ANALYSIS OF ALTERNATIVES

Legal name of applicant(s):	Roche Diagnostics GmbH
Submitted by:	Roche Diagnostics GmbH
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 2: Use of Octyl- and Nonylphenolethoxylates in the formulation and filling of *in vitro* diagnostic (IVD) assays specified in Appendix 1 to the AoA Use 3: Use of Octyl- and Nonylphenolethoxylates in *in vitro* diagnostic (IVD) assays specified in Appendix 1 to the AoA
Use number:	2&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
APAC	Asia-Pacific region
AT	Accutrend® Accutrend®18 is a flexible point-of-care handheld device for the determination of three important cardiometabolic parameters and the lactate level in blood
BGE	Blood gas and electrolyte BGE is part of the Point of Care Roche business unit and the affected product in this portfolio is the Hb Calibrator for the determination of haemoglobins and bilirubin. BGE analysis is used in critical care settings such as Intensive care units (ICU), Emergency department (ED) and Neonatology. The measured parameters comprise pO2, pCO2, pH, Hematocrit, Na+, K+, Cl-, Ca2+, Glucose, Lactate, Urea/BUN total haemoglobin, Oxygen saturation SO2, O2Hb, COHb, MetHb, HHb, bilirubin. These critical parameters indicate for example whether oxygen is adequately delivered to tissues (e.g. pO2, PCO2 and Hematocrit in arterial blood) or help detecting jaundice in new-borns which occurs when total bilirubin values are above a certain threshold.
BILT3	Bilirubin Total Gen 3
CAGR	Compound Annual Growth Rate - the mean annual growth rate of an investment over a specified period of time longer than one year.
CB	Custom Biotech is a segment of Centralised & Point of Care (CPS), which supplies raw materials, reagents, instruments and services within the Diagnostic Division. Custom Biotech customises its offering to the quality and regulatory needs of other biopharmaceutical and diagnostic manufacturers.
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

Term	Explanation
CEC	Corporate Executive Committee
CEN	Cytokeratin 8/19
CER	Coupon Equivalent Rate
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 Center for Medicare and Medicaid Services (CMS) before they can accept human samples for diagnostic testing.
CLP	European Union regulation, which aligns the EU system of classification, labelling and packaging of chemical substances and mixtures.
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.
CRP	C-reactive protein is an annular (ring-shaped), pentameric protein found in blood plasma, whose levels rise in response to inflammation.
CSF	CerebroSpinal Fluid is a clear, colourless body fluid found in the brain and spinal cord.
CSR	Chemical Safety Report
CVD	CardioVascular Disease
CYFRA	Name of a Roche IVD
DAGS	Double-antigen Sandwich
DIG	Digoxigenin

Term	Explanation
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).
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.
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

Term	Explanation
EUR	Euros
EUSES	European Union System for the Evaluation of Substances, version 2.0. National Institute of Public Health and the Environment (RIVM), the Netherlands
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.
GJ	Gigajoule, unit of energy
Hb	Haemoglobin
HDL	High Density Lipoproteins, commonly referred to as "good cholesterol"
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
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

Term	Explanation
IVD	*In vitro* diagnostic medical devices. IVD products are regulated and defined by European Regulation 2017/746/EU. IVD are defined as any medical device which is a reagent, reagent product, calibrator, control material, kit, instrument, apparatus, equipment, or system, whether used alone or in combination, 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 process or state, or ▪ concerning congenital physical or mental impairments, or ▪ concerning the predisposition to a medical condition or a disease, or ▪ to determine the safety and compatibility with potential recipients, or ▪ to predict treatment response or reactions, or to define or monitoring measures.
IVDR	IVD regulation
IW	Industrial worker
LATAM	Latin America
LDLC	Low density lipoprotein cholesterol, commonly referred to as “bad cholesterol”
log Koc	Organic Carbon-Water Partitioning Coefficient
log Kow	Octanol-water partition coefficient
LSD	Lysergic acid Diethylamide
MAC-EQS	Maximum allowable concentration environmental quality standard
MD	Molecular Diagnostic
MDROs	Multidrug-resistant organisms
MDx	Molecular Diagnostics - MDx Enzymes production processes
MDx Enzyme	Enzyme used in molecular diagnostics
MES	2-(N-Morpholino) ethanesulfonic acid
MNQ	Low water discharge
mRNA	Messenger of the ribonucleic acid (RNA)
MRSA	Methicillin-resistant *Staphylococcus aureus*

Term	Explanation
NAD	Nicotinamide Adenine Dinucleotide
NADH	Nicotinamide Adenine Dinucleotide (NAD) + Hydrogen (H)
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
$NP_{equiv.}$	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]
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

Term	Explanation
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]
OSH	Occupational safety and health
PBT	Persistent, Bioaccumulative and Toxic
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
PoC	Point of Care is a segment of Centralised & Point of Care (CPS), which provides the market with instrument systems, tests, software and services that deliver quick, accurate and reliable results for critical- and primary-care clinicians and for patient self-monitoring in areas such as oncology and virology, as well as in cases of cardiovascular, inflammatory and infectious diseases. These instruments are smaller (Portable or bed-side), faster and less complex that the modular solutions of the SWA.
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

Term	Explanation
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).
REACH	Regulation on Registration Evaluation, Authorization and Restriction of Chemicals European Regulation (EC) No 1907/2006
RMD	Roche Molecular Diagnostics
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'
RSV	Respiratory Syncytial Virus
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
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 REACH In fact, listing of a substance as an SVHC by the European Chemicals Agency (ECHA) is the first step in the procedure for limiting the use of a chemical (either with an authorization or a restriction)

Term	Explanation
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.
TM	Tumor Marker
TMPA	Total Mycophenolic Acid
TPA	Tripropylamine
UA	Urinalysis Or Uric Acid
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

DECLARATION

We, Roche Diagnostics GmbH, 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 (16th of May, 2019) the information is not publicly available, and in accordance with the due measures of protection that we have implemented, a member of the public should not be able to obtain access to this information without our consent or that of the third party whose commercial interests are at stake.

Signature: ppa.

Date, Place: Penzberg, 16 MAY 2019

Dr. Kai Simon, Head of Legal Penzberg

Signature: ppa.

Date, Place: Pz, 16. MAY 2019

Dr. Joachim Eberle, Global Head of R&D Centralized and Point of Care Solutions

1 SUMMARY

Roche Diagnostics GmbH (RDG), the applicant of this authorization, is an affiliate of F. Hoffmann-La Roche Ltd. (collectively hereinafter referred to as "Roche"). Roche is one of the world's leading, research-oriented healthcare companies and has two core businesses: diagnostics and pharmaceuticals. RDG, as part of the Roche Group is publicly committed to substituting any Substances of Very High Concern (SVHC) from their processes and products. RDG, is the leading company in the *in vitro* diagnostic (IVD) market in Europe and worldwide.

The current analysis of alternatives (AoA) was developed to support RDG's application for authorisation to continue the use of the two groups of substances OPnEO and NPnEO after the sunset date to keep producing IVD products in Penzberg and Mannheim until substitution of these substances in the affected products can be completed.

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 4th of January 2021.

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 (RDG) 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.

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 (NeoRecormon® and MIRCERA®)
2	Diagnostics	RDG	Formulation	Use of Octyl- and Nonylphenolethoxylates in the formulation and filling of *in vitro* diagnostic (IVD) assays specified in Appendix 1 to the AoA
3	Diagnostics	Downstream Users (e.g. laboratories)	Products	Use of Octyl- and Nonylphenolethoxylates in *in vitro* diagnostic (IVD) assays specified in Appendix 1 to the AoA

Use	Division	User	Short name	Use Name
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 *in vitro* diagnostic (IVD) assays, research or quality control products and other, e.g. analytical applications (processes specified in Appendix 1 to the AoA)

This AoA evaluates Use 2 and Use 3. Use 4 is evaluated in a separate document**.**

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. 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. Several 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 worldwide is estimated to be almost 7 years after the sunset date. In one further case, the affected product needs to be supplied until the planned date of removal from the market due to contractual obligations and to ensure availability of the IVD assays until replacement with an alternative system.

This AoA explains the unique technical and regulatory challenges associated with validating the alternatives. A 7-year authorisation review period will allow RDG to complete the evaluation of alternatives, validate and assure performance of the affected products, and if necessary, submit

change notifications to health authorities as a regulatory requirement for *in vitro* diagnostic assays. As described in the SEA, millions of patients worldwide depend on the accurate, reproducible and reliable results of these assays.

Authorisation for the use of OPnEO / NPnEO for 7 years after the sunset date 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 GmbH**, which is an affiliate of **F. Hoffmann-La Roche Ltd**. (Roche) and one of Roche's legal entities in **Germany.**
- ⇨ The current AoA was developed to support Roche's application for an authorisation to **continue the use of OPnEO / NPnEO after the sunset date until complete substitution**.
- ⇨ **Uses covered in this AoA (Use 2&3):**

  Use of Octyl- and Nonylphenolethoxylates in the formulation and filling of *in vitro* diagnostic (IVD) assays specified in Annex 1 to the AoA, as well as use of the IVD assays
- ⇨ **F. Hoffmann-La Roche Ltd**. is a Swiss multinational healthcare company. The company is subdivided in two main divisions: **Pharmaceuticals** and **Diagnostics**.
- ⇨ 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.
- ⇨ IVDs **are medical devices intended to be used for diagnosis, prevention, monitoring, etc.**
- ⇨ **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 GmbH (RDG), the applicant of this authorisation, is an affiliate of F. Hoffmann-La Roche Ltd. (collectively hereinafter referred to as "Roche")[1]. Roche is one of the world's leading, research-oriented healthcare companies and has two core businesses: diagnostics and pharmaceuticals. RDG, as part of the Roche Group is publicly committed to substituting any Substances of Very High Concern (SVHC) from their processes and products. RDG, is the leading company in the *in vitro* diagnostic (IVD) market in Europe and worldwide.

