party whose commercial interests are at stake.

Signature: Catherine Pawan Date, Place: 8th of July 2022

Catherine Pawan, Director of Legal and Compliance

Signature: Amanda Walker Date, Place: 8th of July 2022

Amanda Walker, Director of Quality and Regulatory Affairs

1 SUMMARY

The applicant for authorisation application is Roche Diagnostics Limited (RDL), a UK-based affiliate company of F. Hoffmann-La Roche Ltd. (collectively hereinafter referred to as "Roche"), which is the leading company in the *in vitro* diagnostic (IVD) market in Europe and worldwide. The current AoA (Analysis of Alternatives) was developed to support RDL's application for authorisation to continue the use of two groups of substances octylphenolethoxylates (OPnEO) and nonylphenolethoxylates (NPnEO) in the UK after the sunset date until complete substitution. RDL, as part of the Roche Group is publicly committed to substituting any Substances of Very High Concern (SVHC) from their products if technically possible.

Octylphenolethoxylates (OPnEO) and nonylphenolethoxylates (NPnEO) were included in Annex XIV (entries 42 and 43) of the regulation on Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) by the European Chemical Agency (ECHA) because of the endocrine disrupting properties for the environment of the degradation products with a sunset date of the 4th of January 2021. UK REACH has been implemented based on the EU REACH regulation including the Annex XIV entries. The group of substances included in this AoA are therefore also listed in Annex 14 of UK REACH in entries 42 (OPnEO) and 43 (NPnEO). As an EU application for authorisation for the same use for these substances was submitted to ECHA before the latest application date (LAD) of the 4th of July 2019, Article 127GA of UK REACH extends the UK LAD/sunset date to the 30th of June 2022. Since the requirements for authorisation under UK REACH were adopted from the EU, the same approach as for the EU dossier is used in this application. Reference is made where applicable to EU requirements and guidance documents.

Roche Diagnostics GmbH (RDG), the applicant of the EU AfA requested a review period of 7 years after the EU REACH Sunset date (the 4th of January 2021) to authorise the use of OPnEO and/or NPnEO until complete replacement of these substances in all affected IVD products, i.e. until the 4th of January 2028. For this application for authorisation under UK REACH, the end of the review period remains the same as substitutions are still planned to be completed by this date. The review period applied for is therefore (approximately) 5.5 years from the 30th of June 2022 till the 4th of January 2028. To simplify, the term end of 2027 is used within the text in the EU Dossier to determine the end of the review period. This terminology is also used in this application by RDL.

Because of the uncertainties associated with the endocrine disrupting properties of the degradation products of OPnEO / NPnEO and the question whether a threshold can reliably be derived, the applicant demonstrates risk / emission minimisation in the Chemical Safety Report (CSR). The applicant (RDL) furthermore demonstrates in the Socio-Economic Analysis (SEA) that the **benefits of continued use outweigh the risks to the environment.**

The two groups of substances OPnEO and NPnEO are addressed in the same dossier since they can be regarded as a group or category.

RDG currently engages OPnEO and NPnEO in four uses, three of which concern RDG's Diagnostics business. For RDL, only Use 3, the use of the IVD assays is relevant. Therefore, this application refers only to the 'Use of Octyl- and Nonylphenolethoxylates in IVD assays specified in Annex 1 to the AoA'. Please note that some product groups (Roche Molecular Diagnostics, Urinalysis and Accutrend) that were covered in Use 3 of the EU are not covered in this application as OPnEO / NPnEO is replaced or they are not sold any more. Further, some products of the product groups Clinical Chemistry (CC) and Drug Monitoring (DM) are not covered in this application because they do not fall under obligation for authorisation or because OPnEO or NPnEO have already been

replaced. Overview of the uses covered in the EU application of authorisation and the use relevant for this AfA is provided in the table below.

Use	Division	User	Short name	Use Name
1	Pharmaceuticals	RDG	Pharma	Use of Octylphenolethoxylates as emulsifier in the siliconisation of glass containers used as primary packaging for medicinal products
2	Diagnostics	RDG	Formulation	Use of Octyl- and Nonylphenolethoxylates in the formulation and filling of IVD assays specified in Appendix 1 to the AoA
3	**Diagnostics**	**Downstream Users (e.g. laboratories)**	**Products**	**Use of Octyl- and Nonylphenolethoxylates in IVD assays specified in Appendix 1 to the AoA**
4	Diagnostics	RDG	Processes	Use of Octyl- and Nonylphenolethoxylates in the production of proteins and the conjugation of latex beads, both being used as components or for the production of components of IVD assays, research or quality control products and other, e.g. analytical applications (processes specified in Appendix 1 to the AoA)

This AoA analyses the function of OPnEO / NPnEO in the affected IVD products, availability and hazards of alternatives as well as steps and time required for substitution.

OPnEO and /or NPnEO are used in IVD kits due to their surface-active properties and are usually used as an auxiliary chemical in one or several liquid reagents. Both substances may fulfil different functions during the performance of the assay with the functions being similar between the two substance groups. Typical functions are increasing solubilisation of reagents, cell lysis, protein stabilisation and wetting agent. The specific function of the substance varies between the different assays.

IVD products are highly regulated in countries worldwide. Therefore, several steps are required to accomplish substitution which focus on performance of the IVD assay. In general, these include pre-selection of alternatives, feasibility studies, validation and, where relevant, regulatory approval / market authorisation from different health authorities. Please note that the production of OPnEO and / or NPnEO - free IVD assays can only be implemented when the change in market authorisations has been approved by health authorities in all relevant countries worldwide. Efforts to identify alternatives for OPnEO / NPnEO in the formulation / production of existing assays and studies on the feasibility of the replacement have already started. In a number of assays, OPnEO / NPnEO have already been replaced. For the remaining assays potential alternative surfactants have been identified. Performance testing of the critical specifications of an assay, such as specificity, stability, precision etc. is key in feasibility assessment of an alternative and, since it is different in the various assays, it has to be assessed separately for each assay. If the specifications are not met, the steps for feasibility assessment and / or validation have to be repeated. This considerably increases the uncertainty of the actual time required to complete the substitution. In some cases, the changes needed to complete the replacement of OPnEO / NPnEO in the formulation are so significant that change of market

authorisations for the affected assays have to be requested from the competent health authorities, adding to the time needed until an assay can be replaced with an OPnEO / NPnEO-free version. Additionally, in one case, the replacement of the complete IVD system, with a new generation assay running on new IVD systems is being performed. In this case the time required to finish the replacement of all existing instruments in the UK is estimated to be until the end of the review period (the 4th of January 2028).

This AoA explains the unique technical and regulatory challenges associated with validating the alternatives. Please note that the use applied for in this authorisation dossier is depending on RDG receiving the EU authorisation, in particular for Use 2, for actually producing the affected assays. RDG applied for an EU authorisation until the end of 2027 to gain more time to complete the evaluation of alternatives, validate and assure performance of the affected products, and if necessary, submit change notifications to health authorities, including the MHRA via the UK Responsible Person, as a regulatory requirement for *in vitro* diagnostic assays.
Without a UK authorisation RDL would need to stop the distribution of many IVD products for years. IVD products used for diagnosis of certain diseases, therapy monitoring or drug abuse detection could not be supplied anymore. This would cause unacceptable impacts on patients and the healthcare system as detailed in the SEA.
RDL therefore applies for an authorisation until the end of 2027 to be able to distribute OPnEO- / NPnEO-containing IVD assays until they have been replaced by RDG and in the case of HIV, to gain the necessary time for the introduction of alternative IVD systems to the market.

Authorisation for the use of OPnEO / NPnEO until end of 2027 is requested to complete the replacement of these substances in all affected IVD products. This period is needed due to the complexity of the substitution projects. IVD's are highly regulated and there are stringent requirements for unchanged specifications of produced IVDs. An extensive validation phase cannot be dismissed and an update of market authorisations will in some cases be required. Furthermore, for one product more time is needed for the introduction to the market of a new IVD system with a new generation NPnEO-free assay.

2 INTRODUCTION

- ⇨ The applicant for this authorisation is **Roche Diagnostics Limited (RDL)**, which is an affiliate of **F. Hoffmann-La Roche Ltd**. (Roche)**.**
- ⇨ The current AoA was developed to support Roche's application for an authorisation to **continue the use of OPnEO / NPnEO after the UK sunset date until complete substitution**.
- ⇨ Roche is the world leader in ***in vitro*** **diagnostics** and **tissue-based cancer diagnostics**, and one of the most well-known companies working on diabetes management.
- ⇨ **Use covered in this AoA:**
- ⇨ Use of Octyl- and Nonylphenolethoxylates in some IVD assays of Roche portfolio. IVDs are **medical devices** intended to be used for **diagnosis, prevention, monitoring**
- ⇨ **IVDs are highly regulated**, in particular by IVD-specific regulations. They can only be placed on the market with a **regulatory approval / market authorisation** by the respective health authorities.

Roche Diagnostics Limited (RDL), the applicant for authorisation, is an affiliate of F. Hoffmann-La Roche Ltd. Roche does not sell its products directly to legal entities (customers) outside of Roche, but has its products sold by its country affiliates dedicated to the sale of Roche's products. RDL is the UK Responsible Person (UK RP) as required by UK legislation to place Roche's IVD products on the UK market. RDL operates in diagnostics, providing a broad and cutting-edge portfolio of tests and technology to prevent, diagnose and manage diseases. RDL is selling Roche's IVD products in the UK and the Republic of Ireland. The products are produced by different legal entities, among them Roche Diagnostics GmbH (RDG), the applicant of the submitted EU authorisation dossier (all Roche entities will be collectively hereinafter referred to as 'Roche'). Founded in 1896, F. Hoffmann-La Roche Ltd. is a Swiss multinational healthcare company that, together with its affiliates, works worldwide under three different main divisions: Pharmaceuticals, Diagnostics and Diabetes Care.

Roche is publicly committed to substituting any Substances of SVHC from their processes and products. Roche is the leading company in the IVD market in Europe and worldwide.

The current AoA was developed to support RDL's application for authorisation to **continue the use of the two groups of substances Octylphenolethoxylates (OPnEO) and Nonylphenolethoxylates (NPnEO) after the sunset date until complete substitution in the UK to meet the requirements of UK REACH.** It is based on the AoA developed for a similar application that has previously been submitted by Roche Diagnostics GmbH (RDG) in the EU[1]. RDG is the producer or importer into the

[1] Links to the submitted EU Dossier: Link for OPnEO: https://echa.europa.eu/applications-for-authorisation-previous-consultations/-/substance-rev/45043/del/200/col/synonymDynamicField_1512/type/asc/pre/2/view and for NPnEO: https://echa.europa.eu/applications-for-authorisation-previous-consultations/-/substance-rev/45044/del/200/col/synonymDynamicField_1512/type/asc/pre/2/view

EU of the IVD assays covered in this application. All concerned IVD assays are delivered by RDG to RDL for sales in the UK.

OPnEO and NPnEO were included in Annex XIV (entries 42 and 43) of the regulation on Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) by the ECHA because of the endocrine disrupting properties for the environment of their degradation products with a sunset date of the 4th of January 2021. UK REACH has been implemented based on the EU REACH Regulation including the Annex XIV entries. The group of substances included in this AoA are therefore also listed in Annex 14 of UK REACH in entries 42 (OPnEO) and 43 (NPnEO). As an EU application for authorisation for the same use for these substances was submitted to ECHA before the (LAD) of the 4th of July 2019, Article 127GA of UK REACH extends the UK LAD/sunset date to the 30th of June 2022. Since the requirements for authorisation under UK REACH were adopted from the EU, the same approach as for the EU dossier is used in this application. Reference is made where applicable to EU requirements and guidance documents.

RDG requested a review period of 7 years after the EU REACH Sunset date (the 4th of January 2021) to authorise the use of OPnEO and/or NPnEO until complete replacement of these substances in all affected IVD products, i.e. until the 4th of January 2028. For this application for authorisation under UK REACH, the end of the review period remains the same as substitutions are still planned to be completed by this date. The review period applied for is therefore (approximately) 5.5 years from the 30th of June 2022 till the 4th of January 2028. To simplify, the term end of 2027 is used within the text in the EU Dossier to determine the end of the review period. This terminology is also used in this application by RDL.

The two groups of substances, OPnEO and NPnEO are addressed in the same dossier since the EU Guidance on the preparation of an Application for Authorisation (AfA), Annex [1] concludes that if the substances were treated as a group or category or a read-across was conducted in the Annex XV dossier of the substances, a reference to the Annex XV dossier in the application for authorisation is sufficient for the substances being regarded as a group or category. In the Annex XV dossier for OPnEO, data on NPnEO are referenced in many instances (e.g. degradation, endocrine effects of the degradation product OP (4-(1,1,3,3-tetramethylbutyl)phenol) and NP (4-nonylphenol) and other endpoints). OPnEO and NPnEO are identified as ‘close analogues’ and are structurally very similar (only 8 instead of 9 CH2 groups in the C-chain). Furthermore, they are employed for the same or similar uses in the framework of this AfA and the same types of substances are possible alternatives. Hence, based on the above stated reasons, OPnEO and NPnEO can be regarded as a group in the application for authorisation and a combined dossier is prepared.

OPnEO and NPnEO are used in a wide array of IVD assays. For RDG’s EU application for authorisation, three distinct uses were identified within RDG and one further use was identified in the Roche Pharmaceuticals Division (Table 1). For RDL, only Use 3, the use of the IVD assays is relevant. Therefore, this application refers only to the ‘Use of Octyl- and Nonylphenolethoxylates in IVD assays specified in Annex 1 to the AoA’. Please note that some product groups (Roche Molecular Diagnostics, Urinalysis and Accutrend) that were covered in Use 3 of the EU AfA are not covered in this application as OPnEO / NPnEO is replaced or they are not sold anymore. Further, some products of the product groups Clinical Chemistry (CC) and Drug Monitoring (DM) are not covered in this application because they do not fall under the obligation for authorisation or because OPnEO or NPnEO have already been replaced. Please note that the use applied for in this authorisation dossier is depending on RDG receiving the EU authorisation, in particular for Use 2, for actually producing the assays.

Table 1. Uses overview of the EU AfA and relevant use for this application

Use	Division	User	Short name	Use Name
1	Pharmaceuticals	RDG	Pharma	Use of Octylphenolethoxylates as emulsifier in the siliconisation of glass containers used as primary packaging for medicinal products.
2	Diagnostics	RDG	Formulation	Use of Octyl- and Nonylphenolethoxylates in the formulation and filling of IVD assays specified in Annex 1 to the AoA.
3	**Diagnostics** **Only use relevant for Roche Diagnostics Limited in the UK**	**Downstream Users (e.g. laboratories)**	**Products**	**Use of Octyl- and Nonylphenolethoxylates in IVD assays specified in Annex 1 to the AoA.**
4	Diagnostics	RDG	Processes	Use of Octyl- and Nonylphenolethoxylates in the production of proteins and the conjugation of latex beads, both being used as components or for the production of components of IVD assays, research or quality control products and other, e.g. analytical applications (processes specified in Annex 1 to the AoA).