The current AoA was developed to support RDG'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**

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 European Chemical Agency (ECHA) because of the endocrine disrupting properties for the environment of their degradation products with a sunset date of 4th of January 2021.

The two groups of substances, OPnEO and NPnEO, are addressed in the same dossier since the Guidance on the preparation of an application for authorization, Annex 1[1], concludes that if the

[1] For clarity: RDG does not sell its products directly to legal entities (customers) outside of Roche, but has its products sold by its affiliates dedicated to the sale of RDG's products. Hence, for facilitation reasons, the term 'Roche' is used in this document to describe the respective selling affiliates and the relationships to customers as well as market shares.

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 Application for Authorisation (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 and production processes of RDG. Three distinct uses were identified within RDG and one further use was identified in the Roche Pharmaceuticals Division:

Table 1. Uses overview

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 *in vitro* diagnostic (IVD) assays specified in Annex 1 to the AoA
3	Diagnostics	Downstream Users (e.g. laboratories)	Products	Use of Octyl- and Nonylphenolethoxylates in *in vitro* diagnostic (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 *in vitro* diagnostic (IVD) assays, research or quality control products and other, e.g. analytical applications (processes specified in Annex 1 to the AoA)

As all uses take place at the same legal entity, but at two divisions, they are covered in two applications for authorisation of RDG. Use 1 is covered in a separate application for authorisation. Uses 2, 3, and 4 are part of the same application. Uses 2&3 are described in the present AoA document. Use 4 is discussed in a separate 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** and one of the most well-known companies working on diabetes management. Roche's healthcare strategy aim is to provide medicines and diagnostics that enable significant improvements in the health, quality of life and survival of patients. Twenty-four medicines developed by Roche are included in the World Health Organisation Model Lists of Essential Medicines[2], among them life-saving antibiotics and chemotherapy. Roche is a **leading provider of clinically differentiated medicines and personalised healthcare**[3]. 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.

RDG is the second largest affiliate within Roche and, with its site in Penzberg, one of the biggest employers in upper Bavaria. Only between 2015 and 2016 Roche has invested around 600 million euros in expanding the Penzberg Biotechnology site and over the last decade more than 2 billion euros in total. Roche has its third largest location worldwide in Mannheim which is the headquarters of RDG. In 2015, Roche opened a new production building for immunodiagnostics in Mannheim with an investment of around 1 billion euros [4].

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, 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 2&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.

[2]World Health Organization (WHO) website: WHO Model Lists of Essential Medicines, 2017: http://www.who.int/medicines/publications/essentialmedicines/en/

[3]Roche website, 'Personalised Healthcare': https://www.roche.com/about/priorities/personalised_healthcare.htm

4Roche website, ‚Arbeiten in der Innovationsstadt':
https://www.roche.com/de/careers/country/germany/de_service/blogs/arbeiten_in_der_inno.htm

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 3.3.8**

OPnEO and NPnEO are used in wide array of IVD assays and production processes of RDG. Table 2 provides an overview of the product groups included in this authorization dossier for Use 2&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 / for NPnEO function in all products. A detailed description for every group can be found in the subsections thereafter.

Table 2. Overview of product groups

Use	Product Group	Abbreviation	Business Area concerned +
Use 2: Formulation **Use 3:** Products	Clinical chemistry	CC	SWA Core reagents
	Drug Monitoring	DM	
Use 2: Formulation **Use 3:** Products	HIV	HIV	SWA Infectious diseases and oncology
Use 3: Products	Blood gas and electrolyte	BGE	PoC

Use	Product Group	Abbreviation	Business Area concerned [+]
Use 2: Formulation **Use 3:** Products	**Accutrend®**	AT	PoC
Use 2: Formulation **Use 3:** Products	Urinalysis	UA	Specialty testing
Use 3: Products	Roche Molecular Diagnostics 1	RMD1	RMD
	Roche Molecular Diagnostics 2	RMD2	
Use 3: Products	Roche Tissue Diagnostic	RTD	RTD

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

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

According to regulation 2017/746/EU [2], *in vitro* diagnostic medical devices are defined as 'any medical device ... to be used *in vitro* for the examination of specimens, including blood, urine and tissue donations derived from the human body, solely or principally for the purpose of providing information:

- concerning a physiological or pathological process or state, or
- concerning congenital physical or mental impairments, or
- concerning the predisposition to a medical condition or a disease, or
- to determine the safety and compatibility with potential recipients, or
- to predict treatment response or reactions, or
- to define or monitoring measures.'

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.

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 the functions on the next section are discussed by 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 Uses 2&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 Product Group 1: Clinical Chemistry

a) Type of sample and parameter measured

Measurement of different **blood and urine clinical parameters**, for example creatinine in serum / plasma to monitor a patient's kidney function or the presence of a special protein (C-reactive protein, CRP) that is a marker to predict the risk of coronary heart disease in apparently healthy persons and is also used to for detecting inflammatory processes related to bacterial infections.

b) Principle of the measurement

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 or
- **latex bead enhanced immunological assays**: similar to the principle of the drug monitoring assays (see Section 3.3.3b)

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

The principle of the analysis is different on the various assays included in this group, 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) Function of the OPnEO F NPnEO in the assays

Variable, depending on the assay: in one case NPnEO or OPnEO are used for blood **cell lysis**, in others 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:

Cell lysis: the affected reagent is used to lyse red blood cells (erythrocytes) in a blood sample to measure glucose. The **cell membrane** consists of a phospholipid bilayer that is **susceptible to detergents**. Therefore, the utilisation of detergents to disrupt the phospholipid bilayer and consequently to lyse the cells is a common practice.

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 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 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 Product Group 2: Drug Monitoring Subgroup 1 and 2

a) Type of sample and parameter measured

Measurement of **concentrations of drugs** (e.g. cocaine, amphetamines, etc) 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.

Kinetic interaction of latex beads in solution, type II (see Figure 2): In the absence of sample drug, soluble drug conjugates bind to antibody-bound beads, 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, it binds to the particle-bound antibody instead of the drug derivative conjugate. As a result, the bead-bound antibody does not precipitate and there is a reduction of absorbance increase that is proportional to the amount of drug present in the sample.

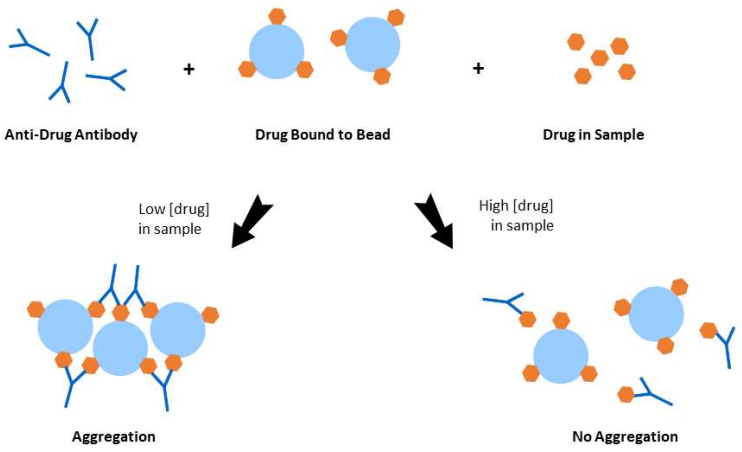


Figure 1. Scheme of kinetic interaction of latex beads in solution, type I

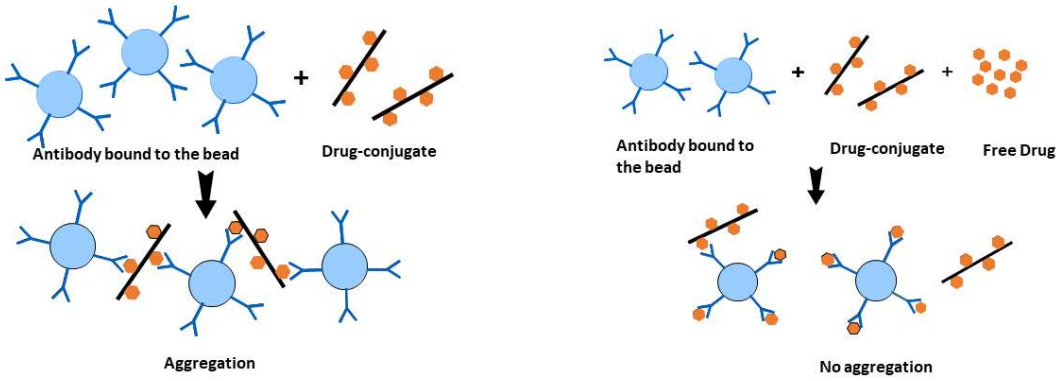


Figure 2. Scheme of kinetic interaction of latex beads in solution, type II

Subgroup 2: **Enzymatic detection** (see Figure 3). 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.