As the world's largest biotech company, Roche develops innovative medicines, improving the standard of care across **oncology, immunology, infectious diseases, ophthalmology and neuroscience.** Roche is the world leader in ***in vitro*** **diagnostics and tissue-based cancer diagnostics, including the launch of several IVD tests during the Covid-19[2] pandemic** and one of the most well-known companies working on diabetes management. As a leading healthcare company, Roche is supporting countries in their fight against COVID-19 and minimising its impact. Roche has developed a growing number of diagnostic solutions that help to detect and diagnose the infection, as well as providing digital support to healthcare systems. Roche is also continuing to identify, develop, and support therapies which can play a role in treating the disease[3]. Roche's healthcare strategy aims to provide medicines and diagnostics that enable significant improvements in the health, quality of life and survival of patients. More than thirty medicines developed by Roche

[2] **Co**rona**vi**rus **D**isease 20**19** according to the Centre for Disease Control and Prevention official site

[3] Roche Media Release, 2021: https://www.roche.com/de/media/releases/med-cor-2021-12-03.htm

are included in the World Health Organisation Model Lists of Essential Medicines[4], among them life-saving antibiotics, antimalarials and cancer medicines. Roche is a **leading provider of clinically differentiated medicines and personalised healthcare**[5]. Personalised healthcare is based on the separation of patients into different sub-groups according to biological differences such as genetic make-up or disease subtype. Using this information, physicians can treat patients more precisely.

Roche is a key player in the UK pharmaceutical and diagnostics industries. Currently RDL employs 769 people. 730 employees are based in the Roche UK supporting headquarters, field technical services and sales-based activities nationwide. Further 39 Roche employees are working in the Republic of Ireland (out of scope of this application). In 2020, **more than 21'260 jobs in the UK** were supported through Roche's business activities, supply chain and direct employment. Only 769 jobs, as indicated above, are direct employment by Roche, the other jobs are generated at other companies through Roche's activities.

In 2020 RDUK generated more than £ 882 million of UK revenue and invested more than £ 400 million in UK-based research and development.

As a result of continued investment in R&D across the globe, Roche supplies 581 different market leading diagnostic tests to the UK that are typically carried out on samples of blood, urine or tissue and analysed on high technology equipment, from a small hand-held device to a large analyser in a hospital laboratory. In addition, since 2010, Roche has delivered eight new medicines, found new ways to use existing medicines across 12 different disease areas, and developed 10 new treatments to help people manage their diabetes[6].

IVD are a category of medical devices, i.e. any apparatus, appliance, software, material or other article intended by the manufacturer to be used for human beings for the purpose of diagnosis, prevention, and monitoring, etc. In contrast to other groups of medical devices, IVD do not come into direct contact with patients, but serve to derive information on the patient's state by analysis of specific parameters e.g. in blood or tissue. This information can concern a physiological, pathological state, or a congenital abnormality, determine the safety and compatibility with potential recipients, or monitor therapeutic measures [2].

IVDs are highly regulated, in particular by IVD-specific regulations. Due to the usage of IVDs in healthcare, they can only be placed on the market with a regulatory approval / market authorisation by the respective health authorities. A change in the specification of an IVD, depending on the extent of the change, can trigger a renewal of regulatory approval / authorisation or require adaptation of an IVD-regulatory approval / authorisation.

In this AoA, the different alternatives to replace the substances in Uses 3 for which authorisation is being applied for are analysed. This includes whether a product can be replaced, or what alternative substances could be used to replace OPnEO and / or NPnEO in the different products, the steps required to complete the replacement and the uncertainties linked to this process. The replacement needs to take place at the Roche entities in Germany and the US where the concerned IVD assays are formulated. Once alternatives have been found, regulatory approval has been obtained and the

[4] World Health Organization (WHO) website: WHO Model Lists of Essential Medicines – 22nd List, 2021: https://www.who.int/publications/i/item/WHO-MHP-HPS-EML-2021.02

[5] Roche website, 'Personalised Healthcare': https://www.roche.com/about/strategy/personalised-healthcare

[6] Roche Website: 'Roche in the UK': https://www.roche.co.uk/en/roche-in-the-uk/roche-in-the-uk.html

adapted products can be produced at the different Roche entities, the adapted products can be delivered to the UK affiliate RDL and sold on the UK market to replace the products containing OPnEO or NPnEO. Therefore, this AoA focuses on substitution efforts is at the production sites.

3 ANALYSIS OF SUBSTANCE FUNCTION

- ⇨ **IVD assays** function **based on different principles**. They all have in common that a target (health) marker in patient samples such as blood or urine shall be qualitatively or quantitatively determined.
- ⇨ Measurements are performed using one or more IVD reagent on a **dedicated Roche-specific instrument.**
- ⇨ **OPnEO and / or NPnEO** are used in the IVD assays due to their **surface-active properties** and are usually used as an auxiliary chemical in one or several liquid reagents.
- ⇨ Typical functions are increasing **solubilisation of reagents, cell lysis, protein stabilisation and as wetting agent.**
- ⇨ Specific function of the OPnEO and / or NPnEO are described in detail for each group of affected products from Section 3.3.1 to Section 3.3.4.

OPnEO and NPnEO are used in wide array of IVD assays. Table 2 provides an overview of the product groups included in this authorisation dossier for Use 3 and concerned business areas (for further information see SEA). In the following sections, a general description of the principles of IVD products is given followed by a summary of the OPnEO and / or NPnEO function in all products. A detailed description for every group can be found in the subsections thereafter.

Table 2. Overview of product groups

Product Group	**Abbreviation**	**Business Area concerned**[+]
Clinical chemistry	CC	SWA Core reagents
Drug Monitoring	DM	
HIV	HIV	SWA Infectious diseases and oncology
Roche Tissue Diagnostic	RTD	RTD

[+] SWA: Serum Work Area; PoC: Point of Care; RTD: Roche Tissue Diagnostics

3.1 General Description of the *in vitro* Diagnostic Products Principle

According to the UK Medical Devices Regulations 2002 (SI 2002 No 618, as amended) (UK MDR 2002)[7], 'in vitro diagnostic medical device (or as referred to herein: in vitro Diagnostics) means a medical device which:

(a) is a reagent, reagent product, calibrator, control material, kit, instrument, apparatus, equipment or system, whether used alone or in combination; and

(b) is intended by the manufacturer to be used in vitro for the examination of specimens, including blood and tissue donations, derived from the human body, solely or principally for the purpose of providing information:

- Concerning a physiological or pathological state,
- Concerning a congenital abnormality,
- To determine the safety and compatibility of donations, including blood and tissue donations, with potential recipients, or
- To monitor therapeutic measures,

and includes a specimen receptacle but not a product for general laboratory use, unless that product, in view of its characteristics, is specifically intended by its manufacturer to be used for in vitro diagnostic examination.'

IVD assays function based on **different principles.** They all have in common that a **target (health) marker** in patient samples such as blood or urine shall be **qualitatively or quantitatively determined**. A reaction takes place between the marker in the sample and different reagents to produce a signal that can be measured by different techniques, depending on the type of assay. For this purpose, different reagents from an IVD kit are usually mixed during the measurement to start the reaction and produce the required **signal.** Measurements are performed with a **dedicated, Roche-specific instrument** and calibrated based on the reagents provided by Roche including any auxiliary substances present in the reagents.

[7] UK MDR 2002: https://www.legislation.gov.uk/uksi/2002/618/pdfs/uksi_20020618_en.pdf

3.2 Summary of Function of OPnEO or NPnEO in the Products

OPnEO and / or NPnEO are used in the IVD kits due to their **surface-active properties** and are usually used as an auxiliary chemical in one or several liquid reagents. Both substances may fulfil different functions during the performance of the assay with the functions being similar between the two substance groups. Typical functions are **increasing solubilisation of reagents, cell lysis, protein stabilisation and as wetting agent.** In the past, before endocrine disrupting properties of the degradation products of these substances had been identified, both substance groups were commonly used surfactants with favourable properties that were readily available in many research and development laboratories. They were selected to be included in the products mainly based on empirical testing. As already completed substitutions of OPnEO and / or NPnEO and experiences in the development of new products have shown, other surfactants can in principle be used to replace OPnEO and NPnEO in applications in IVD assays.

In the case of the uses of OPnEO and NPnEO covered in this AoA, **specific performance requirements** of the IVD assays are decisive for the assessment whether a specific alternative surfactant is suitable for replacement in a specific IVD assay or not. It is not possible to define an alternative for OPnEO and / or NPnEO for a specific function and then generically apply this to several assays as each assay has to be separately validated. For these reasons, the detailed analysis of functions on the next section is discussed by the product group. The assay specific requirements and ongoing efforts to investigate feasibility of substitution with alternative surfactants are also described by group in Section 6.

3.3 Detailed Description of the Different Product Groups and Function of OPnEO or NPnEO in the Products

In this section, a detailed description is given per group of IVD assays covered by Use 3 on the types of samples and parameters measured, principle of the measurement, occurrence and function of OPnEO and / or NPnEO in the assays.

3.3.1 Clinical Chemistry

a) <u>Type of sample and parameter measured</u>

Measurement of different blood and urine clinical parameters, for example bilirubin in serum / plasma to monitor a patient's liver function.

b) <u>Principle of the measurement</u>

Different principles apply for different assays:

- **Colorimetric**: the parameter to be measured reacts with the reagent and the colour produced is measured spectrophotometrically.
- **Enzymatic / colorimetric**: an enzyme reacts with different substrates, including the parameter to be measured and as a result a product can be spectrophotometrically determined.

c) <u>Composition of the kit, occurrence of OPnEO / NPnEO and instrument used for measurement</u>

The principle of the analysis is different on the various CC assays, therefore the OPnEO / NPnEO can be present depending on the assay in **one or two reagents** of the corresponding kit in a concentration range of [redacted]% w/w.

Type of instrument used: cobas® c, and cobas Integra®.

d) <u>Function of the OPnEO / NPnEO in the assays</u>

Variable, depending on the assay: NPnEO or OPnEO are used for **stabilizing the reagents** (e.g. protection of enzymes against mechanical stress by shaking of the reagent container), **for reducing carryover effect** from one sample to the following or to **reduce matrix interferences** and **decrease assay imprecision** (by reducing the surface tension of the solution which leads to more **precise pipetting** in the instruments).

Specifically:

Carry over: the Roche clinical chemistry analysers such as cobas® c501 or cobas® c701 are used to measure multiple samples and multiple diagnostic parameters per sample in a high throughput automated procedure. In order to ensure accuracy and precision of the test results, it is critical to avoid that either fractions of a sample are transferred to the reaction cell of another sample on the analyser during the measurement process or likewise that fractions of a reagent for one parameter is transferred to the reaction cell of a different parameter (such an unwanted transfer is referred to as either 'sample carry-over' or 'reagent carry-over'). This is achieved by sophisticated pipetting routines and extensive wash cycles in between measurements. In addition to these measures, addition of detergent to a reagent can also decrease the risk of carry-over by lowering the surface tension of the reagent and the reaction mixture, thus **minimising the amount of sample / reagent that adheres to surfaces** such as pipetting needles or reaction vessel walls.

Matrix interference: samples for clinical chemistry testing are in most cases serum and plasma, to a lesser extent also urine, cerebrospinal fluid (CSF) and whole blood. All of these sample materials contain a **complex mixture** of proteins, peptides, sugars, lipids, hormones, cells and a multitude of further components. This complex mixture is referred to as 'sample matrix'.

Depending on the test principle, this matrix can interfere with the measurement of a sample to varying extent. A general approach to reduce the interference by the sample matrix is the addition of detergent. The **detergent solubilises the components of the matrix** such as lipids, proteins and peptides and reduces the interaction of these components with the test reaction. At the same time, however, it is important to ensure that the detergent does not itself interfere with the test reaction, e.g. the interaction of an enzyme with its substrate.

As the matrix is very complex and not well defined, the matrix effect itself as well as the impact of detergent on the matrix interference are **hard to predict**. Therefore, the use of detergent to reduce the sample matrix effect is based on experience or the result of an empirical approach.

A function that always will be affected by the surfactants in the reagent is lipemia interference. Lipemia is a turbidity of the sample material (in most cases serum or plasma) caused by the presence of lipid particles [3]. This is a common interference seen in samples of e.g. non-fasting patients. As the turbidity caused by the lipid particles increases the absorption of light in the measurement cuvette, lipemia can interfere with the measurement and lead to falsely elevated or decreased values. A common way to reduce lipemia is the addition of surfactants to the reaction mixture.

3.3.2 Drug Monitoring (Subgroup 1 and 2)

a) Type of sample and parameter measured

Measurement of **concentrations of drugs** (e.g. barbiturates, propoxyphene or their metabolites **in urine** (subgroup 1) **and serum / plasma** (subgroup 2) samples with the goal of detecting abuse of drugs or monitoring therapies performed with these drugs.

b) Principle of the measurement

Subgroup 1: **Kinetic interaction of latex beads in a solution** as measured by changes in light transmission.

Kinetic interaction of latex beads in solution, type I (see Figure 1): In the absence of sample drug, free anti-drug antibodies bind to drug-latex bead conjugates, causing the formation of particle aggregates. As the aggregation reaction proceeds in the absence of sample drug, the absorbance increases. When the urine sample contains the drug being measured, this drug competes with the particle-bound drug derivative for free antibody. Antibody bound to sample drug is no longer available to promote particle aggregation, and subsequent particle precipitation is inhibited. The presence of sample drug diminishes the increasing absorbance in proportion to the concentration of drug in the sample. Sample drug content is determined relative to the value obtained for a known cut-off concentration of drug. This is the mode of action for DM5, DM6, DM8, DM9 and DM11.

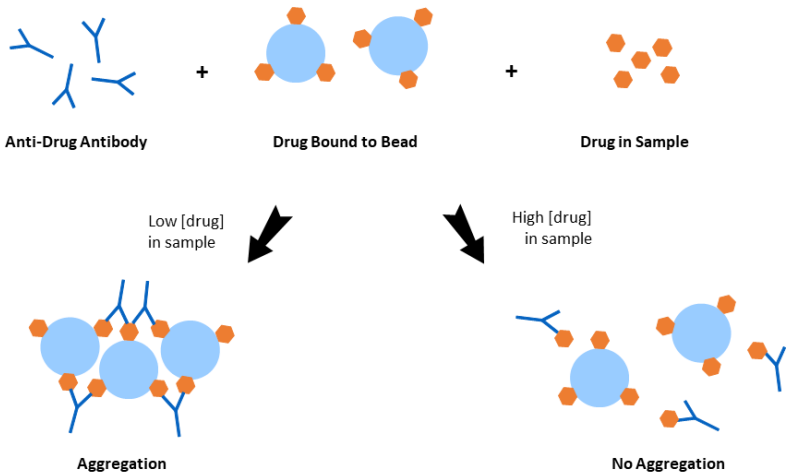


Figure 1. Scheme of kinetic interaction of latex beads in solution, type I

Subgroup 2: **Enzymatic detection** (see Figure 2). The reactive solutions contain an enzyme and its substrates. Normally the enzyme catalyses a transformation of the substrates and when the product of this reaction is released, it can be measured photometrically. When the drug in question is present, the enzymatic reaction is inhibited and there is a decrease in product release, and therefore a decrease in optical density is measured at the selected wavelength.