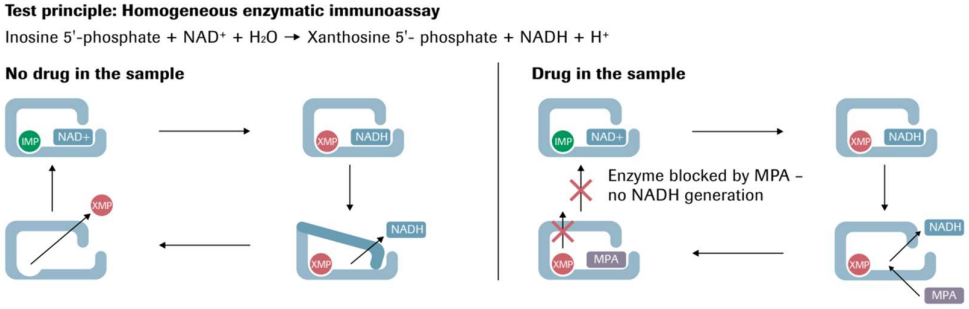


Figure 3. Scheme of enzymatic detection principle

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) Function of the OPnEO / NPnEO in the assays

Subgroup 1: The OPnEO (and additionally NPnEO in the following products: DM1, 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 3.3.1d).
- **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 3.3.1d).

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 Product Group 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 4). 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 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.

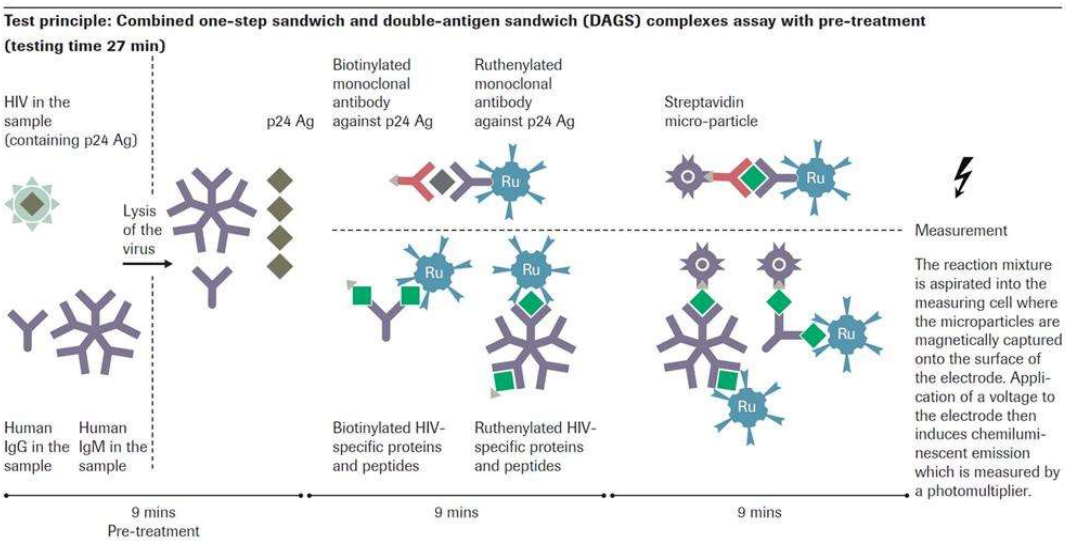


Figure 4. Scheme of ECLIA assay principle

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

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 costumer site.

3.3.4 Product Group 4: Blood Gas and Electrolyte Analysis

a) Type of sample and parameter measured

Measuring of **several parameters** in whole blood, serum, plasma, pleural fluid, aqueous solutions, acetate, bicarbonate and dialysis solutions (for example O_2, CO_2, pH, Glucose, Lactate, Urea, Sodium, Potassium, Bilirubin, Haemoglobin, etc..). BGE systems deliver fast and reliable results in situations critical to patients' welfare: Intensive care unit, Emergency room, Operating room, Neonatal station.

b) Principle of the measurement

There are **several principles** depending on the parameter to be measured. Blood gases and electrolytes present in the samples are measured using **electrochemical sensors and electrodes.** Haemoglobins and Bilirubin are determined **spectrophotometrically**.

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

OPnEO is present in **one calibration solution (Hb-Calibrator)** in a concentration of [redacted]% w/w

Type of instrument used: cobas® b 221 system.

Note: OPnEO and NPnEO are also present in solutions, electrodes and electrochemical sensors used in 9180 Electrolyte Analyzers, cobas® b 121 systems, cobas® b 221 systems and cobas® b 123 POC systems. OPnEO and NPnEO are present in concentrations below 0.1% w/w in these products. These sensors and solutions are produced in Switzerland and are therefore not in scope of this AfA. However, their production will be subject to authorisation requirements in Switzerland as soon as OPnEO and NPnEO have been added to the respective list in Swiss legislation.

d) Function of the OPnEO in the assays

The function of the OPnEO in the product subject to authorisation (Hb-Calibrator) is as **wetting agent** to reduce the surface tension and increase wetting ability of the calibrator solution to improve the transport of the calibrator solution in the tubing and measurement cell.

3.3.5 Product Group 5: Accutrend®

a) Type of sample and parameter measured

Control solution for checking the performance of the test strips for **whole cholesterol** measurement in **blood**

b) Principle of the measurement

Colorimetric determinations. The cholesterol in a blood sample reacts with chemicals fixed to the test strip producing a colour. The colour can be measured using the appropriate instrument. The intensity of the colour is proportional to the amount of cholesterol present in the blood.

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

Control solution containing the OPnEO at a final concentration of [redacted]% w/w.

Type of instrument used: Accutrend®.

d) Function of the OPnEO in the assays

Solubilisation and stabilisation of the reagents in the control solution, by stabilising the lipoprotein (cholesterol) complexes in the aqueous solution.

3.3.6 Product Group 6: Urinalysis

a) Type of sample and parameter measured

Urine multiple test strips are used to measure certain **constituents in urine** which are indicative of renal, urinary, hepatic and metabolic **disorders**. One of the parameters measured is protein content in urine which is indicative of kidney damage or acute inflammation.

b) Principle of the measurement

Testing for protein is based on the phenomenon called the **'Protein Error of pH-indicators'** (ability of protein to alter the colour of some acid-base indicators without altering the pH). In a solution without proteins, a pH-indicator fixed to the test paper, has a certain colour. However, in the presence of protein, the colour changes to other colours depending on the concentration.

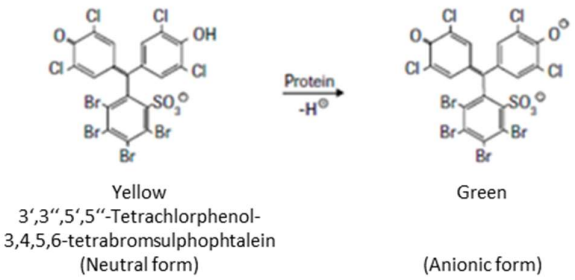


Figure 5. Principle of the protein detection in urine samples

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

Multiple test strips containing **one field** (PRO) with the NPnEO at a final concentration of [redacted]% w/w. The concentration of NPnEO in the product (test strip) is approximately [redacted]% w/w.

Type of instrument used: cobas® u 411, cobas® u601, Urisys 1100, Urisys 2400 urinalysis instruments, or visual reading using a colour coding provided on the packaging label of the strips.

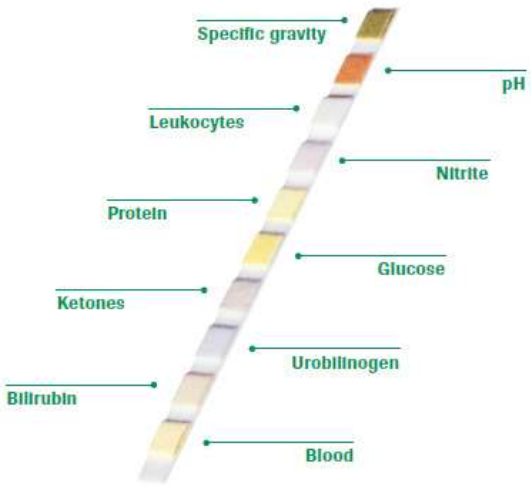


Figure 6. Urinalysis test strip. The marked field contains NPnEO

d) Function of the NPnEO in the assays

Wetting agent to ensure even distribution of the sample on the filter paper leading to more homogenous colour development and consequently higher test performance.

3.3.7 Product Group 7: Roche Molecular Diagnostics

Subgroup RMD1

a) Type of sample and parameter measured

This test is being used to **detect Flu A and B in nasopharyngeal swab**. The assay allows the rapid *in vitro* qualitative detection and discrimination of Influenza A virus and Influenza B virus RNA.

b) Principle of the measurement

Liat® is based on **Real-Time RT-PCR** (Reverse Transcription Polymerase Chain Reaction). The sample material is added to a solution that contains, among other components, primers (pieces of DNA used to start copying a specific DNA part) and TaqMan probes (also pieces of DNA that bind to specific regions of DNA). TaqMan probes are labelled on one end with a reporter dye and on the other with a quencher (that quenches the reporter dye, so that the reporter dye cannot emit light).

If the sample contains influenza A or B virus, the primers and the TaqMan probes will bind to the genetic material of influenza A or B and this genetic material will be copied many times. As the reaction proceeds, the TaqMan probe will be cleaved (cut) and the reporter dye will be released. When this occurs, the quencher is separated from the reporter dye. As a result, there is a measurable increase in reporter dye fluorescence.

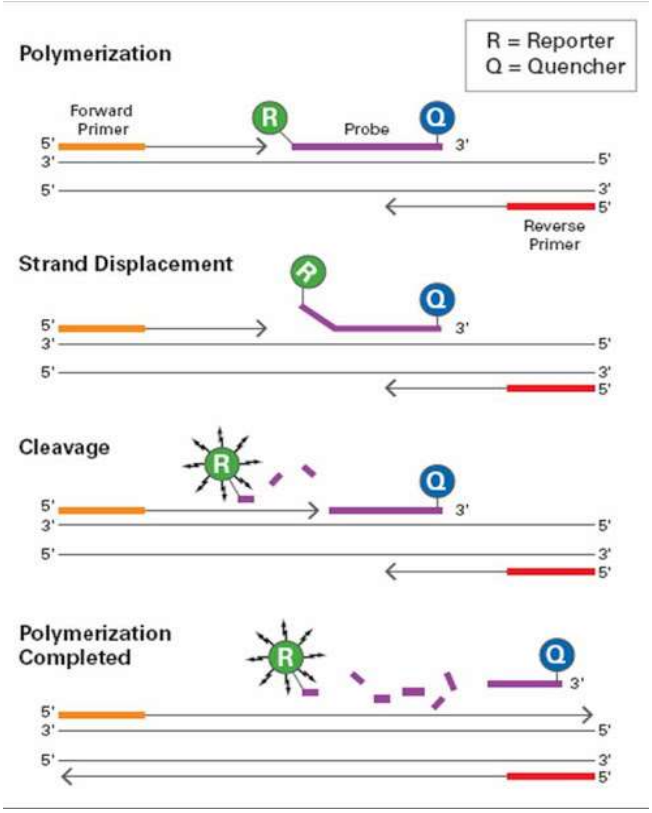


Figure 7. principle of the Real-Time RT-PCR

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

OPnEO is present in [redacted]% w/w
Type of instrument used: cobas® Liat® System
Sealed tube containing all the reagents

Figure 8. Liat® sealed tube containing all necessary reagents

d) Function of the OPnEO in the assays

Cell lysis of the viruses in the sample to make the genetic material (RNA) accessible for detection by the assay.

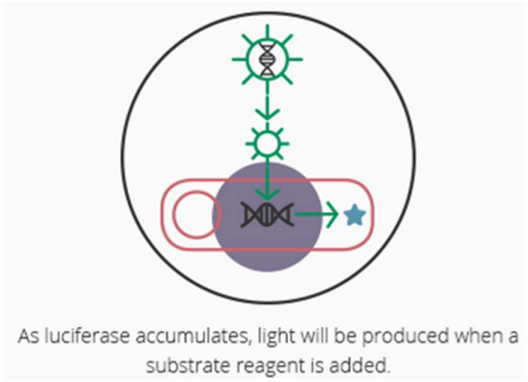
Subgroup RMD2

a) Type of sample and parameter measured

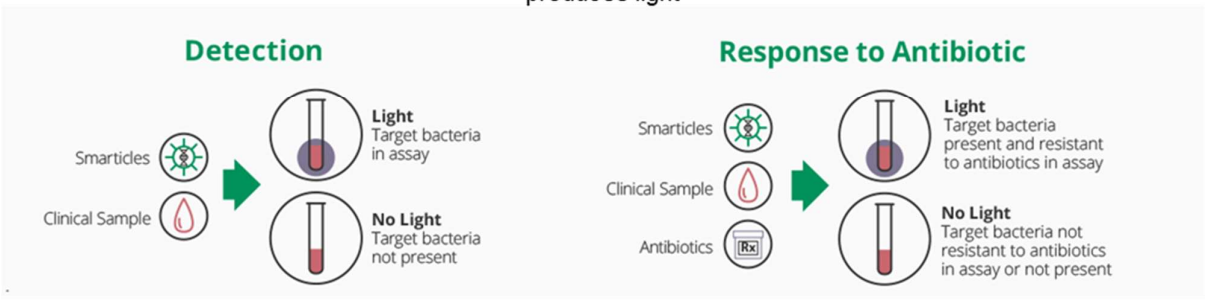
Assay for the detection of **bacteria and its antibiotic susceptibility profile**: MRSA Test for the direct detection of methicillin-resistant *Staphylococcus aureus* from **nasal swabs** and its antibiotic susceptibility profile.

b) Principle of the measurement

Smarticle technology consists of DNA-delivery bioparticles combined with custom-designed DNA molecules that cause live bacteria to produce light. If the targeted bacteria are present in the sample, it will produce light. When an antibiotic is added, susceptible bacteria targeted by bioparticles will remain dark, while drug-resistant bacteria produce light (see Figure 9).



Smarticles bioparticles bind to their target and deliver a custom-designed DNA molecule that causes viable bacteria to express luciferase — a molecule that produces light



In the presence of antibiotics, susceptible bacteria targeted by bioparticles will remain dark, while drug-resistant bacteria produce light—quickly and efficiently.

Figure 9. Principle of Smarticle Assay

c) Composition of the kit, occurrence of OPnEO and procedure for measurement

Cartridge (cap for a test tube) contains all necessary reagents in two blisters (see Figure 10). In **one blister** OPnEO is present at a concentration of 0.5% w/w.

Type of instrument used: cobas® vivoDx

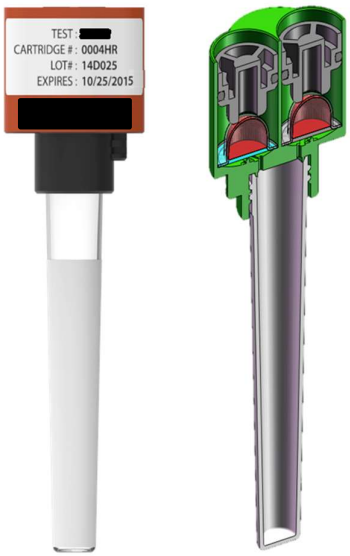


Figure 10. Test tube with cap cartridge for cobas® vivoDx

d) Function of the OPnEO in the assays

OPnEO is added due to its surface-active properties / flow properties; important for complete **mixing** of substrate (sample) and reagents. Furthermore, the **luminescence signal is sensitive** to the surfactant.

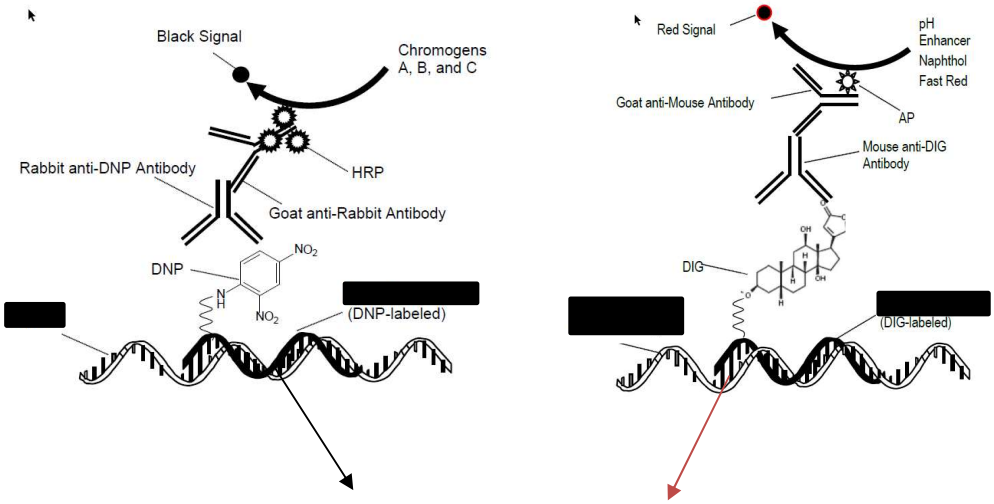
3.3.8 Product Group 8: Roche Tissue Diagnostics

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 11). 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.



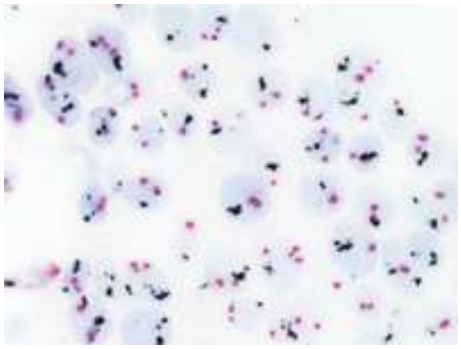


Figure 11. Principle of *in situ* hybridization for tissue samples

c) Composition of the kit, occurrence of OPnEO and procedure for measurement

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) Function of the OPnEO in the assays

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 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 this AfA, RDG therefore applies for the use of a maximum annual tonnage of 1326 kg/a of OPnEO and 217.4 kg/a NPnEO for Use 2 and 646.3 kg/a of OPnEO and 54.8 kg/a NPnEO for Use 3. For more details on how this maximum was defined please refer to the CSRs for Use 2 and for Use 3.

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

Use	**Substance**	**Sunset date**	**Maximum (amount applied for)**
		kg/a	
Use 2	OPnEO	1121.5	1326
	NPnEO	197	217.4
Use 3	OPnEO	529.1	646.3
	NPnEO	53.3	54.8

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.