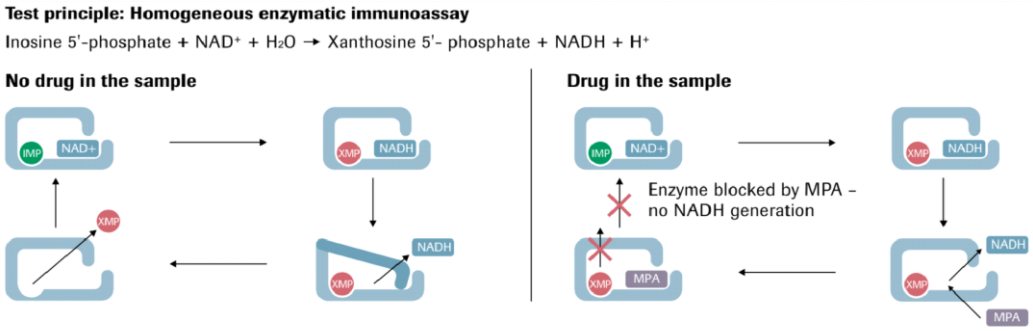


Figure 2. Scheme of enzymatic detection principle

c) <u>Composition of the kit, occurrence of OPnEO / NPnEO and instrument used for measurement</u>

Subgroup 1: Kit contains two to three reagents depending on the assay. **One of the reagents** contains the latex beads. This reagent has **OPnEO as part of its formulation**. Furthermore, **other reagents** containing the antibodies, conjugates and / or solutions for sample dilution **contain OPnEO and / or NPnEO as well**. The concentrations of OPnEO / NPnEO in all reagents is variable from [redacted] w/w.
Subgroup 2: Kit contains two reagents, R1 and R2. **Both reagents contain NPnEO** at a concentration of [redacted] w/w.

Type of instrument used: cobas® c, and cobas Integra®.

d) <u>Function of the OPnEO / NPnEO in the assays</u>

Subgroup 1: The OPnEO (and additionally NPnEO in the following products: DM5, DM6, DM8) is present in the reagents to improve the assay performance by:

- **Stabilising the beads in solution**: the OPnEO stabilises the bead suspension by prevention of coagulation and delay of sedimentation of solids finely dispersed in the liquid buffer. OPnEO is solid-liquid adsorbed at the interface between the solid bead surface and the liquid buffer. The adsorbed OPnEO prevents the aggregation and coagulation of the dispersed solid particles by means of steric screening.
- **Reducing the carryover and assay imprecision**: the OPnEO / NPnEO reduces the surface tension of the solution, thus minimising the amount of sample / reagent that adheres to surfaces such as pipetting needles or reaction vessel walls. As a result, this leads to a more precise and robust pipetting performance of the instrument and prevents carryover (i.e. transference of some sample to the next sample, see detailed explanation in Section 3.3.1.d).
- **Reducing interferences**: OPnEO / NPnEO interact with proteins which are exposed in urine matrix. The proteins are incorporated into the micelles and their interaction with the reactive components are reduced (see detailed explanation in Section 3.3.1.d).

Subgroup 2: the NPnEO is present in the reagent to:

- **Improve stability** (i.e. the detergent protects the enzyme from adsorption on surfaces such as reagent container of an assay) and
- **Reduce assay imprecision** by reducing the surface tension of the solution, which leads to more precise pipetting in the instruments.

3.3.3 HIV

a) Type of sample and parameter measured

Screening test to determine the **presence of HIV** (Human Immunodeficiency Virus) antigens and antibodies in blood or plasma samples for **early detection** of HIV infection.

b) Principle of the measurement

Electro**c**hemi**l**uminescence **i**mmuno**a**ssay 'ECLIA' (see Figure 3). First, the human serum or plasma sample, containing the virus or the immunoglobulins (Ig), produced against the HIV when the patient is exposed to it, are pre-treated with reagent R0 (containing NPnEO) to break the membrane (lysis) of the virus and release the antigen p24. If p24 antigen from the HIV or Ig against HIV antigens are present in the sample, they will bind to the biotinated (reagent R1) and ruthenylated (reagent R2) HIV specific antigens / peptides and Ig's. In a second step, the formed immune complexes bind to the streptavidin coated magnetic beads. On the measuring device, the magnetic beads are attracted with a magnet. The rest of the sample is washed to take away all the remaining particles and tripropylamine (TPA) is added. When a voltage is applied, the TPA and the ruthenium react and produce light. A sensor can measure the light produced by the ruthenium. The amount of light produced is proportional to the amount of antigen or Ig present on the human serum or plasma sample.

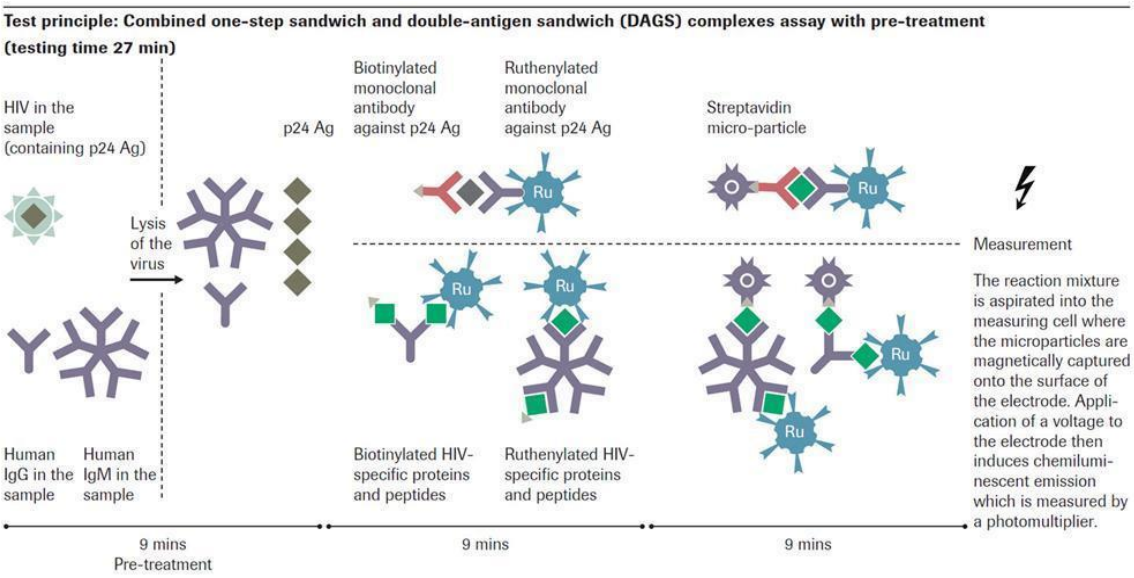


Figure 3. Scheme of ECLIA assay principle

c) Composition of the kit, occurrence of NPnEO and instrument used for measurement

The kit contains a reagent rackpack with four working solutions (M, R0, R1, R2) and two of them **R0 and R1 contain NPnEO** in concentrations of 1.5% w/w and 0.2% w/w respectively.

Type of instrument used: **cobas® e** analysers.

d) Function of the NPnEO in the assays

R0: **Viral lysis** to release the p24 antigen of the virus into the reaction solution to increase sensitivity (i.e. the surfactant breaks the viral membrane).

R1: improvement of assay performance through increase of long-time reagent stability of the biotinylated components. The NPnEO **increases the resistance** of the biotinylated reagent to mechanical stress produced by shipment and handling at the customer site.

3.3.4 Roche Tissue Diagnostics

a) Type of sample and parameter measured

Tissue samples are evaluated by selective staining with *in situ* hybridisation (ISH) probes to aid in the diagnostic of different **types of cancer**, such as cervical cancer, breast cancer, etc. INFORM HER2 Dual ISH DNA Probe Cocktail Assay is a good example of a cancer diagnostic with therapeutic implications. The assay is used to assess amplification status of the HER2 gene. Patients who have breast cancer with HER2 amplification are candidates for Roche's Herceptin (trastuzumab) treatment.

b) Principle of the measurement

Tissue samples are exposed to specifically designed ***in situ*** **hybridisation probes** which are marked and can be detected using **various detection methods**. An *in situ* hybridisation probe is a piece of nucleic acid that can bind to the DNA of a cell if it contains the specific target gene or DNA section. If the tissue being analysed contains the gene being tested, the hybridisation probe will bind to it and the cells containing the analysed gene will be stained. For example: The INFORM HER2 Dual ISH DNA Probe Cocktail uses two detection kits: one probe labelled with dinitrophenyl (DNP) would bind cells that express the HER2 gene and another probe labelled with digoxigenin (DIG) would bind Chromosome 17 (Figure 4). After the probes bind to the different target genes, there is a series of washing and staining steps and as a result, the cells that express the HER2 gene will be stained black and chromosome 17 will be stained red. Then the expression status of the gene HER2 expression can be determined by enumeration of the ratio of HER2 to Chromosome 17 using light microscopy.

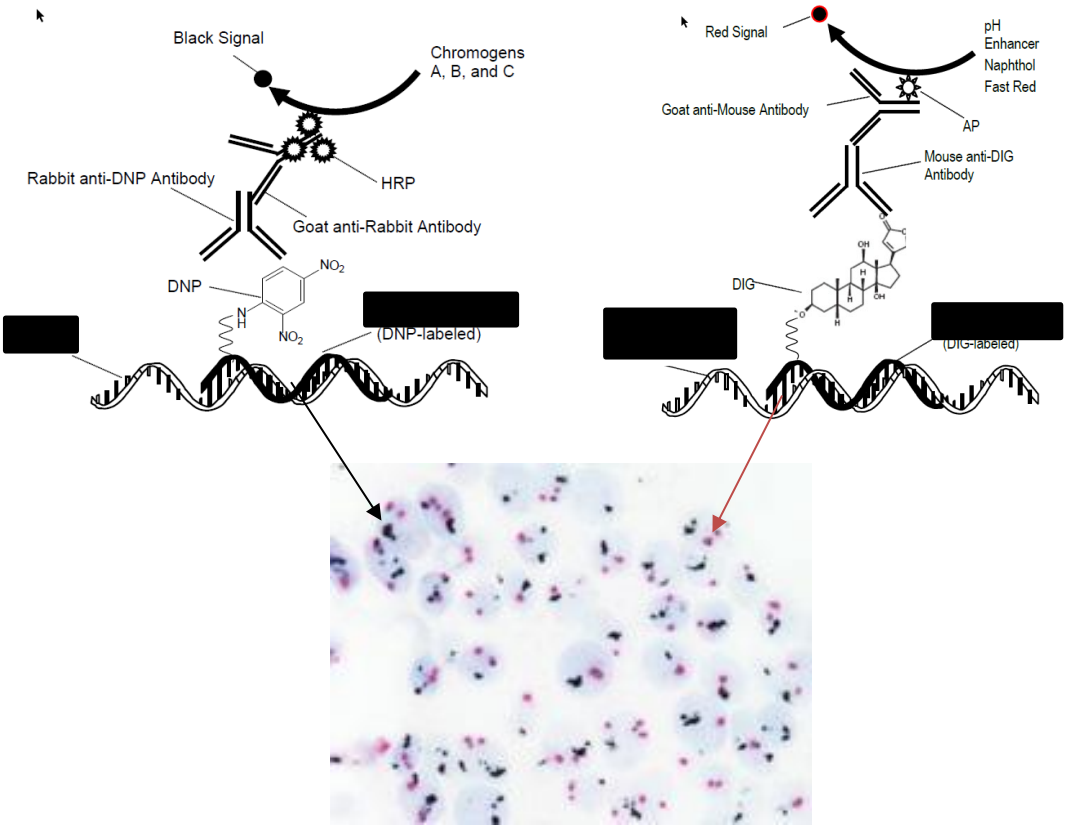


Figure 4. Principle of in situ hybridization for tissue samples

c) <u>Composition of the kit, occurrence of OPnEO and procedure for measurement</u>

OPnEO is present in a concentration of [redacted] % w/w in the Sodium Chloride Sodium Citrate buffer solution.

Type of instrument used: automated slide stainers (BenchMark GX, XT and ULTRA) Ventana Medical Systems.

d) <u>Function of the OPnEO in the assays</u>

Surface tension reduction. This surfactant is used in a salt wash that removes unbound DNA or RNA probes from a tissue specimen slide. The primary active ingredient in the wash is the salt, but the surfactant is required to minimise non-specific target staining (i.e. staining of cells that are not targeted by the assay) and reduce the likelihood of a false positive result.

4 ANNUAL TONNAGE

In Table 3 the annual use tonnage is given at the UK sunset date assuming that all substitutions are delayed. In addition, the **maximum annual tonnage** is given that could be reached in the course of the review period as a worst-case if all substitutions are delayed.

In case of OPnEO, the amount is given at the UK sunset date and, in addition, the maximum annual amount is given that could be reached until the end of the review period (end of 2027) as a worst-case if all substitutions are delayed. In both cases, i.e. on time and delayed substitutions, the usage at the UK sunset date is the same, as for all products the shelf life would still be running.

In case of NPnEO, the amount is given at the UK sunset date assuming that all substitutions are delayed. The maximum annual amount over the course of the review period is reached at the UK sunset date. After this date, the usage of NPnEO will constantly decrease, even if the substitutions are delayed.

In this AfA, RDL therefore applies for the use of a maximum annual tonnage of 48.65 kg/a of OPnEO and 0.39 kg/a NPnEO for Use 3. For more details on how this maximum was defined please refer to the CSR.

Table 3. Overview of annual tonnage of OPnEO and NPnEO used at the UK sunset date (worst-case) as well as the maximum annual tonnage over the course of the review period (amount applied for).

Use	**Substance**	**Amount at UK sunset date**	**Maximum annual amount applied for**
		kg/a	
Use 3	OPnEO	40.19	48.65
	NPnEO	0.39	0.39

5 IDENTIFICATION OF POSSIBLE ALTERNATIVES

⇨ Several alternatives were analysed:

1) **Substitution** of OPnEO / NPnEO with alternative surfactants in the existing IVD assays.
2) **Use of alternative assays** from RDG which are already on the market.
3) Development of **new-generation products**.
4) **Replacement of the products** with assays (or reagents) from competitors.

⇨ In most cases, the most realistic alternative is the **substitution of OPnEO / NPnEO** in the existing assays with alternative surfactants. This should also be completed in the shortest time.

⇨ In the case of the HIV assay, replacement by a **new generation assay** and system is pursued.

⇨ A shortlist of **potential alternative surfactants** was compiled based on theoretical hazard assessment of available surfactants.

⇨ 'One alternative for all' is not possible.

⇨ **Technical feasibility** testing per product with selected surfactants is ongoing.

⇨ For some product groups that were still covered in the corresponding EU AfA, OPnEO / NPnEO have already been successfully replaced.

⇨ **Hazard profile** of alternatives in order to avoid regrettable substitution:

- No regulatory alerts.
- No aromatic rings or halogens.
- No suspected SVHCs.
- No classification as acute or chronic toxicity to aquatic organisms.
- No classification as human health hazard Cat. 1 except H318.

5.1 Description of Efforts Made to Identify Possible Alternatives

In principle, **several options** for replacement of the OPnEO and / or NPnEO containing products could be considered from Roche's perspective.

1) **Substitution** of OPnEO / NPnEO with alternative surfactants in the existing IVD assays.
2) **Use of alternative assays** from RDG which are already on the market.
3) Development of **new-generation products**.
4) **Replacement of the products** with assays (or reagents) from competitors adapted to run on Roche instruments.