⇨ **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 / 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 / NPnEO in the existing assays with alternative surfactants. As already completed substitutions of OPnEO / 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 have already started in 2015. The **exact criteria** applied to identify the possible alternatives **depend on the group of assays and the specific function of the OPnEO / NPnEO** in the assay. Performance testing of the critical specifications of an assay, such as specificity, stability, precision etc. 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 / NPnEO in the assays:

Alternative 2: Replacement of the assay used by other OPnEO / 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), but cannot serve as an immediate replacement for the older system due to the ongoing process to obtain market authorisation for the new system and limitations in the applicability (currently only high-throughput instrument available) leading to a need to keep the older product on the market for another ca.10 years. Therefore, even in the cases where alternative / newer generation products are available, they are not yet a suitable alternative for the OPnEO / 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 before the sunset date or in a shorter time that Alternative 1. Due to the high competitiveness in the IVD market, there is also a probability of refusal from third parties to sell to RDG 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 / NPnEO free (or, in case manufactured outside the European Economic Area (EEA), contain < 0.1% w/w OPnEO / NPnEO) and that it would meet RDG 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 RDG's customers:

In Use 3, RDG's customers, i.e. laboratories and hospitals are using OPnEO / NPnEO by running RDG'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 / 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. Therefore, such an option would only be pursued if RDG's OPnEO / NPnEO containing IVD assays were not available anymore (i.e. in the case of the non-use scenario or in the case of removal of the system from the market for BGE) 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 all over the world. 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 and critical micelle concentration (CMC) 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[5], surfactants were additionally checked for regulatory alerts and surfactants with an aromatic ring or containing halogens were excluded[6].

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). Table 4 summarises the different alternatives considered for each product group, including the status of feasibility testing. Please see footnote on table for explanation on status abbreviations.

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

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

Table 4. Alternative surfactants for replacement of OPnEO / NPnEO considered or already tested for the different product groups

Alternative Number	DM	HIV	CC	UA	AC	BGE	RMD1	RMD2	RTD
1	F-					Vo			F-
2	F-					Vo			
3	Fo (1)		F- (2) F+ (1)			F-			
4		F+				(A+)		Fo	
5									
6	A1 for all products. F- (1) Fo (5) Vo (1)	F+	A+ (2) F+ (6) F- (2)	F-			A2		Vo
7	A2 (1) Fo (2)	F-	F- (1)	F-			A1		F-
8				F-					
9					A2				
10				F-					
11	F-			F-					
12				F-					
13					A2				
14				Vo					
15					Vo	F- (2)			
16					A+				
17					A2				
18		A+ (Brij 58)		F+		F- (4)			
19	F-		F- (2)	F-					
20			F- (1)						
21	F-					F- (2)			
22	F-					F- (2)			
23	F-		F+ (1)		F+	F- (2)		Fo	
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.

5.3 Hazard Profile of the Alternative Surfactants

OPnEO / 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 (see Table 4). This search focused on substances that had already been shown to work as substitutes for OPnEO / NPnEO in other products or processes and substances suggested as substitutes by suppliers. The **hazard profile** of all alternative surfactants was assessed in 2016 and 2017, and the surfactants were **checked for regulatory alerts**. 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: Comité Européen des Agents de Surface et de leurs Intermédiaires Organiques - European Committee of organic surfactants and their organic intermediates) guide on classification of surfactants 2017 [5]), published data [9], the SIN (Substitute It Now!) list[7] 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 in the Uses by RDG 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. The alternatives shown in the table below were checked and the ones that were not excluded based on the hazard properties were considered for feasibility testing (see table in previous subsections). If technically suitable alternatives to be used in larger quantities are lacking information on hazards, corresponding studies will be performed before the substance is definitively used.

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

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

Table 5. Hazard properties of the alternatives.

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
4669-23-2	Triethylenglykol-monodecyl ether	-	-	-	-	Further data needed

CAS No.	Chemical name	CLP classification	CLP classification source	Biodegradation	Biodeg. source	Alternative further considered based on hazard properties
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
68131-39-5	Alcohols, C12-15, ethoxylated	<2.5 EO: H400-H412 >2.5<5 EO: H400-H412-H319 >15<20 EO: H319 >20 EO: not classified 5 EO: H400-H412-H318 >5<7 EO: H412-H318 >7<15 EO: H412-H302-H318	[5]	Readily biodegradable (61-72% after 28 days)	[6]	yes
68131-40-8	Alcohols, secondary C11-15, ethoxylated	H412	[5]	readily biodegradable (65% in 28 days, OECD 301 C)	[6]	yes
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

CAS No.	Chemical name	CLP classification	CLP classification source	Biodegradation	Biodeg. source	Alternative further considered based on hazard properties
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
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

CAS No.	Chemical name	CLP classification	CLP classification source	Biodegradation	Biodeg. source	Alternative further considered based on hazard properties
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
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)	[10][11]	yes
9043-30-5	Alcohol C13-iso, ethoxylated (14 EO)	H302 - H318	[7]	readily biodegradable (up to 20 EO)	[10][11]	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 12

Roche is dedicated to substituting OPnEO and NPnEO by alternative surfactants in all products. The authorisation is needed to continue production and use of the assays until replacement is completed including phase-out of the existing products at the customers (i.e. laboratories, hospitals, physicians' practices) in the cases where this is not feasible before the 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 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	• 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 / NPnEO based on shelf life and: o Replacement with OPnEO / 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 assessing that the alternative detergent is 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 / NPnEO at RDG 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 an RDG-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.

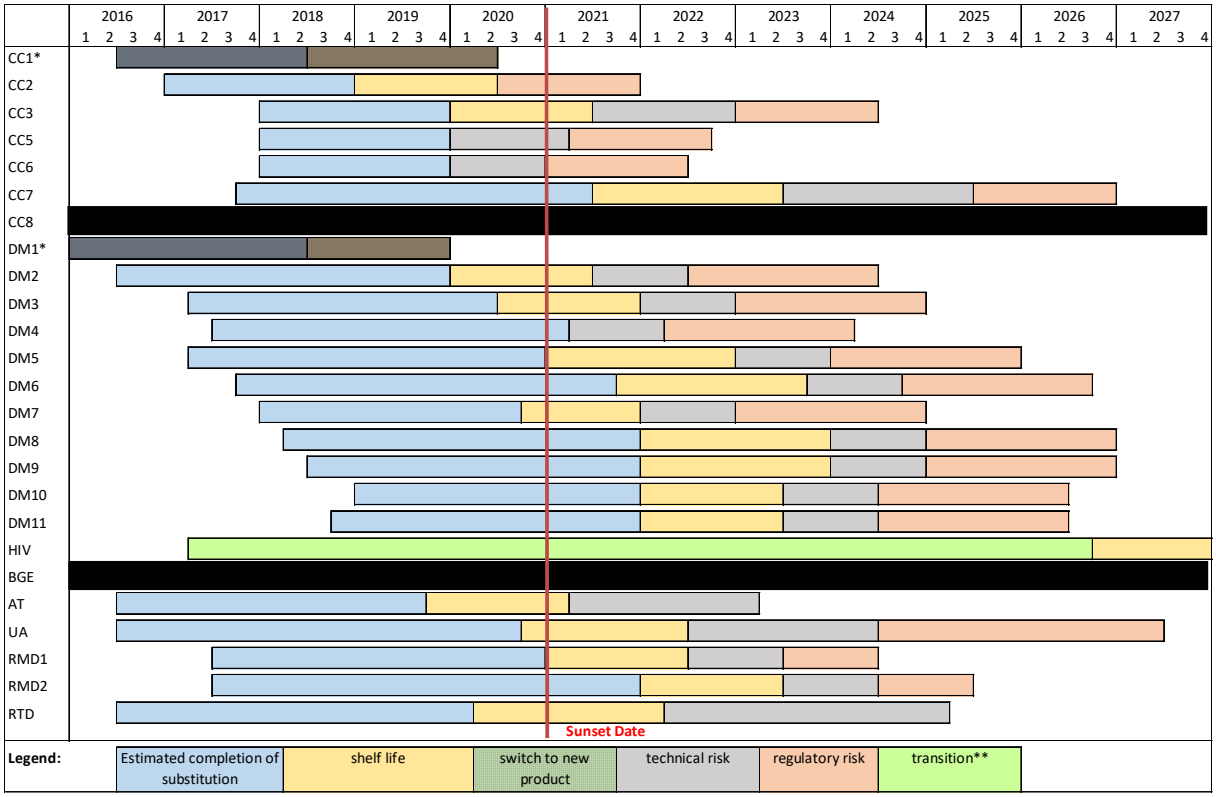
A **change may trigger different authorisation requirements in different countries**. For example, in China the change of a critical ingredient requires efforts like an initial product registration, while in Europe this may not require any regulatory actions at all. Processing times also differ quite 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.

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 12. 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, CC8, a new product is being developed and there will be an overlapping period during which the old

product will be produced and sold until all clients can be switched to the new product (green dotted bar). In two cases, the affected products will not be produced anymore and the clients will be switched to a new system during a transition period (green bar), detailed information on this can be found on Sections 6.3 and 6.4.

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 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).



* Product is not in the scope of this AfA Dossier as substitution will be 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 successfully completed replacement projects.

** Transition due to existing contracts and / or replacement of complete IVD systems. For further details please see Sections 6.3 and 6.4.

Figure 12. Replacement timelines

For some assays, replacement is expected to be achieved before the sunset date. However, they are included in this dossier due to the shelf life of the products with OPnEO / NPnEO to allow remaining stocks to be used by customers until after the sunset date. More importantly, some technical or regulatory difficulties may occur, and the replacement may be delayed until after the sunset date. Two products, CC1 and DM1, have been substituted and shelf life of remaining stocks will expire before the 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 NPnEO-free assay is described, please refer to Section 6.3.

As shown in Figure 12, 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 close to 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.

6.1 Product Group 1: Clinical Chemistry

6.1.1 Steps and Time Required for Substitution

There are **three different cases** 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, and Table 9.

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

Table 7. Clinical Chemistry replacement plan (silent change, most tests)

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 preliminary manufacturing instructions	[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 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 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]
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 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

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 test (see Figure 12). As a result, the overall timeline for substitution for all CC assays that will undergo a silent change is estimated to be around 6 years (including use of old products by clients until end of shelf life).

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** **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: for one assay, CC8, not only the surfactant is being replaced, but the formulation is being changed to improve the overall performance of the test and therefore 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 this assay is being replaced, RDG will 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 (dotted green bar in Figure 12). During this time, production of the old product will continue. Once these [redacted] are over, the product containing OPnEO will no longer be produced, but clients may use their products stocks until end of shelf life (24 months).

Table 9. Clinical chemistry replacement plan for a test that requires re-registration (CC8)

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 alter-native 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 specificity, only for most critical specifications	[redacted]

Step	Substep	Details on required activities	Duration likely (and min-max)
	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. Deliverables required for re-submission of the formal change	[redacted]

Step	Substep	Details on required activities	Duration likely (and min-max)
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 authorities	CE market, 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 Market: conformity with health, safety, and environmental protection standards for products sold within the European Economic Area.; CFDA: Chinese Food and Drug Administration

6.1.2 Technical Feasibility Status and Replacement Schedule

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

Replacement for one assay (CC1) is already completed so that the use of all the remaining assays at customers will be achieved before the sunset date. The use of OPnEO in this assay and its formulation is therefore not covered any more 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 other 4 assays: CC2, CC3, CC5 and CC7. For CC6 there are three possible candidates and testing is ongoing to identify the best alternative.

The expected times of substitution in the formulation and / or products for CC2, CC3, CC5 and CC6 are between beginning of 2019 and end of 2019. In the case of CC2, even though a slight delay from the original timeline has occurred, the assay without NPnEO is expected to be launched in May 2019 but customers may potentially use the assay after the substitution is completed until end of 2021 due to shelf life. For CC5 and CC6, the resulting IVD assays are out of scope of this authorisation (not affected by Use 3) because the final product contains less than 0.1% OPnEO, and therefore shelf life does not need to be considered.

In the case of the assays CC7 and CC8, longer timelines than for the other assays in this group are expected (as already explained in section 6.1.1) due to the technical challenges on the detergent replacement (CC7) and time required for new registration in the required countries (CC8). The expected times of completion for CC7 including overlapping of old and new products in the market due to shelf life is end of June 2023 and is on plan with the original timeline. For CC8 launch in the EU is planned for [redacted], and registration is China is expected to be completed by [redacted] (delay of 12 months in comparison to the original timeline). After this, a period of [redacted] is needed to complete the change at the customers. This means that the change is expected to be finalised by mid-2024.

Some of these replacement projects are running according to plan and the substitution is expected to occur as depicted in Figure 12. There are however uncertainties linked to these replacement timelines (grey and light red bars in Figure 12). Should technical difficulties be encountered, or the very unlikely situation occur that changes cannot be performed as silent changes from a regulatory point of view, e.g. due to additional requirements by health authorities in different countries, complete substitution might be delayed until mid-2024 for CC3, or CC5 (see Figure 12). It could happen for example that at a later stage it becomes apparent (i.e. during verification) that a specific performance specification cannot be maintained with the selected alternative. In that case, a different alternative would have to be selected (2nd choice of feasibility) to repeat performance testing (this is actually the case for CC5 as of June 2018). If no surfactant can be found to maintain all performance characteristics the product needs 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). As of end of 2018, a delay of 18-24 and 12 months from the original timeline is expected for CC3 and CC5 respectively. This is due to unexpected performance issues discovered during verification of the assays. In the case of CC5 for example, a problem with the performance of the test formulated using the alternative surfactant was observed. A complex interaction with the preservative was determined to be the main cause. As a result, the preservative needs to be exchanged and verification needs to be repeated. This example illustrates the complexity of the interactions among all components in an IVD assay and shows why technical risks could delay the completion of the replacement projects. Moreover, as result of the technical difficulties encountered during the verification of some products, delays of up to 6 months are expected for other replacements projects due to resources constrains (this is the case for example for CC6 and CC8). In case of additional delays due to technical or regulatory difficulties, substitution for CC7 and CC8 might only be completed end of 2026.

6.2 Product Group 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). The bead production process is covered in Use 4 as the surfactants are used as processing aids in the production process (see AoA for Use 4). As the substitution process is strongly interlinked, 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. 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).

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)	
	Performance testing	• Precision tests • Stability tests • Functional tests (method comparison / clinical sensitivity / …)	
	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]
	Assay production in operations (1 batch)	• Latex bead production • Buffer for Integra and cobas® c formulation • Adjustment of the reagents (antibody and conjugate)	[redacted]

Step	Substep	Details on required activities	Duration likely
	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**

In case a re-registration is needed (Scenario C), the requirements on the feasibility and validation steps are higher and would require more time (see Table 11). An RDG-internal committee evaluates whether the substitution can be done as a major change or if a re-registration of the assays is required as a worst-case. Due to more extensive data requirements to verify and validate the performance of the assays the validation / verification step is expected to take [redacted] longer. The re-registration process would take [redacted] including preparation of the documents in comparison to [redacted] for a major change. Furthermore, approval by the regulatory authorities is needed and this also adds extra time. Therefore, the overall time required per assay is expected to be 8-10 years.

See a detail of the steps required for substitution in case Scenario C applies on Table 11.

Table 11. Drug Monitoring replacement plan for substitutions in case a re-registration 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 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 / …) • Cross reactivity • Interferences	[redacted]
	Real-time stability	• Check reagent stability	[redacted]
Validation / Verification	Assay production in operations (2 batches)	• Latex beads production • Buffer for Integra and cobas® c formulation • Adjustment of the reagents (antibody and conjugate)	[redacted]
	Verification measurements	• 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	Documents for registration	• Application report • Instruction for use • Etc	[redacted]

Step	Substep	Details on required activities	Duration likely
	New submission	• Globally per region	[redacted]
Introduction to the market	Replacement of old product by new generation	• Launch of new product	
Overall timeline for substitution per assay		Estimated completion date depends on the iterations needed to find the appropriate replacement.	**~7 years per assay**
Overall timeline for substitution of all assays (assuming some assays can be substituted in parallel, but for one or more assays a re-registration is needed)		**Comment:** **7 to 10 years are expected due to several risks and high complexity of the different assays.**	**7-10 years**

Technical feasibility status and replacement schedule

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

For this group of assays, alternatives have been identified (as of 1st of January 2018) for DM1 so that complete phase-out of the old assay at customers' will be completed before the sunset date. The use of NPnEO 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 or processes. Substitutions for DM3 and DM2 assays are already advanced so that replacement in production may be completed before the sunset date (see Figure 12).

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. In other cases, the internal process control of the manufactured assay was out of specification. Therefore, additional alternatives need to be evaluated and feasibility will require more time (6 to 12 extra months) than originally estimated.

A total of substitution time of 5 to 8 years for all assays is expected. Several assays are tested in parallel, but this number depends on the availably of qualified personal resources. Currently estimated completion date including replacement of existing products in the market is end of 2023. However, technical difficulties that require repetition of several steps in the process as described above may prolong this timeline by 12 months. Furthermore, in case a re-registration of the products is required, an estimated additional 24 months will be needed. Considering these risks, the substitution process for all 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 2026.

6.3 Product Group 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. In Figure 13 the estimated duration of the timeline for replacement of NPnEO in HIV combi PT is depicted. The blue bar shows the estimated duration of the internal feasibility and validation studies and the yellow bar the estimated duration of the external validation studies. After a period required to obtain the market authorisation by the regulatory authorities (dark grey bar), introduction to the market of the updated HIV combi PT assay (HIVcPT) would be estimated by Q4 of 2025. This timeline takes into account some technical and regulatory risks.

Figure 13. Estimated hypothetical timeline for replacement of NPnEO in HIVcPT

, 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 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 worldwide by new generation instruments (**cobas® e** 801 [redacted] After the introduction of the new generation instruments, an average of five years of support (that includes providing the HIV combi PT assay) is required [redacted] Therefore, these assays need to be on the market until [redacted] Even though a newer generation HIV assay (HIV Duo), which is OPnEO / 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 markets and costumers. A high-throughput analyser **cobas® e** 801, is already launched worldwide. However, the HIV Duo running on these analyser needs additional country specific approval supported by internal and external validation studies (as explained in the previous section). [redacted] launch of this product will depend on the approval [redacted] that impose a high level of regulations when it comes to HIV testing products. [redacted]

Despite the ongoing activities regarding new generation instruments, the HIV Duo is not a suitable alternative that can be implemented before the sunset date. Market authorisation will not be available for the new assay in all markets by the sunset date [redacted] Overall, it should be considered that >10'000 instruments are installed at customers worldwide and even when market authorisations have been received for all markets, >10'000 instruments cannot be replaced worldwide in a short timeframe.

In summary, authorisation is therefore needed to allow for the continued use of HIV combi PT on the older-generation instruments until all costumers 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. 4th of January 2028.