Alternative 1: The **most realistic** alternative is the **substitution** of OPnEO and / or NPnEO in the existing assays with alternative surfactants. As already completed substitutions of OPnEO and / or NPnEO and experiences in the development of new products have shown, other surfactants can in principle be used to replace OPnEO and NPnEO in applications in IVD assays. Efforts to identify specific alternative surfactants had already started in 2015. The **exact criteria** applied to identify the possible alternatives **depend on the assay and the specific function of the OPnEO and / or NPnEO** in the assay. Performance testing of the critical specifications of an assay, such as specificity, stability, precision is key in feasibility assessment of an alternative. It is therefore not possible to define a set of properties that have to be fulfilled by an alternative surfactant for all assays. Also, due to the specific requirements for each assay, it will not be possible to substitute with one or two single alternative surfactants in all assays as past experiences have shown.

Three further alternatives could be considered, to **replace the complete reagents or assay**, instead of substituting the OPnEO and / or NPnEO in the assays.

Alternative 2: Replacement of the assay used by other OPnEO and / or NPnEO free RDG existing assays. This is **not a suitable alternative** as usually only one assay is available for each system / analyser.

Alternative 3: Development of **new-generation products**, i.e. entirely new formulations. Development of new generation products **takes a long time** as new-generation products must be registered as new IVDs with different health authorities. Often, such new generation products run on new generation instruments and thus customers first have to be switched to the new instrument to be able to use the new assay. For example, in the case of the HIV assay, a new generation NPnEO-free product is available (see Section 6.3 on HIV) and approved in the UK. Even though, this newer generation HIV assay is already developed and introduced to the market for part of Roche's customers, it cannot be considered a suitable alternative. The timeframe for the switch for all customers will depend on the capacity of the analyser manufacturer (HITACHI high Technology). Currently the transition to the new instrument family is delayed due to the worldwide shortage of electronic components. This situation will continue stay for at least throughout 2022, thus leading to a need to keep the older product on the market for another ca. 5.5 years after the UK sunset date. Therefore, even in the cases where alternative / newer generation products are available, they are not yet a suitable alternative for the OPnEO and / or NPnEO containing product.

Alternative 4: Replacement of the affected assays with **assays from competitors**. This is also **not a suitable alternative** as the **Roche systems only run with Roche assays (or reagents)**. The tests are specifically validated and calibrated for the respective instrument. Examples teach that it takes 3-4 years in general to apply third party products on Roche systems. This scenario would also require market authorisation efforts. Consequently, it is not a possible scenario on a short-term notice and would not be completed in a shorter time than Alternative 1. Due to the high competitiveness in the IVD market, there is also a probability of refusal from third parties to sell to Roche or the risk for third parties to provide their reagents only at very high transfer prices. Moreover, in the unlikely case that the product could be acquired from a third party, there is no certainty that it would be OPnEO and / or NPnEO free (or, in case manufactured outside the European Economic Area (EEA) and UK, contain < 0.1% w/w OPnEO / NPnEO) and that it would meet Roche quality / performance standards.

In summary, replacement by alternative surfactants (Alternative 1) is considered the most realistic alternative that is pursued for most assays. In the case of the HIV assay, replacement by a new generation assay and system is pursued (Alternative 3). For further details on how the different alternatives will be implemented in each individual product group please refer to Section 6.

Perspective of RDL's customers:

In Use 3, RDL's customers, i.e. laboratories and hospitals are using OPnEO and / or NPnEO by running RDL's IVD assays on Roche systems. In principle, the customers themselves could therefore look for alternatives. However, replacement of the affected assays with assays from competitors is not possible as the Roche systems only run with Roche assays (or reagents) (see Alternative 4 discussed above). The only other option available to customers would therefore be to **change the whole system (instrument) to the system of a competitor.** This would however not be a viable alternative if competitors also use OPnEO and / or NPnEO. In addition, such changes require **great economic efforts**, since e.g. acquisition of new equipment and training of the personnel in the use of the new IVD systems is necessary. Validation of the new system would also be required in order to control that the results are consistent to those obtained with the old systems. Therefore, such an option would only be pursued if RDL's IVD assays containing OPnEO and / or NPnEO were not available anymore (i.e. in the case of the non-use scenario) and it is estimated to take ca. 2 years for all laboratories if capacities at competitors were available. However, it is not clear if competitors could produce on time the required amount of new equipment to replace the IVD systems from Roche currently in use in the UK. For more details on what a change of IVD system entails for a laboratory see 'description of economic impacts' in the SEA.

5.2 Short List of Possible Alternative Surfactants

A shortlist of alternatives to be considered for feasibility testing was defined per assay or groups of assays **based on basic chemical properties of the surfactants**. For example, for the Drug Monitoring assays about 40 detergents were analysed by High Performance Liquid Chromatography (HPLC). Two important properties of surfactants, cloud point[8] and critical micelle concentration (CMC)[9] in different buffers were determined. Based on these results, many detergents could be excluded and favourites were identified. In addition, **availability** of the surfactants, **economic feasibility** and **past experiences** were considered. In addition, a **hazard assessment** of the surfactants was performed (see Section 5.3). In order to avoid regrettable substitutions[10], surfactants were additionally checked for regulatory alerts and surfactants with an aromatic ring or containing halogens were excluded[11].

Should the current list of possible alternatives per assay not contain a surfactant that is suitable for substitution, further surfactants could be identified for feasibility studies.

Based on the compiled shortlist, the selected alternatives for each product group are **tested for feasibility** in order to select the appropriate substance for further validation in a next step (see detailed description of the Steps required for substitution in Section 6). summarises the different alternatives considered for each product group, including the status of feasibility testing at the time of preparation of the EU AfA. This overview is shown to illustrate the effort put into the identification of alternatives. The status has progressed since then. The current status of selection of alternatives and

[8] The cloud point of a non-ionic surfactant or glycol solution is the temperature at which the dissolution of solids is no longer complete, and the mixture starts to phase separate and two phases appear, thus becoming cloudy.

[9] The critical micelle concentration (CMC) is defined as the concentration of surfactants above which micelles form and all additional surfactants added to the system will form micelles

[10] https://chemicalwatch.com/65734/basf-and-automotive-industry-group-agree-substitution-criteria

[11] Criteria for selection of a detergent – Roche internal communication - 8 April 2017

substitution is discussed in the individual section on each product group (see Section 6). Please see footnote on table for explanation on status abbreviations.

Table 4. Alternative surfactants for replacement of OPnEO / NPnEO considered or already tested for the different product groups (status as indicated in the EU AfA)

Alternative Number[12]	**DM**	**HIV**	**CC**	**RTD**
1	F-			F-
2	F-			
3	Fo (1)		F- (2) F+ (1)	
4		F+		
5				
6	A1 for all products. F- (1) Fo (5) Vo (1)	F+	A+ (2) F+ (6) F- (2)	Vo
7	A2 (1) Fo (2)	F-	F- (1)	F-
11	F-			
18		A+ (Brij 58)		
19	F-		F- (2)	
20			F- (1)	
21	F-			
22	F-			
23	F-		F+ (1)	
24			A+ (2)	
25	F-		F+ (1) F- (2)	
26	F-		A+ (1) F- (1)	
27			F- (1)	
28			F- (3)	
29			F- (1)	
30			F- (1)	
31			F- (3)	
32			A+ (1)	
33			F- (1)	
34			F- (1)	
35			F- (1)	
36	F-		F- (1)	
37			F- (1)	
38			F- (1)	F-
39			F- (2)	
40	A2 (4) Fo (2)			
41		F-		

A1, A2, A3, A4, A5, Ax: Alternative considered 1st, 2nd choice etc.., (if not yet tested, or alternatives that have been considered, but were not tested as an alternative has already been found).
Fo: Feasibility test ongoing
F-: Feasibility test performed, negative result (i.e. not suitable)
F+: Feasibility test performed, positive result
Vo: Validation ongoing
V-: Validation negative, further substances need to be tested
A+: this surfactant will be used as replacement for the OPnEO / NPnEO
(A+): this surfactant was also tested and would be appropriate but was not selected as replacement.
The numbers in brackets indicate for how many assays this information applies.

[12] The alternative number is not consecutive since some entries were only applicable to product groups in the EU dossier that are not in scope of this UK AfA

5.3 Hazard Profile of the Alternative Surfactants

OPnEO and / or NPnEO were included on Annex XIV to REACH for the endocrine disrupting properties arising from their degradation products causing probable serious effects to the environment based on scientific evidence. Therefore, alternative substances without endocrine disrupting properties and without any other hazard properties making them possible candidates for Annex XIV are needed.

An **extensive search for alternative surfactants** was performed, resulting in a list of about 40 substances for all products in scope of the EU AfA (see Table 4). As for the previous table, the table including the hazard properties reflects the status at the time of preparation of the EU AfA and includes alternatives for product groups where substitution has already been completed. This overview is shown to illustrate the effort put into the identification and assessment of alternatives. As information on hazard properties are continuously updated, some of the information may be outdated.

The search focused on substances that had already been shown to work as substitutes for OPnEO and / or NPnEO in other products or processes and substances suggested as substitutes by suppliers. The **hazard profile** of all alternative surfactants was originally assessed in 2016 and 2017, and the surfactants were **checked for regulatory alerts**. This information is continuously updated to account for new information. In particular, information from REACH registrations and all potentially listed regulatory activities / alerts on a substance listed in ECHA's substance database were considered. Also, additional information e.g. from trade associations (CESIO[13]) guide on classification of surfactants 2017 [5]), published data [9], the SIN (Substitute It Now!) list[14] and data generated by Roche (OECD 201, 202, 203, 209 and 301 F studies) were considered. Surfactants with aromatic rings or halogens as well as, in particular, any surfactants with potential SVHC status (substances with known properties meeting any of the criteria set out in Article 57 of REACH) were excluded from the shortlist. Data on classification are available from REACH registrations or the CESIO classification guide for nearly all alternatives. The substances were also checked for their **biodegradability**. Although the substances to be used in IVD assays are not subject to the regulation on detergents (Regulation (EC) No 648/2004), substances that meet the biodegradability requirement for surfactants according to that regulation are preferred. In addition to the main criteria already mentioned, the alternatives should not be classified according to the Classification, Labelling and Packaging (CLP) Regulation [4] in the hazard categories acute or chronic toxicity to aquatic organisms and human health hazard Cat. 1, except H318 (causes serious eye damage). The alternatives shown in the table below (see Table 5) were checked and the ones that were not excluded based on the hazard properties were considered for feasibility testing (see Table 4 in previous subsections). If technically suitable alternatives to be used in larger quantities are lacking information on hazards, corresponding studies are performed before the substance is definitively used.

Through the described selection procedure, it is ensured that Roche will only apply alternatives that reduce the overall risk in comparison to OPnEO and / or NPnEO based on available knowledge.

[13] Comité Européen des Agents de Surface et de leurs Intermédiaires Organiques - European Committee of organic surfactants and their organic intermediates

[14] SIN list, The International Chemical Secretariat, http://chemsec.org/sin-list/

Table 5. Hazard properties of the alternatives (status as indicated in the EU AfA)

CAS No.	Chemical name	CLP classification	CLP classification source	Biodegradation	Biodeg. source	Alternative further considered based on hazard properties
1119-97-7	TTAB (1-Tetrydecanaminium, N,N,N-trimethyl-, bromide	H302-H315-H318-H335-H373-H400	[6]	Readily biodegradable under conditions where tetradonium bromide does not exert toxicity to the microorganisms.	[6]	no
1338-41-6	Sorbitan stearate	Not classified	[6]	readily biodegradable (88% after 28 days, OECD 301 C)	[6]	yes
1400790-00-2	Polyoxyethylene Polyoxypropylene (C9-11) Alkyl Ether	possible high toxicity to aquatic organisms	-	-	-	Further data needed
151-21-3	Na-Dodecylsulfat / SDS	H228-H302-H332-H315-H318-H335-H412	[5] [6]	readily biodegradable (95.8% after 28 days)	[6]	yes
160875-66-1	1-Heptanol, 2-propyl-, 7 EO	H302-H318	[7]	readily biodegradable (74% after 28 days)	[8]	yes
169107-21-5	Alcohols, C9-11, branched, Ethoxylated	>2.5 < 4 EO: H319 >4 < 5 EO: H318 >5 < 10 EO: H302-H318 >10 < 15 EO: H318	[5]	readily biodegradable if EO < 30 (read-across from supporting substance)	[10]	yes
24342-68-5	Hexaethylene Glycol Monobenzyl Ether	-	-	-	-	no
24938-91-8	Polyoxyethylene Tridecyl Ether	H302-H318-H315-H319-H400-H411	[7]	readily biodegradable	[11]	Further data needed
26266-57-9	Sorbitan-Monopalmitate	Not classified	[7]	readily biodegradable (read-across from supporting substance (structural analogue or surrogate))	[6]	yes
3055-99-0	3,6,9,12,15,18,21,24,27-nonaoxanonatriacontan-1-ol	H302-H319-H318 (depending on EO) Environment: >5-15 EO: H412 ≥15 EO: not classified	[5]	Alcohol ethoxylate homologues with linear hydrocarbon chain lengths from C8 to C15 and mean values ranging from 3-20 EO units are readily biodegradable	[5]	yes
4536-30-5	2-(dodecyloxy)ethane	Not classified	[6]	-	-	Further data needed

CAS No.	Chemical name	CLP classification	CLP classification source	Biodegradation	Biodeg. source	Alternative further considered based on hazard properties
4669-23-2	Triethylenglykol-monodecyl ether	-	-	-	-	Further data needed
57671-28-0	Pentaethylene glycol monobenzyl ether	-	-	-	-	no
60828-78-6	2,6,8-Trimethyl-4-nonylpolyethylene glycolether (10 EO)	H318-H412-H315	[7]	not readily biodegradable; expected to biodegrade slowly in the environment	supplier brochures	Further data needed
61725-89-1	Oxirane, 2-methyl-, polymer with oxirane, tridecyl ether	not classified	Public SDS	-	-	Further data needed
64366-70-7	Ethoxylated propoxylated 2-ethyl-1-haxanol	H412	[7]	Ready: 58% (new test) Inherent: 81% (new test) => not readily but inherently biodegradable	[8]	yes
68002-97-1	Alcohols, C10-16, ethoxylated	H400-H412 or H412 or not classified depending on EO H318 or H319 or not classified depending on EO	[5]	readily biodegradable if EO < 30 (read-across from supporting substance)	[10]	yes
68131-40-8	Alcohols, secondary C11-15, ethoxylated	H412	[5]	readily biodegradable (65% in 28 days, OECD 301 C)	[6]	Yes, but potential sensitizing properties to be checked
68213-23-0	Alcohols, C12-18, ethoxylated	<5 EO: H400 (M=1) <15 EO: H412 ≥15 EO: not classified H319, H318 depending on EO	[5]	readily biodegradable (read-across based on grouping of substances (category approach))	[6]	yes
68439-46-3	Alcohols, C9-11, ethoxylated	H302-H318	[6]	readily biodegradable: (89% after 28 days)	[8]	yes
68439-49-6	Alcohols, C16-18, ethoxylated (50 EO or 80 EO)	H318	[7]	<30 EO: readily biodegradable >30 EO: inherently biodegradable	[10]	yes
68603-25-8	Alcohols, C8-10, ethoxylated propoxylated	H302-H315-H318-H319-H411-H412-H335	[7]	-	-	Further data needed