Figure 14. [redacted]

6.4 Product Group 4: Blood Gas and Electrolyte Analysis

6.4.1 Steps and Time Required for Substitution

The HB CALIBRATOR is needed for measuring haemoglobins and bilirubin on the cobas® b 221 system. If the HB CALIBRATOR could not be supplied any longer, then customers would not be able to use the cobas® b 221 system because it is required to determine all analytes from the same patient sample simultaneously.

The cobas® b 221 system and the corresponding HB CALIBRATOR is planned to be removed from the European market, i.e. support is planned to end by [redacted] because of the new IVD regulation (IVDR)[8] and REACH regulations.

Replacement of the cobas® b 221 systems on the market by an alternative system, cobas® b 123 POC, is not feasible because the cobas® b 123 POC system is not directly equivalent to the cobas® b 221 system. The cobas® b 123 POC system addresses needs in premium market segments requiring ease of use and low maintenance, whereas the cobas® b 221 system is typically used in settings with a larger number of samples per day. It is expected that [redacted] of the customers could be switched to cobas® b 123 POC. This, however, would not be feasible before the sunset date based on RDG's obligations from existing contracts for cobas® b 221. Furthermore, there may be an interruption of diagnostic services for patients in emergency settings as it will take time for all customers to install a new system. In order to allow customers to identify suitable alternative systems based on their needs, HB CALIBRATOR needs to be supplied until the planned date of removal from the market. In addition, contractual penalties and compensation claims would have to be paid by Roche if cobas® b 221 systems had to be removed before existing contracts end. Interruption of the cobas® b 221 system sales and support before the planned date of removal from the market [redacted] would lead to a loss of [redacted] of the cobas® b 221 system business in the EEA market. For further details on social and economic impacts and customers claims, please see the SEA, Section 3.3 and 3.4.

6.4.2 Technical Feasibility Status and Replacement Schedule

The activities for replacing OPnEO in the HB CALIBRATOR had started in 2016. Feasibility for a replacement material compatibility and wetting compatibility could be demonstrated. Preliminary analytical performance could also be demonstrated. After stability verification, implementation in production and change registration in China would be required. It is estimated that the overall time needed for substitution would be 5 to 7.5 years. However, since the cobas® b 221 system and the corresponding HB CALIBRATOR is planned to be removed from the European market by [redacted], the replacement of OPnEO in HB CALIBRATOR was stopped. It is economically not viable to replace OPnEO in the HB CALIBRATOR before removal from the market of the cobas® b 221 system because of the large efforts involved in verification (including potential technical risks), implementation in production and change registration in China. Furthermore, it is not certain that replacement would even be completed before the removal of the system from the market.

Note: As previously mentioned in Section 3.3.4, OPnEO and NPnEO are also present in concentrations below 0.1% w/w in other BGE solutions and electrodes produced in Switzerland. They are therefore not in the scope of this AfA. However, their production will be subject to authorisation requirements in Switzerland as soon as OPnEO and NPnEO have been added to the respective list in Swiss legislation.

6.5 Product Group 5: Accutrend®

6.5.1 Steps and Time Required for Substitution

The expected scenario for this replacement is A (silent change). Therefore, there is no need to request market approval or authorisation. The required steps for substitution are detailed in Table 12. Although replacement is planned to be finished before the sunset date, authorisation is required in case an unexpected delay due to technical difficulties or failure to complete the validation in the planned timeframe occurs and the replacement cannot be completed on time.

Table 12. Replacement Plan for Accutrend®

Step	Substep	Details on required activities	Duration likely (and min-max)
Feasibility	Feasibility (laboratory scale)	Literature research on substitution candidates Laboratory scale production of control solution Testing on detection systems	[redacted]
	Feasibility (small scale production)	Small scale production of solutions Testing on detection systems Accelerated stability testing ([redacted])	[redacted]
	Verification (production machine)	Production of control solution on production machine Testing of process robustness Testing on exemplary detection systems Accelerated stability testing ([redacted])	[redacted]
Validation / Verification	Preparation of validation	Qualify new raw materials (specification, routine testing, material numbers…) Risk analysis Validation plan including all critical process steps and testing	[redacted]
	Process validation	1-3 lots including performance testing	[redacted]
	Stability assessment	1-3 lots in real-time stability testing	[redacted]

Step	Substep	Details on required activities	Duration likely (and min-max)
Regulatory approval / market authorisation	Not needed		
Introduction to the market	Replacement of OPnEO / NPnEO containing products		1.5 years replacement due to shelf-life
Overall timeline for substitution			**56 months (likely) 61 months (max) (4.6-5 years)**

6.5.2 Technical Feasibility Status and Replacement Schedule

The substitution process for the AT assay has started in July 2016.

The alternative has already been identified (see Table 4). Validation is ongoing. If no unexpected delay occurs and the control solution fulfils the validation criteria, replacement is planned to be finished by Q3 2019. To this, 18 months have to be added during which the old product would still be used by the costumers due to shelf life, leading to a complete replacement by end of Q1 2021 (slightly over the sunset date). However, if technical difficulties occur, this date could be delayed by up to 24 months (see also Figure 12).

6.6 Product Group 6: Urinalysis

6.6.1 Steps and Time Required for Substitution

The expected scenario for this replacement is A (silent change). Therefore, there is no need to request market approval or authorisation. The required steps for substitution are detailed in Table 13. Although replacement is planned to be finished before the sunset date, authorisation is required in case an unexpected delay due to technical difficulties or failure to complete the validation on the planned timeframe occurs and the replacement cannot be completed on time.

Table 13. Replacement plan for Urinalysis assuming a silent change

Step	Substep	Details on required activities	Duration likely (and min-max)
Feasibility	Feasibility (laboratory scale)	Literature research on substitution candidates Laboratory scale production of test strips Testing on exemplary detection systems	[redacted]
	Feasibility (small scale production)	Small scale production of test strips Testing on exemplary detection systems Accelerated stability testing [redacted])	[redacted]
	Verification (production machine)	Production of test strips on production machine Testing of process robustness Testing on exemplary detection systems Accelerated stability testing ([redacted])	[redacted]

Step	Substep	Details on required activities	Duration likely (and min-max)
Validation / Verification	Preparation of validation	Qualify new raw materials (specification, routine testing, material numbers…) Risk analysis Validation plan including all critical process steps and testing	[redacted]
	Process validation	1-3 lots including performance testing	[redacted]
	Stability assessment	1-3 lots in real-time stability testing	[redacted]
Regulatory approval / market authorisation	Not needed		
Overall timeline for substitution			**47 months (likely)** **61 months (max)** **(3.9-5 years)**

6.6.2 Technical Feasibility Status and Replacement Schedule

The substitution process for the UA assay has started in July 2016.

The alternative has already been identified (see Table 4). Validation is ongoing. If no unexpected delay occurs and the test strips fulfil the validation criteria, the replacement is planned to be finished by end of Q3 2020. To this, up to 24 months have to be added during which the old product would still be used by the costumers due to shelf life (shelf life varies from 15 to 24 months depending on the package size and the composition of the strip), leading to a complete replacement at customers by mid-2022. However, if technical difficulties occur, this date could be delayed by up to 24 months. Moreover, for this assay, there is still a risk that a re-registration has to be requested. This adds a further uncertainty to the replacement timeline and in worst-case, replacement would only be completed by end of Q3 2025 (see also Figure 12).

6.7 Product Group 7: Subgroup RMD1

6.7.1 Steps and Time Required for Substitution

The expected scenario for this change is C (re-registration), a new version of the assay [redacted] is being developed. The OPnEO substitution will be included in the new version submission.

The required steps for substitution are listed in Table 14. Although replacement is planned to be finished before the sunset date, authorisation is required in case an unexpected delay due to technical difficulties or failure to complete the validation in the planned timeframe occurs and the replacement cannot be completed on time.

Table 14. Replacement plan for RMD1

Step	Substep	Details on required activities	Duration likely (and min-max)
Feasibility	Feasibility	Complete feasibility studies with new assay design and chemistry without OPnEO or use any other substitute. Check stability of Reagents	[redacted]
Validation / Verification	Preparation of validation	Full Technical Performance Verification studies with new design	[redacted]
	Process validation	Test method and Process validation at manufacturing site	[redacted]
	Clinical validation	Clinical validation studies	[redacted]
Regulatory approval / market authorisation	CE Market authorisation	CE Market	[redacted]
	USA Market authorisation	FDA 510(k) Clearance and CLIA Waiver*	[redacted]
Introduction to the market	Replacement of Obsolete existing assay in the market		18 months replacement due to shelf-life
Overall timeline for substitution			**55-69 months (4.6-5.8 years)**

* Clearance means that the product has approval from the FDA to market in US. 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.

6.7.2 Technical Feasibility Status and Replacement Schedule

The substitution process for RMD1 has started in July 2017.

Feasibility studies for new assay are ongoing. Three possible alternatives have been proposed based on Roche manufacturing inventory (use history and availability), degree of ethoxylation and preliminary functional performance assessment tests (see Table 4). Validation / verification studies are planned until [redacted]. Clinical validation studies are planned [redacted]. The OPnEO-free assay if no technical difficulties arise is planned to be available in 2021. Replacement of existing assay in the market should then be completed by end of Q3 2022. As of end of 2018, the estimated probability of completing the replacement in the planned timeframe is 90%. However, there is still a possibility that if unexpected technical or regulatory delays occur, the process might only be completed up to two years later (see Figure 12).