CAS No.	Chemical name	CLP classification	CLP classification source	Biodegradation	Biodeg. source	Alternative further considered based on hazard properties
69227-22-1	Polyoxypropylene (C10-16) Alkyl Ether	H302-H318-H315-H319-H400-H411	[7]	readily biodegradable	[11]	Further data needed
71060-57-6	Alcohols, C8-10, ethoxylated	H302-H411	[7]	readily biodegradable (80-90% in 28 d, GLP test)	[6]	yes
75621-03-3	CHAPS (3-[(3-Cholamidopropyl) dimethylammonio]-1-propanesulfonate)	H315-H319-H335-H336	[7]	-	-	Further data needed
8047-15-2	Saponin	H319-H335	[6]	readily biodegradable (90.1 % degradation after 28 days)	[6]	yes
81239-45-4	3-[benzyl(dimethyl)azaniumyl]propane-1-sulfonate	-	-	-	-	Futher data needed
82473-24-3	3-([3-Cholamidopropyl] dimethylammonio)-2-hydroxy-1-propanesulfonate (Chapso)	H302-H315-H319-H335	[7]	-	-	Further data needed
84133-50-6	Alcohols, C12-14-secondary, ethoxylated	H315-H318	[7]	readily biodegradable (identified by name, not CAS)	Supplier brochures	Further data needed
868594-48-3	Nonaethylene glycol Monobenzyl ether	-	-	-	-	no
9002-92-0	Dodecan-1-ol, ethoxylated	H302-H319-H318 (depending on EO) Environment: >5-15 EO: H412 ≥15 EO: not classified	[5]	Alcohol ethoxylate homologues with linear hydrocarbon chain lengths from C8 to C15 and mean values ranging from 3-20 EO units are readily biodegradable	[5]	yes
9003-11-6	2-methyloxirane	not classified	[7]	± readily (SDS supplier); evidence of inherent biodegradation (new study sponsored by Roche acc. OECD 302 C)	[8] / new study	yes
9004-95-9	Hexadecan- l-ol, ethoxylated	H302-H315-H318-H319-H400	[7]	Alcohol ethoxylate homologues with C16 or C18 hydrocarbon chain lengths and mean values between 2 and more than 20 ethylene oxide units are readily biodegradable.	[11]	yes

CAS No.	Chemical name	CLP classification	CLP classification source	Biodegradation	Biodeg. source	Alternative further considered based on hazard properties
9005-00-9	Octadecan-1-ol, ethoxylated	<5 EO: H411 >5<10 EO: H400 (M=1), H412 > 10 EO: not classified	[6] [5]	readily biodegradable (83.6% after 28 days, OECD 301B)	[6]	yes
9005-64-5	Sorbitan monolaurate, ethoxylated	Not classified	[7]	Biodegradable in a concentration of 100 mg/l (58% after 28 days) / Readily biodegradable in a concentration of 25 mg/l (62.5% after 28 days)	[8]	yes
9005-65-6	Sorbitan monooleate, ethoxylated	Not classified	[7]	readily biodegradable	[7]	yes
9005-67-8	Sorbitan monostearate, ethoxylated	Not classified	[6]	readily biodegradable based on QSAR model (50% degradation in 15 days)	[6]	yes
9043-30-5	Alcohol C13-iso, ethoxylated (8 EO)	H302 - H318	[7]	readily biodegradable (up to 20 EO)	[11][10]	yes
9043-30-5	Alcohol C13-iso, ethoxylated (14 EO)	H302 - H318	[7]	readily biodegradable (up to 20 EO)	[11][10]	yes

Legend: "-" no data available. EO *degree of ethoxylation*. H228: *Flammable Solid*, H302: *Harmful if swallowed*, H315: *Causes skin irritation*, H318: *Causes serious eye damage*, H319: *Causes serious eye irritation*, H332: *Harmful if inhaled*, H335: *May cause respiratory irritation*, H336: *May cause drowsiness or dizziness*, H373: *May cause damage to organs through prolonged or repeated exposure*, H400: *Very toxic to aquatic life*, H411: *Toxic to aquatic life with long lasting effects*, H412: *Harmful to aquatic life with long lasting effects; QSAR: Quantitative structure activity relationship*

6 SUBSTITUTION PROGRAM

- ⇨ **Several steps** are required to accomplish substitution which focus on performance of the IVD assay.
- ⇨ The general steps required for substitution are summarized as follows (Table 6):
  1. **Feasibility assessment.**
  2. **Verification / Validation** of the assays.
  3. If necessary, request for **regulatory approval / updated market authorisation.**
  4. Introduction to the **market.**
- ⇨ IVD products are **highly regulated** in countries worldwide. Usually, a specific **market authorisation by the health authorities** is required.
- ⇨ Changing an ingredient in the product often has an **impact on the current authorisation**. **Three scenarios** describe the potential impact on the IVD market authorisation:

  Scenario A: silent or minor change.
  Scenario B: major change.
  Scenario C: re-registration (same product number) or new product registration.
- ⇨ A summary of the estimated **timelines for replacement** is depicted in Figure 5.
- ⇨ Roche-internal processes are in place to monitor progress of substitution projects.

Roche is dedicated to substituting OPnEO and NPnEO by alternative surfactants in all products. The authorisation is needed to continue use of the assays in the UK until replacement is completed including phase-out of the existing products at the customers (i.e. laboratories and hospitals), in the cases where this is not feasible before the UK sunset date.

Many potential alternative surfactants are known (see Table 4 in Section 5). However, detailed research and development is needed to select one or several alternatives that allow continued reliable functioning and high quality of the products. As discussed previously, alternative surfactants can only be pre-selected based on their intrinsic properties. The critical parameters to be verified are performance specifications of each individual assay for which the alternative is intended to be used.

Several steps are therefore required to accomplish substitution which focus on performance of the IVD assay. In general, these include pre-selection of alternatives, feasibility assessment, validation and where relevant, regulatory approval / market authorisation from health authorities (in addition to the UK REACH authorisation). These steps are summarised in Table 6.

Table 6. General steps required for substitution.

Step	Details
Feasibility assessment	● Identify alternative surfactants available in the market ● Qualify supplier and raw material ● Production of first laboratory lots of reagents / assays with alternative surfactant(s) ● Performance testing of the IVD assays to test the most critical assay specifications
Verification / Validation	● Verification of shelf-life and on-board stability of the new reagents ● Update of manufacturing instructions ● Production of pilot lots of reagent with selected surfactant for detailed assay performance verification ● Validation of production process
Regulatory approval / market authorisation worldwide	● Notification to the authorities of the changes (minor or major change) or ● Application for new market authorisation (re-registration)
Introduction to the market	● Phase-out of assay with OPnEO and / or NPnEO based on shelf life and: o Replacement with OPnEO and / or NPnEO-free assay (the product remains on the market with the same material number) or o Introduction to the market of new assays / instruments (the product is introduced with a new material number)

In the **feasibility step**, **alternative surfactants are assessed**. This also includes an availability assessment of the alternative detergent which needs to be available in constant quality and reliable supply. To this end, available suppliers have to be assessed and usually qualified (as detergents are in most cases considered as critical raw materials for assay performance). For qualification of a supplier and a critical raw material at least 3 independent lots of the material need to be evaluated during the feasibility assessment, while the supplier has to fulfil certain criteria defined by Roche procurement. Laboratory lots of reagents / assays with alternative surfactant(s) need to be produced in order to test performance of the IVD assays regarding the most critical specifications. Examples of such specifications include precision, linearity and specificity as well as stress stability of the test. If an alternative has been identified which fulfils all specifications, pilot lots of the reagent with the selected alternative surfactant are produced in Operations (i.e. in the respective production facilities). **Verification of assay performance** including all specifications and testing of shelf-life and on-board stability is performed in the R&D (Research and Development) department. The production process is validated during the manufacturing of the pilot lots. To this end, the manufacturing instructions (including in process control and quality control release procedures) need to be updated and approved. Once the validation is successfully completed, a launch lot can be produced.

Furthermore, **notification to the corresponding health authorities of the changes or application for new authorisation** is required in the relevant countries. Once approval has been received from all relevant health authorities, production can be switched to the new surfactant and the adapted product can be introduced to the market. With the **market introduction** of changed products, stocks of assays with OPnEO and / or NPnEO at Roche and at customers will be phased out meaning that the maximum time of this transition period will correspond to the shelf life of the assay.

In vitro diagnostic products are **highly regulated in countries worldwide**. Usually, a country specific market authorisation by the health authorities is required. Changing an ingredient in the product often has an impact on the current authorisation. Three scenarios describe the potential impact on the IVD market authorisation:

- **Scenario A**: silent or minor change.
- **Scenario B**: major change.
- **Scenario C**: re-registration (same product number) or new product registration.

In Scenario A, no re-approval of the IVD market authorisation by authorities is needed as the process change does not impact information requirements of that market authorisation (silent change) or the impact on information requirements are minor and can be notified by a simplified procedure.

In scenario B, the changes to the IVD product and thus the IVD-regulatory documentation are significant and have to be communicated to authorities as a major change. The change is subject to detailed review by authorities.

In scenario C, the changes to the IVD product are so important that the product is regarded as a new product. A complete dossier for a new market authorisation has to be prepared.

For each product or group of products, it has been assessed by a Roche-internal committee which of the scenarios are likely to apply (see subsections per group of products). The **time required for substitution depends**, among other factors, **on the scenario** that will apply as from scenario A to C data requirements as well as time for processing by health authorities increase. Likewise, the costs and required personnel resources associated with the different scenarios increase from A to C.

A **change may trigger different authorisation requirements in different countries**. For example, in China the change of a critical ingredient requires efforts like an initial product registration, while in Europe and the UK[15] this may not require any regulatory actions at all. Processing times also differ quite substantially among countries. For example, processing times in Europe (CE Mark) are usually 4-6 weeks while in China 12-18 months or even up to 36 months for some products are required. As additional requirements may be imposed after submission of dossiers to authorities and requirements may change over time in different countries, it cannot be determined for certain, which scenario will apply for each product per country. This adds significantly to the uncertainty around the time required to complete substitution. Please note that the production of OPnEO and / or NPnEO - free IVD assays can only be implemented when the change in market authorisations has been approved by health authorities in all relevant countries worldwide. This is due to the fact that it is not feasible to produce assays with different compositions for different countries. A country-specific production with a different composition would mean the introduction of a new product. This would require the

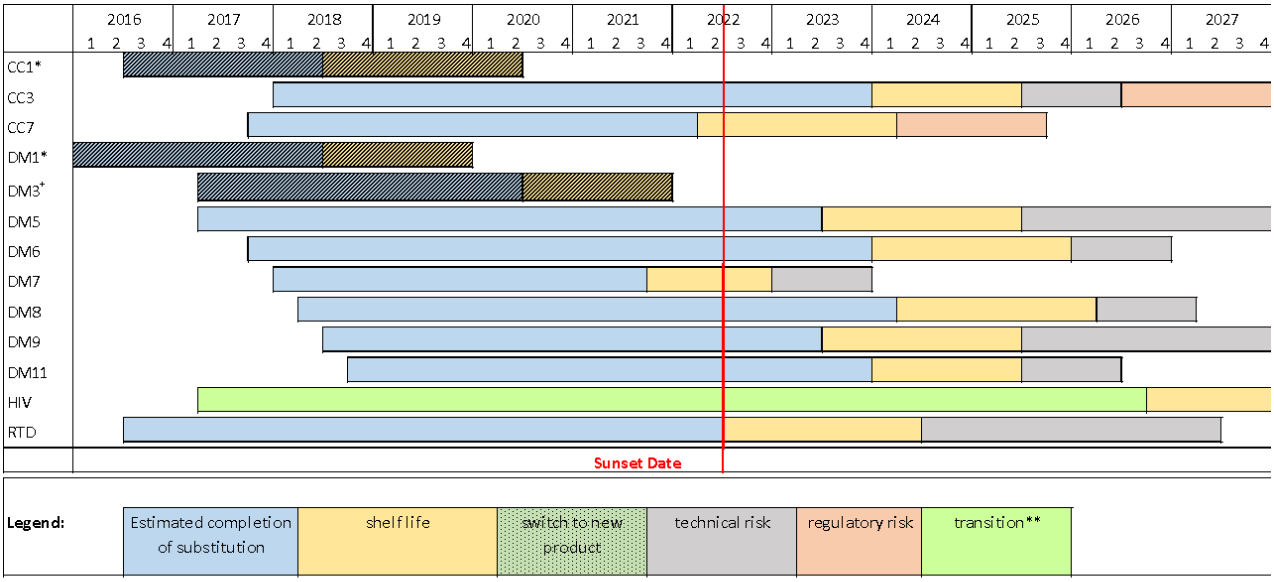
[15] UKCA (UK Conformity Assessed) marking to be applied following declaration of conformity or conformity assessment by a UK Approved Body.

registration of this product in these markets including the respective efforts (see scenario C above). Furthermore, such a country-specific production would not be economically feasible, due to high manufacturing costs and logistical burden for the small number of products required for one country only. Therefore, the substitution of the products on the UK market is depending on market authorisations by health authorities worldwide.

The **detailed requirements** for each step and the time needed to complete the different steps are **different from assay to assay**. Detailed requirements and estimated times including ranges based on uncertainties in the different steps and the status of substitution per group of assays are described in detail for each product group from Subsection 6.1 onwards.

A summary of the estimated timelines for replacement is depicted below in Figure 5. The estimated completion of substitution is the **date when production of the corresponding assay is planned to be started with the alternative surfactant** (end of blue bars). From that moment on, old products will be used by the customers, as a maximum, until the end of shelf life (yellow bars). In one case (HIV), the affected product will not be produced anymore and the clients are being switched to a new system during a transition period (green bar), detailed information on this can be found on Sections 6.3.

The effective dates of completion could be however delayed if unforeseen technical difficulties surface during the replacement process and one or more steps of the process need to be repeated (uncertainty as grey bars). In some assays, if the changes required for replacing the surfactant are more important than expected, re-registration with the competent health authorities might be needed. Or, as outlined above, additional requirements may be imposed by health authorities. This would produce further delays on the expected date of completion (uncertainty as light red bars). For some products, the feasibility step is in such an advanced stage that a regulatory risk is no longer considered. This is the situation for RTD. For DM[redacted]. Therefore, regulatory risk is also not considered in the timelines.



* Product is not in the scope of this AfA Dossier as substitutionn was completed before the Sunset Date, and replacement of all stock containing OPnEO / NPnEO will have been completed before the Sunset Date. The inclusion of this products in this timeline is to illustrate succesfully completed replacement projects and it is marked with a striped shading.
+ Product that has been already replaced before the submission of the AoA document for the UK Dossier. No longer in scope for UK Dossier. It is marked with a striped shading.
** Transition due to existing contracts and/or replacement of complete IVD Systems. For further details please see Sections 6.3 and 6.4

Figure 5. Replacement timelines[16]

For two assays (CC7 and DM7), replacement was expected to be already implemented by the time of submission of this dossier based on the original timelines. Some difficulties occurred, but the replacement is still planned before the UK sunset date for CC7. For DM7 the replacement may be slightly delayed until after the sunset date, but implementation is planned at the latest by the end of 2022. Three products, CC1, DM1 and DM3 have been substituted and shelf life of remaining stocks will expire before the UK sunset date. These are included here to illustrate progress of substitution. For details on the HIV replacement timeline, where the replacement of older systems with a new system using a NPnEO-free assay is described, please refer to Section 6.3.

As shown in Figure 5, it was estimated that risks to occur with a certain likelihood (i.e. technical and regulatory risks as indicated in the figure) would only for some cases prolong the timelines of the substitution projects until the end of the review period. In the other cases, a prolongation until the end of the review period cannot be excluded if further difficulties arise but it is not very likely. However, as a worst-case it is assumed in the assessment in the SEA and CSR that all substitutions could be delayed until the end of the review period.

[16] Please note that numbering of assays is kept as it was given in EU AfA. As some assays are not relevant for this application, the numbering is therefore not always consecutive.

6.1 Clinical Chemistry

6.1.1 Steps and Time Required for Substitution

Initially, **three different cases** were expected for the replacement of OPnEO and NPnEO in affected **Clinical Chemistry assays** mainly differing with respect to regulatory requirements and complexity. The assays and the steps required for replacement are listed in Table 7, Table 8, Table 9.

First case: for CC3 a silent change is currently expected (Scenario A). The required steps for this case are listed in Table 7.

Table 7. Clinical Chemistry replacement plan (silent change)

Step	Substep	Details on required activities	Duration likely (and min-max)
Feasibility	Assessment of alternative surfactants	Literature search, patent analysis, etc. Typically, 3 alternatives are selected for evaluation in feasibility	[redacted]
	Production of laboratory lots of reagents with alternative surfactant(s)	The reagent is produced in R&D at laboratory scale with the alternative detergent	[redacted]
	Performance testing	Laboratory lots are evaluated by Roche R&D for most critical specifications, e.g. precision, linearity, interferences, stability, etc. – depending on the function of the surfactant	[redacted]
	Documentation	Feasibility report, preliminary manufacturing instructions, draft QC methods, etc. These deliverables are required to proceed with the project and to initiate production of pilot lots in Operations	[redacted]
Verification	Production of laboratory lots of reagent with selected surfactant	Based on the feasibility results, a final formulation of the reagent is defined and laboratory lots are produced by R&D in small scale according to	[redacted]

Step	Substep	Details on required activities	Duration likely (and min-max)
		preliminary manufacturing instructions	
	Performance testing	Performance testing of all relevant specifications using laboratory lots. Test on 2 representative instrument systems: - Specificity - Recovery of controls - Method comparison - Precision - Linearity - Interferences - on board stability - carry over	[redacted]
	Documentation	Application report, etc. Deliverables required for re-submission of the formal change	[redacted]
Manufacturing / Validation (performed in parallel with Verification steps)	Update of manufacturing instructions	Manufacturing instructions need to be changed, approved and entered into the quality system	[redacted]
	Update of QC/IPC procedures at Roche	QC/IPC[17] procedures need to be changed, possibly validated, approved and entered into the system	[redacted]
	Validation of production process	Validation of production process (bulk, formulation, filling) including documentation (plan, report)	[redacted]
	Production of launch lot	Manufacturing of launch lot based on validated manufacturing instructions, including QC release	[redacted]

[17] In-process methods are key components of quality control in a chemical manufacturing plant. These methods ensure that a production reaction step conducted by trained operators within the entire validated process will produce a quality chemical entity in the expected yields.

Step	Substep	Details on required activities	Duration likely (and min-max)
Regulatory approval / market authorisation (after finalization of verification, in parallel to Manufacturing / Validation	Review of verification data	Review of verification data by Regulatory Affairs to assess whether change can be implemented via silent switch	[redacted]
	Documentation for finalization of the change	Compilation of all deliverables required to complete the change process	[redacted]
Introduction to the market	Replacement of former product on stock at Roche	To avoid scrap costs, product with former formulation will be sold first. This may take several weeks depending on shelf life and market demand	[redacted]
	Replacement of former product on stock at customers	Customers will not be informed about the change ('silent switch') so they will use the original product that they have on stock.	up to 24 months depending on the shelf life of the assay.
Overall timeline for substitution per assay			**96 (80-132) weeks Or 2 (1.5-2.5) years*** **+ 12 to 24 months overlapping time due to shelf life of old assays still in the market.**

*Some steps are done in parallel, therefore the overall duration is not the sum of all individual durations.
Legend: QC: Quality Control; IPC: In-Process Control; R&D: Research and development

Please note that OPnEO / NPnEO in further CC assays also needs to be replaced. They were described in the EU dossier (Use 2), but they are not covered in this AfA since they do not fall under the obligation for authorisation. Since the personal resources available for executing this replacement program are limited, some assays can be tested in parallel, but not all. This leads to a time shift among the different tests.

Second case: CC7 is a special case. This assay is an OEM (Original Equipment Manufacturer) test, developed by a RDG's OEM Partner (third party producer). The reformulation of the reagent is their responsibility. RDG is supporting the OEM in the evaluation of alternative formulations and is responsible for the application of the new formulation on Roche's instrument platforms. The OEM provides bulk reagent to RDG that is then filled and labelled by RDG. Therefore, manufacturing at Roche comprises incoming quality control, filling, labelling and QC release of the final product.

This assay has the added difficulty that the CC7 reagent is a complex mixture of several surfactants that are used to generate specificity of the assay. LDLC (low density lipoprotein cholesterol, commonly referred to as 'bad cholesterol') is one of several species of lipoprotein particles in serum / plasma that needs to be specifically quantified in the presence of biochemically similar, but physiologically very different lipoprotein particles such as chylomicrons, very low-density lipoproteins (VLDL) and high-density lipoproteins (HDL, commonly referred to as 'good cholesterol'). As the indicator reagent in the assay is generic for all of these species, specificity is generated by selective solubilisation / masking of distinct populations of lipoprotein particles by adding combinations of surfactants, salts and / or sugars to the reagent mixture.

In this complex biochemical situation, it is hard to predict which surfactants or other ingredients, or combinations thereof provide specificity towards a distinct lipoprotein population or which chemical properties of a surfactant are responsible for specificity. Therefore, suitable substitution of a surfactant in the existing formulation needs to be determined empirically and requires extensive evaluations with challenging sample material.

It is expected that this test can also be replaced as a silent change (Scenario A). However due to the circumstances explained above the whole replacement plan is expected to take longer than for other CC assays. The required steps for this replacement are listed in Table 8.

Table 8. Clinical Chemistry replacement plan for one test which is developed by an OEM Partner outside of the EEA (CC7)

Step	**Substep**	**Details on required activities**	**Duration likely (and min-max)**
Feasibility	Assessment of alternative surfactants	Re-work of the current formulation with different alternative surfactants by the OEM, presentation of results to Roche Diagnostics, selection of new formulation	[redacted]
	Production of laboratory lots of reagents with alternative surfactant(s)	Laboratory lots are produced by the OEM in small scale and provided to Roche for evaluation	[redacted]
	Performance testing	Laboratory lots are evaluated by Roche R&D mostly for specificity, only for most critical specifications	[redacted]
	Documentation	Feasibility report, discussion with the OEM about results, next steps	[redacted]
Verification	Production of laboratory lots of reagent with selected surfactant	Based on the feasibility results, a final formulation of the reagent is defined and laboratory lots are produced by the OEM in small scale according to preliminary manufacturing instructions and provided to Roche Diagnostics	[redacted]

Step	Substep	Details on required activities	Duration likely (and min-max)
	Performance testing	Performance testing of all relevant specifications using laboratory lots Test on 2 master systems: ● Specificity ● Recovery of controls ● Method comparison ● Precision ● Linearity ● Interferences ● on board stability ● carry over	[redacted]
	Documentation	Application report, etc. Deliverables required for re-submission of the formal change	[redacted]
Manufacturing / Validation (performed in parallel with Verification steps)	Production of pilot lots at OEM	Manufacturing (filling, labelling) of pilot lots (bulk) in final scale according to valid manufacturing instructions, including formulation, QC release by the OEM	[redacted]
	Update of manufacturing instructions at Roche	Manufacturing instructions (filling, labelling, etc.) need to be changed, approved and entered into the system	[redacted]
	Update of QC/IPC procedures at Roche	QC/IPC procedures need to be changed, possibly validated, approved and entered into the system	[redacted]
	Validation of production process at Roche	Validation of filling process including documentation (plan, report)	[redacted]
	Production of launch lot	Manufacturing of launch lot based on validated manufacturing instructions, including QC release at OEM Shipment to Roche, incoming QC, filling, labelling, QC release final product	[redacted]
Regulatory approval / market authorisation (after finalization of verification, in parallel to Manufacturing / Validation	Review of verification data	Review of verification data by Regulatory Affairs to assess whether change can be implemented via silent switch	[redacted]
	Documentation for finalization of the change	Compilation of all deliverables required to complete the change process	[redacted]

Step	Substep	Details on required activities	Duration likely (and min-max)
Introduction to the market	Replacement of former product on stock at Roche	To avoid scrap costs, product with former formulation will be sold first. This may take several weeks to months depending on shelf life and market demand	[redacted]
	Replacement of former product on stock at customers	Customers will not be informed about the change ('silent switch') so they will use the original product that they have on stock.	
Overall timeline for substitution			**206 (186-248) weeks or 4 (3.6-4.7) years***

*Some steps are done in parallel, therefore the overall duration is not the sum of all individual durations.

Third case: in case the formulation of an assay needs to be changed in the course of replacing OPnEO or NPnEO with an alternative surfactant, a new registration in all countries is required (Scenario C). In this case there is extra time required for validation, regulatory approval and market authorisation. The required steps for this replacement are detailed below in Table 9. As the assay is being replaced, Roche would provide clients with the old and new product for a period of [redacted] after introduction to the market to allow the clients time for comparison to the new product and any necessary adjustments on their operative procedures. During this time, production of the old product needs to continue. Once these [redacted] are over, the product containing OPnEO would no longer be produced, but clients may use their products stocks until end of shelf life (17 months).

For CC3 current replacement efforts aim at performing the substitution as a silent change (see Scenario A). However, if current tests fail, the assay may need to be re-formulated and scenario C will apply as a worst-case (see Section 6.1.2).

Table 9. Clinical chemistry replacement plan for a test in case it requires re-registration (worst-case for CC3)

Step	Substep	Details on required activities	Duration likely (and min-max)
Feasibility	Assessment of alternative surfactants	Literature search, patent analysis, etc. Typically, 3 alternatives are selected for evaluation in feasibility.	[redacted]
	Production of laboratory lots of reagents with alternative surfactant(s)	Laboratory lots are tested for e.g. precision, linearity, interferences, stress stability - depending on the function of the surfactant.	[redacted]
	Performance testing	Laboratory lots are evaluated by Roche R&D mostly for	[redacted]

Step	Substep	Details on required activities	Duration likely (and min-max)
		specificity, only for most critical specifications.	
	Documentation	Feasibility report, preliminary manufacturing instructions, draft QC methods, etc. These deliverables are required to proceed with the project and to initiate production of pilot lots in operations.	[redacted]
Manufacturing / Validation (performed in parallel with Verification steps)	Update of manufacturing instructions	Manufacturing instructions need to be changed, approved and entered into the system.	[redacted]
	Update of QC/IPC procedures at Roche	QC/IPC procedures need to be changed, possibly validated, approved and entered into the system.	[redacted]
	Production of pilot lots (used for verification)	Manufacturing of pilot lots in final scale according to valid manufacturing instructions, including formulation, filling, labelling, QC release.	[redacted]
	Validation of production process	Validation of filling process including documentation (plan, report).	[redacted]
	Production of launch lot	Manufacturing of launch lot based on validated manufacturing instructions, including QC release.	[redacted]
Verification	Performance testing	Performance testing of all relevant specifications using laboratory lots Test on all systems (7 instrument platforms): • Recovery of controls • Method comparison • Precision • Linearity • Interferences • on board stability • carry over.	[redacted]
	Documentation	Application report, etc.	[redacted]

Step	Substep	Details on required activities	Duration likely (and min-max)
		Deliverables required for re-submission of the formal change.	
Regulatory approval / market authorisation	External evaluation	Evaluation of reagent at external sites, including plans, data analysis, reports.	[redacted]
	Review of verification data by Regulatory affairs	Detailed review of all application reports, external evaluation reports, finalization of documentation.	[redacted]
	Approval by EU and UK authorities	CE and UKCA marks, declaration of conformity.	[redacted]
	Approval by US authorities	Review by FDA, update of documentation based on FDA feedback.	[redacted]
	Approval by authorities in China	Production of pilot lot for China (8 weeks), type testing (24 weeks), clinical study (36 weeks), submission of documents to CFDA (10 weeks), review by CFDA (60 weeks), update of documentation based on CFDA feedback (12 weeks).	[redacted]
Introduction to the market	Overlapping period of former and new formulation	New assay with new material numbers, Roche needs to provide an overlapping period for all affiliates to switch all customers to the new reagent generation.	[redacted]
Overall timeline for substitution			**Approximately 3 years** [redacted]*

*Some steps are done in parallel, therefore the overall duration is not the sum of all individual durations.
Legend: FDA: US Food and Drug Administration; CE Mark: conformity with health, safety, and environmental protection standards for products sold within the European Economic Area.; UKCA mark: conformity with the health, safety, and environmental protection standards for products sold in the UK; CFDA: Chinese Food and Drug Administration

6.1.2 Technical Feasibility Status and Replacement Schedule

The substitution process for the CC assays started in July 2016.

Replacement for one assay (CC1) had already been completed before the EU sunset date (the 4th of January 2021) so that the use of all the remaining CC1 assays at customers had ceased before the EU sunset date. The use of OPnEO in this assay and its formulation is therefore not covered anymore in this AfA, but the project is included here to illustrate the progress of substitution and Roche's commitment to substitute any SVHC used in its products and processes.

Alternatives have already been identified for the 2 assays covered in this dossier: CC3 and CC7.

When the EU Dossier was submitted, the expected time of substitution in the formulation for the product CC3 was expected to be end of 2019. However, technical difficulties have occurred. Adjustments had to be made for replacement with the same surfactant and performance verification had to be repeated several times. Current feasibility tests are promising and if these tests and the subsequent performance verification are successful, substitution will be completed by end of 2023 (end of blue bar in in Figure 5). However, uncertainties remain linked to this timeline (grey and light red bars in Figure 5). Further technical difficulties may be encountered, i.e. if the currently tested surfactant does not maintain all performance characteristics the product may need to be reformulated. This would then have the consequence that a silent switch is not possible and that the updated product would have to be re-registered in the required countries (regulatory risk). In case of additional delays due to regulatory difficulties, substitution for CC3 might only be completed by end of 2027.

The expected technical challenges on the detergent replacement for CC7 have been solved and substitution was expected to be already implemented by the time of submission of this dossier based on the original timeline. Some difficulties occurred but the replacement is still planned before the UK sunset date (Q2 2022). Due to shelf life, it is now expected that CC7 will not be used anymore by downstream users at the latest by Q2 2024. At this advanced stage of the substitution project, further technical or regulatory issues are not expected anymore.