6.8 Product Group 7: Subgroup RMD2

6.8.1 Steps and Time Required for Substitution

The expected scenario for this replacement is A (minor change). Therefore, there is no need to request market approval or re-registration. The required steps for substitution are listed on Table 15. Although many replacement steps are planned to be finished before the sunset date, authorisation is required for clinical validations, subsequent regulatory and market approvals, and in case an unexpected delay due to technical difficulties or failure to complete the validation in the planned timeframe occurs, and the replacement cannot be completed on time.

Table 15. Replacement plan for RMD2

Step	Substep	Details on required activities	Duration likely (and min-max)
Feasibility	Surfactant preselection	Literature research on substitution candidates Laboratory scale production of control solution Testing on detection systems	[redacted]
	Stability of reagent bulk solution with alternative surfactant	Stability of substrate must be monitored in both bulk form and kitted (in blister format) form at 2-8C.	[redacted]
	Feasibility Studies	Complete feasibility studies with new assay design and chemistry without OPnEO.	[redacted]
	Internal Study with Clinical Specimens	Study to determine feasibility sensitivity and specificity with prospectively collected nares specimens. Total of 650 specimens.	[redacted]
Validation / Verification	Preparation of validation	Full Technical Performance Verification studies with new design	[redacted]
	Process validation	Test method and Process validation at manufacturing site	[redacted]
	Clinical validation	Clinical validation studies	[redacted]
Regulatory approval / market authorisation	CE Market authorisation	CE Marking*	[redacted]
	USA Market authorisation	FDA 510(k) Filing and Review**	[redacted]

Step	Substep	Details on required activities	Duration likely (and min-max)
Introduction to the market	Replacement of obsolete existing assay in the market		18 months (shelf life)
Overall timeline for substitution			**52-72 months (4.3-6 years)**

* CE marking is a certification mark that indicates conformity with health, safety, and environmental protection standards for products sold within the European Economic Area
** FDA 510(k) Clearance means that the product has approval from the FDA to be marketed in US. It is requested for updating market authorisation of products that are already on the market.

6.8.2 Technical Feasibility Status and Replacement Schedule

The substitution process for RMD2 has started in July 2017.

As of 01.06.2018 surfactant preselection has been completed. Two alternatives have been identified based on Roche manufacturing inventory (use history and availability), degree of ethoxylation, and preliminary functional performance assessment tests (see Table 4). Feasibility tests using these alternatives are ongoing. Validation and verification studies are planned until [redacted]. Clinical validation studies are planned [redacted]. Replacement of the assay with of the OPnEO-free assay is planned to be completed in 2021 / 2022 (including replacement of existing assay in the market). As of end of 2018, the likelihood of finishing the replacement in time is high.

The major factors influencing the time required are optimisation of the assay chemistry to meet the required claims and availability of clinical specimens. A large number of clinical specimens must be collected for the validation tests to have statistical significance and clinical specimens for this test are only stable for 16 hours, reducing the amount of specimens that can be processed at one time. This might increase the time needed for validation and verification.

6.9 Product Group 8: Roche Tissue Diagnostics

6.9.1 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).

Table 16. 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]
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	USA market approval	Report to FDA impacted PMA products and receive authorization 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)**

6.9.2 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, [redacted]. Currently three concentrations of the alternative in the affected buffer are being tested in ongoing stability studies.

The major factor influencing the time required to complete the substitution is the availability of tissue samples. Tissue testing with enough tissue cases is necessary to statistically analyse the impacted ISH products. This is necessary to assess whether candidate substitutes can be used as replacement of the OPnEO based on impact to performance and real-time stability testing.

Stability testing is expected to be completed by Q1 2020 (95% confidence this will be successfully completed). Distributed product will expire by Q1 2022 (due to shelf life). However, as customers usually have stocks of this product for less than one year, it is likely that few products will remain at customers at the sunset date.

However, if there is any problem with the feasibility studies for the alternative currently being tested, a new alternative has to be tested and this could add up to 36 months to the replacement timeline.

6.10 Costs of the Substitution

RDG's R&D department is currently working on the complete substitution of OPnEO / NPnEO in Use 2&3. RDG 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 17 considering the likely and worst-case scenario regarding regulatory requirements for substitution which are an important driver for cost. A re-registration to obtain market authorisation represents the worst-case scenario due to the additional costs of a re-registration. Total investment cost for the likely scenario is ca. [redacted] mio EUR for the products covered under Use 2&3. The main cost driver are the additional regulatory requirements in case of a re-registration. These requirements directly translate into 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 required. Should re-registrations be required, this could be more than twice as high. The cost includes cost for the required personnel to perform the projects or the clinical studies (e.g. for HIV).

Table 17. Substitution: investment costs including cost for required personnel.

Use	Product group	Cost (mio EUR)	
		Likely scenario	Worst-case scenario*
Use 2&3 Use 4	CC	[redacted]	[redacted]
	DM (incl. process group 3)	[redacted]	[redacted]
Use 2&3	HIV	[redacted]	[redacted]
Use 3	BGE[c]	[redacted]	[redacted]
Use 2&3	AT	[redacted]	[redacted]
Use 2&3	UA	[redacted]	[redacted]
Use 3	RMD1	[redacted]	[redacted]
	RMD2		
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]
[c] Due to phase-out of the affected product based on existing contracts, no additional cost for substitution project.
[d] Cost for likely and worst-case are the same re-registration is needed for these products (AT under Use 2&3).

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 **tenth year running**.

Since 2015, RDG, as part of the Roche group, has a public company-wide commitment[8] 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 AoAs of an additional AfA submitted by RDG. 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 [9].

In 2018[10], for the tenth consecutive 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.

[8] 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.
[9] Roche Website: 'Sustainable development goals': https://www.roche.com/sustainability/un-sdgs.htm
[10] Roche Website: 'Media Release': https://www.roche.com/media/releases/med-cor-2018-09-13.htm

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.

Many of these replacement projects are currently on track and are expected to be completed on time with a high likelihood (e.g. RTD and some CC assays). For some CC and 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 two assays that employ a small portion of the overall amount of OPnEO / NPnEO, different alternatives are being implemented.

In one case, the HIV combi PT assay, substitution with an alternative product will be pursued. The new HIV generation Elecsys® HIV Duo which was launched April 2017 in the EU already reflects the REACH regulation aspect and uses a surfactant with no concerns. The old IVD systems are being replaced with new generation systems with a NPnEO-free assay of increased sensitivity and specificity that runs on these new systems. The new generation systems have already been developed and are being introduced stepwise to the market. The time required to finalise the necessary tests and obtain market authorisation from the different health authorities is however much longer, since IVD products used for HIV detection are more highly regulated that other IDV assays. Market authorisation will not be available for the new instruments and assays in all markets by the sunset date. Furthermore, introduction to the market is much longer than for a substitution of the surfactant since a high number of instruments needs to be replaced worldwide. In this case, it is expected that the complete instrument replacement process can only be finalised ca. 7 years after the sunset date. During this period, the old assay needs to be produced to allow for the continued use of the old systems until replacement is complete at all customers.

In one other case, BGE, support for the cobas® b 221 system will end by [redacted]. Replacement of OPnEO in the HB CALIBRATOR before removal of the market of the cobas® b 221 system may not be possible due to the time required and is not economically viable because of the large efforts involved in verification (including potential technical risks), implementation in production and change registration in China. Roche can provide an alternative system to a part of his clients, but this system is not suitable for all laboratory settings. Due to contractual obligations and to ensure

availability of IVD assays for Blood Gas and Electrolyte measurements, the cobas® b 221 system HB CALIBRATOR needs to be supplied until the planned date of removal from the market. This will allow customers to replace their instruments with an alternative provided by Roche or to identify a new suitable alternative system based on their needs.

Without an authorisation RDG would need to stop the production of many IVD products for years. IVD products used for diagnosis of certain diseases, therapy monitoriang or drug abuse detection could not be supplied any more. This would cause unacceptable impacts on patients and the healthcare system as detailed in the SEA.

RDG therefore applies for an authorisation to gain more time for the necessary evaluations and regulatory approvals based on IVD regulations, and where needed, the introduction of alternative IVD systems to the market. Based on the status of the substitution projects and the timeline foreseen for their successful completion, RDG hereby applies for a review period of 7 years.

Authorisation for the use of OPnEO / NPnEO for 7 years after the sunset date 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.

6 REFERENCES

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[6] ECHA. Database of the registration dossiers. Version: October 2018. https://echa.europa.eu/de/information-on-chemicals
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[11] Human & Environmental Risk Assessment on ingredients of European household cleaning products (HERA). Alcohol ethoxylates. Version 2.0, September 2009.
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APPENDIX I – ASSAYS INCLUDED IN THIS APPLICATOPN FOR AUTHORISATION

Product name	Use	Product Group
ALB_BCG	2&3	Clinical Chemistry (CC)
BILT3		
LDLC3		
CREP	2	
CRP		
Glucose hemolysis reagent		
AMPS2	2	Drug Monitoring (DM)
BARB BENZ Plus COC2 MDN2 PCP TMPA	2&3	
LSD MTQL PPX	3	
Elecsys® HIV combi PT	2&3	HIV
Hb-Calibrator	3	Blood Gas and Electrolyte (BGE)
Accutrend® Cholesterol Control	2&3	Accutrend® (AC)
Combur and Chemstrip portfolio, cobas u pack and IDEXX strips	2&3	Urinalysis (UA)
cobas® Influenza A/B test	3	Roche Molecular Diagnostics (RMD)
cobas® vivoDx MRSA		
10X SSC Sodium Chloride Sodium Citrate Buffer	3	Roche Tissue Diagnostic (RTD)