6.2 Drug Monitoring

6.2.1 Steps and Time Required for Substitution

For the substitution of OPnEO and NPnEO in the affected Drug Monitoring assays, change of these surfactants in reagents as well as in the production process of latex beads conjugated with antibodies or the drug substance are necessary (see Section 3.1 for functioning of the assays and role of the beads). In the bead production process, the surfactants are used as processing aids in the production process (this takes place at RDG in Germany and the use was covered in Use 4 of the EU AfA). Substitution in the latex bead production process as well as in the reagents is performed at the same time to allow performance of validation and updates of market authorisation once for each product. The latex bead is part of the final reagent formulation Therefore, all steps, including exchange in the bead production process is shown here. It is expected that updated market authorisations for the DM assays can be obtained through submission of a major change without need of re-registration (scenario B). The necessary steps are described in Table 10. So far, all DM substitution projects to replace OPnEO / NPnEO have been executed under the scenario B. It is expected that the scenario B can also be applied to the substitution projects in scope of this AfA. In the case scenario B applies, the expected minimal time required for the substitution of all DM assays is 5 years and the maximal time required is 8 years. Timelines per product vary due to varying shelf lives (15 – 24 months) and consequently varying time requirements to test the stability of the reagents over the length of the shelf life (real-time stability). If a re-registration was needed, [redacted] and the requirements in case of a re-registration are not shown.

Table 10. Drug Monitoring replacement plan for substitutions as planned in case a major change is needed

Step	Substep	Details on required activities	Duration likely
Feasibility	Assessment alternative surfactants	• Evaluation of physicochemical properties • Check lot to lot consistency • Check availability and pricing	[redacted]
	Manufacturing of latex beads	• Coating of latex beads	[redacted]
	Manufacturing final reagents	• Adjustment of the reagents (antibody and conjugate)	[redacted]
	Performance testing	• Precision tests • Stability tests • Functional tests (method comparison / clinical sensitivity / …)	[redacted]
	Real-time stability	• Check reagent stability	[redacted]
Validation / Verification	Transfer of manufacturing documents to operations	• New documents for latex bead production • New documents for buffer production • Internal documentation procedure	[redacted]

Step	Substep	Details on required activities	Duration likely
	Assay production in operations (1 batch)	• Latex bead production • Buffer for Integra® and cobas® c formulation • Adjustment of the reagents (antibody and conjugate)	[redacted]
	Verification measure-ments	• Test on several analysers • Functional tests (method comparison / clinical sensitivity / …) • Precision tests • Stability tests	[redacted]
	Real-time stability	• Control recovery for the claimed shelf life	[redacted]
Regulatory approval / market authorisation	Change request	• Plan Phase Preparation and submission of the change request (e.g. feasibility study) • Build Phase Collection of data needed for decision (e.g. Validation / verification) • Implement Phase Implementation of the change	[redacted]
Introduction to the market	Replacement of OPnEO / NPnEO containing products	• Major change without re-registration: customer will not notice a change in the formulation	15-24 months replacement due to shelf-life (depending on the assay)
Overall timeline for substitution per assay			Best-case: 3.5 years Worst-case: 5.5 years
Overall timeline for substitution of all assays (assuming some assays can be substituted in parallel)			**Best-case: 5 years** **Worst-case: 8 years**

6.2.2 Technical feasibility status and replacement schedule

The substitution process for the DM assays has started in 2016.

For this group of assays, an alternative had been identified for DM1 so that complete phase-out of the old assay at customers' was already completed before the EU sunset date. Substitution for DM3 assays has also been completed and complete phase-out of old assays at customers' will be completed

before the UK sunset date (Figure 5). The use of NPnEO / OPnEO in these assays is therefore not covered anymore in this AfA, but the projects are included here to illustrate the progress of substitution and Roche's commitment to substitute any SVHC used in its products.

For some assays, technical issues have emerged during feasibility testing as the identified preferred alternative does not fulfil the required product specifications for some assays, e.g. test performance during stress stability was not maintained. There are examples where a one-to-one substitution of the detergent is not feasible and that e.g. the coating bead process has to be optimized for the preferred alternative. In addition, preferred alternatives failed at a very late stage of a project. In one incident a pilot lot did not pass the internal process control and therefore the feasibility had to be restarted with a new alternative. In the second incident issues came up during the stress stability of a pilot lot. Taking these experiences into account the technical risk is accounted for with an increased possible duration of 12 - 30 months.

A total substitution time of 5 to 8 years for all assays is expected. Several assays are tested in parallel, but this number depends on the availability of qualified personal resources. Replacement in one assay (DM7) is advanced and was expected to be implemented before the UK sunset date. The replacement may be slightly delayed until after the sunset date, but implementation is planned at the latest by the end of 2022. For the other assays, estimated completion date including replacement of existing products in the market is expected between mid-2025 and beginning of 2026. However, technical difficulties that require repetition of several steps in the process as described above may prolong this timeline by 12 - 30 months depending on the assay. Considering these risks, the substitution process for some of the DM assays including introduction to the market and use of existing assays containing OPnEO and NPnEO at laboratories / hospitals may last up to end of year 2027. As discussed above, it is expected that from a regulatory point of view a major change (Scenario B) will be possible. If a re-registration was needed, [redacted] Therefore, not regulatory risk is considered in the timeline.

6.3 HIV

6.3.1 Hypothetically Required Time for Replacement of NPnEO in HIV combi PT

HIV diagnostic assays are subjected to very strict regulations and if any change in the composition, e.g. replacement of the surfactant, or production is introduced, they need to be thoroughly tested. From the regulatory perspective a silent change is not possible. Additionally, to the internal assay performance and stability studies that are required for checking the feasibility of all IVD assays (Feasibility and Validation Steps as in Table 6), clinical validation studies on blood banks and routine samples worldwide are required. The later mentioned studies are sponsored by Roche and performed by commercial laboratories on several testing sites in Europe, Asia, Africa and America. Therefore, due to the high regulatory requirements for these assays, validation of the assays and market authorisation by the respective health authorities are expected to require several years. The estimated duration of the timeline for replacement of NPnEO in HIV combi PT was ca. [redacted] years: [redacted] years internal feasibility and validation studies, an estimated [redacted] years of the external validation studies and ca. [redacted] years to obtain market authorisation by the regulatory authorities. This timeline takes into account some technical and regulatory risks.

However, the cobas® analysers **cobas**® e 602, **cobas**® e 601, and **cobas**® e 411 are being replaced by new generation instruments that use a new generation assay that is NPnEO-free (see next section). As a result, only a low proportion and constantly declining number of customers would have benefited from the updated formulation of HIV combi PT until all old generation instruments are replaced. Therefore, the possible period on which the updated HIV combi PT assay could be sold was expected to be short. The costs for replacement of NPnEO in HIV combi PT was calculated to be [redacted], a considerable effort was made to evaluate the feasibility of substitution. The substitution process for the HIV combi PT assay started in Q2 2017. Feasibility studies for surfactant substitution in HIV combi PT are finished and an alternative to NPnEO has been identified (see Table 4). Additionally, the new HIV generation Elecsys® HIV Duo which was launched April 2017 in the EU, including UK, already reflects the REACH regulation aspect and uses a detergent with no concerns.

6.3.2 Replacement Schedule by New Generation Assay and Instruments

The analysers on which HIV combi PT is running (cobas® e 602, cobas® e 601 and cobas® e 411) are being stepwise replaced in the UK as well as worldwide by new generation instruments (cobas® e 801 (or cobas® pro), cobas® e 402 (or cobas® pure)). The high-throughput instrument (cobas® e 801 (or cobas® pro)) had been launched in the UK in 2016 while the mid-throughput (cobas® e 402 (or cobas® pure) instrument has only been launched in the UK in 2020. The NPnEO-free HIV Duo running on these analysers is also approved in the UK and a part of Roche's customers has already been switched to these new generation instruments. Even though this newer generation HIV assay (HIV Duo), which is NPnEO-free, has already been developed and is currently introduced to the market, this new assay cannot be considered a suitable alternative for the HIV combi PT containing

NPnEO for all customers. The timeframe for the switch will depend on the capacity of the analyser manufacturer (HITACHI high Technology). Currently the transition to the new instrument family is delayed due to the worldwide shortage of electronic components. This situation will continue at least throughout 2022. In addition, after the introduction of the new generation instruments, an average of at least five years of support for the old instruments (that includes providing the HIV combi PT assay) is required. Therefore, these assays need to be on the market (including shelf life) until ca. end of 2027, which corresponds to the estimated time necessary for replacing the old instruments with the new generation instruments in the UK.

Despite the ongoing activities regarding new generation instruments, the HIV Duo is not a suitable alternative that can be implemented before the sunset date for all of Roche's customers. In summary, authorisation is therefore needed to allow for the continued use of HIV combi PT on the older-generation instruments until all customers have been provided with new-generation analysers (using HIV DUO assays) and trained on their use. Due to contractual obligations and the long time required to replace all older systems, the replacement process of HIV combi PT is estimated to be completed only by the end of the review period, i.e. the 4th of January 2028.

6.4 Roche Tissue Diagnostics

6.4.1 Steps and Time Required for Substitution

The expected replacement scenario is silent or minor change. Required verification and validation testing, including stability will be needed to support the change and this would be an end of year reportable to FDA for pre-market approval (PMA) for the products impacted. (PMA is the FDA process of scientific and regulatory review to evaluate the safety and effectiveness of Class III medical devices[18]).

Table 11. Replacement plan for RTD

Step	Substep	Details on required activities	Duration likely (min-max)
Feasibility	Initial functional tissue staining and antimicrobial assessment	Identification of alternative detergents and initial demonstration that new formulation does not negatively impact sensitivity / specificity of ISH assays. Microbial challenge assessment to demonstrate robustness of candidate formulations.	[redacted]

[18] One of the categories established by the FDA. They are done based on the level of control necessary to assure the safety and effectiveness of the device. For Class III devices, a premarket approval application (PMA) will be required unless your device is a preamendments device (on the market prior to the passage of the medical device amendments in 1976, or substantially equivalent to such a device) and PMA's have not been called for.

Step	Substep	Details on required activities	Duration likely (min-max)
Validation / Verification / Stability	Statistically powered functional staining assessment	Larger study to evaluate across ISH portfolio that final candidate formulation does not negatively impact safety or efficacy of ISH products.	[redacted]
	Real-time stability	Execution of real-time stability testing which includes functional stain assessment on tissue [redacted] expiry testing requires [redacted] of testing.	[redacted]
Regulatory approval / market authorisation	U.S. market approval	Report to FDA impacted PMA products and receive authorisation for change	[redacted]
Introduction to the market	Replacement of obsolete existing assay in the market	Customer use of distributed product	24 months (shelf life)
Overall timeline for substitution			**6 years (5-6.8 years)**

6.4.2 Technical Feasibility Status and Replacement Schedule

The substitution process for RTD has started in July 2016.

Testing was performed to assess if the assay would perform properly without any surfactant. This is not an option because the new formulation without surfactant negatively impacted *in situ* hybridisation staining. The same was the case of Alternatives 7 and 38 (see Table 4). The main technical problems encountered were insufficient slide coverage leading to inconsistent staining or increase in background staining.

One alternative was selected based on the feasibility studies. Stability testing has been initiated, verification / validation was started in Q4 of 2018 and was completed in 2022. During performance verification for one of the products the new OPnEO-free formulation of the wash buffer had impacted the performance. This resulted in additional verification work. Due to the identified issues and the impacted product being close to its end of life, the implementation of the OPnEO-free formulation was aligned with the end of life for the impacted product. This led to the delay with the respect to the substitution timeline as outlined in the EU AfA.

The alternative in the affected buffer has successfully been tested in stability studies. If there was any problem with the stability studies for the alternative, the testing of a new alterative could have added up to 36 months to the replacement timeline (technical risk, see grey bar in Figure 5). However, as of April 2022, this technical risk can be excluded.

As testing of the selected alternative was successful, substitution was planned to be completed by May 2022 and distributed old products would have expired by Q2 2024 (due to shelf life). However, two specific assays are not compatible with this new buffer formulation which is used for all ISH products. These assays will be phased-out and consequently not in use at customers anymore latest by March 2024 due to the expiry date. Due to compatibility reasons the new buffer formulation can only be introduced when these assays have expired and the old buffer will have to remain available until then. Shelf-life of the last batches of the old buffer will therefore expire by March 2026. However, as customers usually have stocks of this product for less than one year, it is likely that the old buffer will be phased-out earlier, i.e. in early 2025.

6.5 Costs of the Substitution

Roche's R&D department is currently **working on the complete substitution of OPnEO / NPnEO** in all affected IVD assays. As described in this AoA substitution projects are already ongoing and OPnEO / NPnEO have already been replaced in several products. Roche is and will be investing a large amount of resources into this change process. The estimated **investment costs** for the substitution are given in Table 12 considering the likely and worst-case scenario regarding regulatory requirements for substitution which are an important driver for cost.

Since RDL is only an affiliate of Roche, no direct investment costs are covered by RDL. The investments cost as given in Table 12 are the total cost for all uses applied for in the EU in the product groups where substitution is not yet completed and thus reflect the total of Roche's investment into substitution of OPnEO / NPnEO in these product groups. Part of this cost are related to the tests covered by this AfA. The cost related only to the tests covered in this AfA are not shown since such a selection would not be meaningful at the level of Roche as a company. For Roche, the total investment costs for the likely scenario are ca. [redacted] **mio £**[19] for the product groups where substitution is not yet completed (Use 2&3 and 4 (where relevant for DM), for an overview of the Uses of the EU dossier, please consult the Table in the Summary Section). The main cost driver in the worst-case scenario are the additional regulatory requirements in case of a re-registration. These requirements directly translate in additional experiments that need to be performed to provide the requested data. R&D efforts to generate this data are more than double if a **re-registration is needed**. If the **worst-case scenario** applied for all products and processes, cost could reach ca. [redacted] **mio £**. The cost includes cost for the required personnel to perform the projects or the clinical studies (e.g. for HIV). Please note that in case assays in the product group DM would need to undergo a re-registraton, [redacted]

Table 12. Substitution: investment costs including cost for required personnel.

Use	Product group	Cost (mio £)	
		Likely scenario	Worst-case scenario*
Use 2&3 Use 4	CC	[redacted]	[redacted]
	DM (incl. changes in processes related to DM)	[redacted]	[redacted]
Use 2&3	HIV	[redacted]	[redacted]
Use 3	RTD	[redacted]	[redacted]

* Re-registration to obtain market authorisation.

[a] Scenario for a development of an HIV assay on all instruments.

[b] Scenario if there are two developments. [redacted]

[19] *For the conversion an exchange rate of 1 EUR = 0.8 £ was used. The exchange rate of the first working day of 2022 (3 January) was used for all conversions from EUR to £. The exchange rate was obtained from https://www.statista.com/statistics/1034391/monthly-exchange-rate-gbp-eur-worldwide/

6.6 Monitoring of the Implementation of the Substitution Plan

Roche has implemented the structure to oversee that the substitutions are implemented according to the substitution plan in a successful and timely manner.

The organisational structure and setup of the substitution projects for the different products covered under Use 3 are very similar.

The organisational structure is shown as an example for CC[20] / DM[21] products in Figure 6 and the structure and procedures are described for all products in the following. For HIV, the implementation of the alternative is equivalent to the introduction of the new generation instruments and the NPnEO-free assay to the market. This is managed and monitored in the same way as described for the other substitution projects.

The substitution projects are carried out by interdisciplinary project teams involving R&D, Operations[22] , Regulatory, Quality Assurance, Quality Control, Business[23] and Global Planning[24]. The project team is led and coordinated by a Development Leader from the R&D department or by a project leader from the Lifecycle for RTD[25]. The team is responsible for feasibility, verification and implementation.

The Product Care and Quality Teams (PCQT) were informed by the Head of Diagnostics Environmental Regulations that the REACH Regulation required a substitution of OPnEO and / or NPnEO in RDG's products and processes (see Figure 6).

The PCQT asked the Product Group Teams (for HIV[26]: the Lifecycle Core Team (LCCT)) to analyse the respective portfolios (products and processes) for the use of OPnEO and / or NPnEO in order to assess the level of impact.

Based on these analyses, preliminary project plans for the substitution projects (for products and processes) were defined to come up with a budget, timeline and resource estimate. This estimate was communicated to the PCQT. The PCQT informed the International Business Team (IBT) and the LCCT (for HIV) about the required budget, timeline and resources who in turn brought this to the Lifecycle Team (LCT) for budget approval.

The LCT adjusted the priorities for the respective portfolio and approved the projects and the respective budgets.

This decision was communicated back to the PCQT which informed the Product Groups (PGs) with the task to do a detailed planning and staffing of the substitution projects.

The substitution projects were then started with the individual project teams.

[20] CC: Clinical Chemistry, see SEA Section 2.7

[21] DM: Drug Monitoring, see SEA Section 2.7

[22] Responsible for manufacturing of the reagents

[23] Responsible for marketing of the products

[24] Responsible for planning of the entire supply chain of the products

[25] RTD: Roche Tissue Diagnostics, see SEA Section 2.7.3

[26] HIV: Human Immunodeficiency Virus, see SEA Section 2.7.2

Compliance to regulations in general is of highest priority for the Roche Group. Environmental goals are of particular importance as described in the SHE (Safety, Health and Environment) goals and corporate policies. These goals and policies are incorporated by the LCCTs into their strategy and prioritisation.

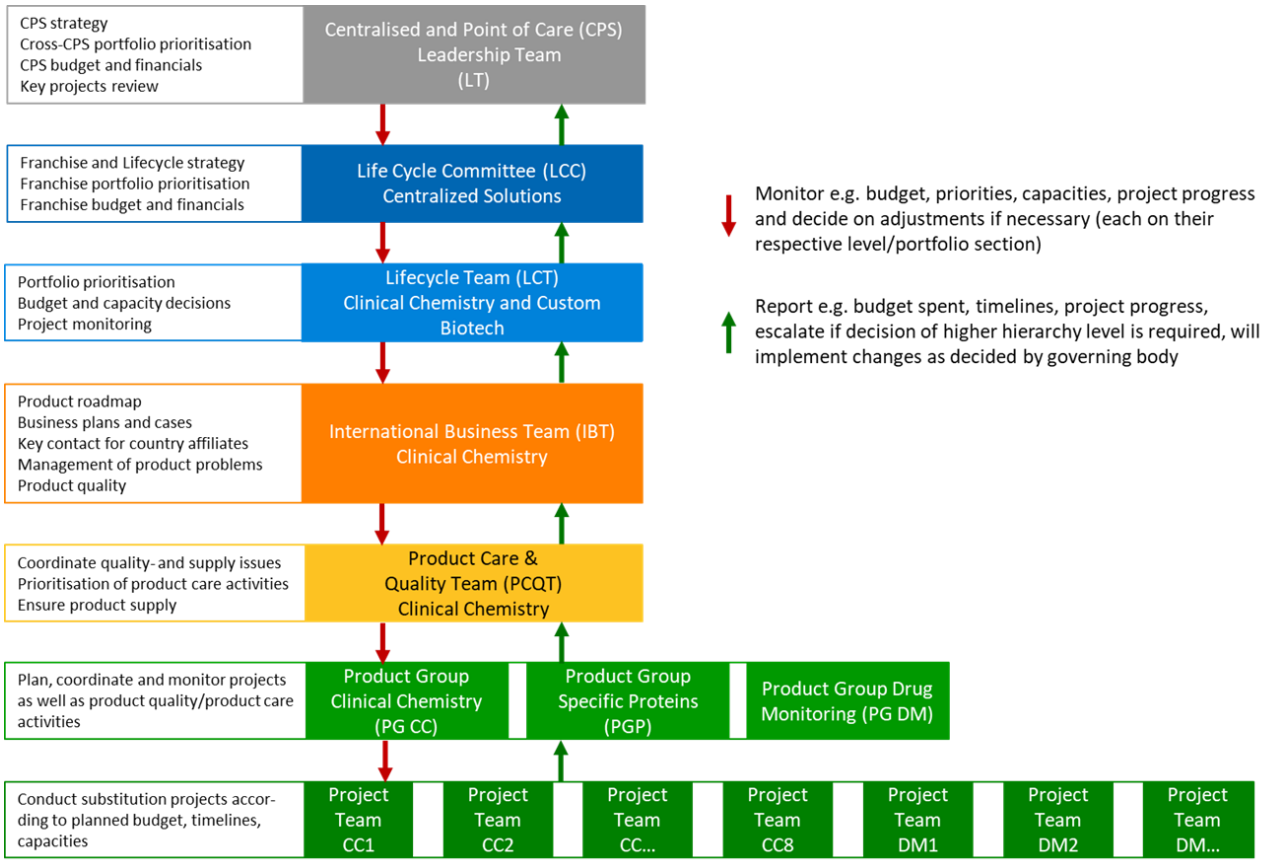


Figure 6. The organisational structure of substitution projects as an example for CC / DM products

The individual teams of the substitution projects report the progress into the different teams which hold meetings every 2 months. The PGs in turn report the progress in line with the project plans (or, if necessary, deviations from the plans) to the PCQT which also have regular bi-monthly meetings. This reporting line ensures that the projects are executed according to the approved project plans. For RTD the project team reports directly into the LCT which meets monthly.

In case there is a change in respect to timelines, budget or resources, this is decided in the PCQT or is further escalated to the IBT/LCT if it cannot be managed within the PCQT budget.

A dashboard report is communicated to the LCT with consolidated information about the projects progress on a portfolio level.

The progress to identify alternatives is also monitored within the described structure. Potential alternatives are selected and compiled by the individual project teams and/or within the PGs.

Selection criteria and acceptance criteria (specifications) are defined and presented to the PCQT. These alternatives are tested in the feasibility phase of each project which is planned and scheduled

in the respective project plans. The feasibility phase is finalised with the milestone ‘alternative selected’, the milestone is communicated to and approved by the PCQT.

In case all selected alternatives prove to be unsuitable, the PCQT approves additional budget and resources to extent and/or intensify the feasibility phase. If the required budget exceeds the PCQT budget, the decision is escalated to the IBT and (if necessary) the LCT.

The implementation of the substitution is described in the individual project plans that are written by the development leaders or project leaders of the respective project teams. All relevant functions (R&D, Operations, Regulatory, Business, Quality Assurance, Quality Control, Global Planning) are part of the project team and ensure that the required resources and expertise is available to execute the project including implementation of the alternative within the approved budget and timeline. All projects within R&D are performed within the Roche Quality Management System that is based on ISO13485 and all documentation requirements are followed. All production is performed under GMP (Good Manufacturing Practice) with the respective documentation requirements. Therefore, appropriate documentation of the substitution projects and the implementation of alternatives in production is ensured.

7 FURTHER EFFORTS REGARDING SUBSTITUTION

- ⇨ Roche's public commitment: **to substitute any Substances of Very High Concern within 10 years of listing** on the Candidate list, if technically possible.
- ⇨ Roche is an active member of the American Chemical Society **Green Chemistry** Institute Pharmaceutical Roundtable.
- ⇨ Roche supports the United Nations Sustainable Development Goals.
- ⇨ Roche ranked the **most sustainable healthcare company** in the Dow Jones Sustainability Indices for the **eleventh year running**.

Since 2015, Roche has a public company-wide commitment[27] which has been approved by the Corporate Executive Committee (CEC) to substitute any SVHCs used in its products or processes. This public commitment states that the company will **stop the use of SVHCs** after they are put on the EU Candidate List - **where technically possible within 10 years of listing**.

This goal is supported by an internal document [12] where it is already recommended **to avoid substances on this list in the development of new products and processes.** Roche engages to avoid regrettable substitutions by close collaboration of product and process development with regulatory experts and toxicologists as well as ecotoxicologists. Following this commitment, Roche has **successfully replaced OPnEO and NPnEO in a number of products / processes** during re-development. The replacement of OPnEO and NPnEO in the remaining products has already been planned and started as described in this AoA and the AfAs submitted by RDG in the EU. An authorisation is however required to allow for sufficient time to switch to the alternatives taking into account uncertainties in the timelines.

Roche is also an active member of the **American Chemical Society (ACS) Green Chemistry Institute Pharmaceutical Roundtable** which encourages innovation while catalysing the integration of green chemistry and green engineering into the pharmaceutical industry. In parallel, it has its own internal Green Chemistry Group which aims to make Roche processes safer and find less hazardous alternative chemicals to use throughout Roche.

As a global healthcare company, Roche is committed to supporting the UN SDGs (United Nations Sustainable Development Goals) in line with the business strategy; in particular SDG3, which aims at ensuring healthy lives and promoting wellbeing for all[28].

In 2020[29], for the eleventh year, **Roche has been recognised as Group Leader in sustainability within the Pharmaceuticals**, Biotechnology & Life Sciences Industry index of the Dow Jones Sustainability Indices (DJSI). This is based on an analysis of economic, social and environmental performance of the company.

[27] Roche Website: 'Our SHE Goals and Performance', 2018; under 'environmental goals': https://www.roche.com/sustainability/environment/our_she_goals_and_performance.htm?tab_id=tab1.
[28] Roche Website: 'Sustainable development goals': https://www.roche.com/sustainability/un-sdgs.html
[29] Roche Website: 'Media Release': https://www.roche.com/media/releases/med-cor-2020-11-16.html

8 CONCLUSION

A large number of alternative substances to replace the OPnEO / NPnEO in the IVD assays is available. Feasibility studies have identified technically suitable alternatives or it is expected that such alternatives will be identified. Due to the complexity of requirements for the *in vitro* diagnostic assays a considerable effort is needed for performance and stability testing. In addition, in some cases, change of specific IVD market authorisations or re-registration will be needed before OPnEO / NPnEO can be substituted in the products. If a validation test for an assay fails, the existing product with OPnEO or NPnEO needs to be maintained to avoid a market gap and allow further research and development on a product with a suitable substitute. Due to the quality and regulatory requirements outlined above, identified alternatives cannot be implemented even if considered in principle 'technically feasible' until validation is completed and, where required, regulatory approval is obtained by the corresponding health authorities.

For most products, the substitution of the OPnEO / NPnEO in the IVD assays by an alternative surfactant is expected to be a technically and economically feasible alternative.

Three products, CC1, DM1 and DM3 have already been substituted and shelf life of remaining stocks will have expired before the UK sunset date. For two assays (CC7 and DM7), replacement was expected to be already implemented by the time of submission of this dossier based on the original timelines. Some difficulties occurred, but the replacement is still planned before the UK sunset date for CC7. For DM7 the replacement may be slightly delayed until after the sunset date, but implementation is planned at the latest by the end of 2022. For one assay (RTD), replacement was expected before the UK sunset date, but due to compatibility reasons, implementation of the alternative needs to be delayed so that the old product will expire latest by March 2026. For one CC and some DM assays, there is a possibility that the timelines of the substitution projects could be prolonged until close to the end of the review period due to technical or regulatory difficulties. In the other cases, a prolongation until the end of the review period cannot be excluded if further difficulties arise but is not very likely. Therefore, it is highly unlikely that the full review period will be needed for substitution in all assays. However, as a worst-case it is assumed in the assessment in the SEA and CSR that all substitutions could be delayed until the end of the review period.

For one assay that employs a small portion of the overall amount of OPnEO / NPnEO a different alternative is being implemented. Specifically, in the case of the HIV combi PT assay, substitution with an alternative new product will be pursued. The new HIV generation Elecsys® HIV Duo which was launched April 2017 in the UK already reflects the REACH regulation aspect and uses a surfactant with no concerns. The old IVD systems are being replaced with new generation systems, i.e. instruments, with a NPnEO-free assay of increased sensitivity and specificity that runs on these new systems. Even though this newer generation HIV assay (HIV Duo), has already been developed and is currently introduced to the market, this new assay cannot be considered a suitable alternative for the HIV combi PT containing NPnEO for all customers. The timeframe for the switch to the new instruments and consequently the new assay will depend on the capacity of the analyser manufacturer (HITACHI high Technology). Currently the transition to the new instrument family is delayed due to the worldwide shortage of electronic components. This situation will stay for at least 2022. In addition, after the introduction of the new generation instruments, an average of at least five years of support for the old instruments (that includes providing the HIV combi PT assay) is required. Therefore, these assays need to be on the market (including shelf-life) until ca. end of 2027, which corresponds to the estimated time necessary for replacing the old instruments with the new generation instruments in the UK. During this period, the old assay needs to be provided to the customers to

allow for the continued use of the old systems until replacement is complete at all customers (by end of the review period, i.e. the 4th of January 2028).

Please note that the use applied for in this authorisation dossier is depending on RDG receiving the EU authorisation, in particular for Use 2, for actually producing the affected assays. RDG applied for an EU authorisation to gain more time for the necessary evaluations and regulatory approvals based on IVD regulations.

Without a UK authorisation, RDL would need to stop the distribution of many IVD products for years. IVD products used for diagnosis of certain diseases, therapy monitoring or drug abuse detection could not be supplied anymore. This would cause unacceptable impacts on patients and the healthcare system as detailed in the SEA.

RDL therefore applies for an authorisation to be able to distribute OPnEO- / NPnEO-containing IVD assays until they have been replaced by RDG and in the case of HIV, to gain the necessary time for the introduction of alternative IVD systems to the market.

In EU application for authorisation, RDG requested a review period of 7 years after the EU REACH Sunset date (the 4th of January 2021) to authorise the use of OPnEO and/or NPnEO until complete replacement of these substances in all affected IVD products, i.e. until the 4th of January 2028. For this application for authorisation by RDL under UK REACH, the end of the review period remains the same as substitutions are still planned to be completed by this date. The review period applied for is therefore (approximately) 5.5 years from the 30th of June 2022 till end of 2027.

Authorisation for the use of OPnEO / NPnEO until end of 2027 is requested to complete the replacement of these substances in all affected IVD products. This period is needed due to the complexity of the substitution projects. IVD's are highly regulated and there are stringent requirements for unchanged specifications of produced IVDs. An extensive validation phase cannot be dismissed and an update of market authorisations will in some cases be required. Furthermore, for one product more time is needed for the introduction to the market of a new IVD system with a new generation NPnEO-free assay.

9 REFERENCES

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[8]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

[9]J.O. Straub, R. Shearer, M. Studer. Rational selection of alternative environmentally compatible surfactants for biotechnology production of pharmaceuticals – A step towards green biotechnology. Environmental Toxicology and Chemistry. 10th June 2014. p. 2140-2146. DOI: 10.1002/etc.2660.

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APPENDIX I – ASSAYS INCLUDED IN THIS APPLICATION FOR AUTHORISATION

Product name	Use	Product Group
BILT3 LDLC3	3	Clinical Chemistry (CC)
BARB BENZ Plus PCP TMPA	3	Drug Monitoring (DM)
MTQL PPX		
Elecsys® HIV combi PT	3	HIV
10X SSC Sodium Chloride Sodium Citrate Buffer	3	Roche Tissue Diagnostic (RTD)