SOCIO-ECONOMIC ANALYSIS

Legal name of applicant(s): Roche Diagnostics Limited

Submitted by: Roche Diagnostics Limited

Substance:

1) 4-(1,1,3,3-tetramethylbutyl)phenol, ethoxylated (covering well-defined substances and UVCB substances, polymers and homologues) also called 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); NPnEO;

Use title: Use 3: Use of Octyl- and Nonylphenolethoxylates in *in vitro* diagnostic (IVD) assays specified in Appendix 1 to the AoA

Use number: 3

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GLOSSARY

Term	Explanation
AA-EQS	Annual average environmental quality standard
ACS	American Chemical Society
AfA	Application for Authorisation
AIDS	Acquired Immunodeficiency Syndrome
AoA	Analysis of Alternatives
BILT3	Bilirubin Total Gen 3
BIVDA	The British In Vitro Diagnostics Association
CAGR	Compound Annual Growth Rate - the mean annual growth rate of an investment over a specified period of time longer than one year.
CC	Clinical chemistry is a diagnostic method which tests for various components of blood and urine and enables healthcare professionals to overview significance of abnormal values. CC portfolio are part of the Serum Work Area.
CE mark	CE marking proves that your product has been assessed and meets EU safety, health and environmental protection requirements
CEC	Corporate Executive Committee
CESIO	Comité Européen des Agents de Surface et de leurs Intermédiaires Organiques - European Committee of organic surfactants and their organic intermediates
CFDA	China Food and Drug Administration
CH	Switzerland
CHF	Swiss francs
CLIA Waver	CLIA waiver means that this product is waived from Clinical Laboratory Improvement Amendments (CLIA) regulations that regulates laboratory testing and therefore do not require clinical laboratories certification by a state as well as the Centre for Medicare and Medicaid Services (CMS) before they can accept human samples for diagnostic testing.
CLP	European Union regulation, which aligns the EU system of classification, labelling and packaging of chemical substances and mixtures. The EU CLP Regulation as amended is retained in the UK law under the SI 720 of 2019.

Term	Explanation
CMC	Critical micelle concentration
cobas®	Trade name of Roche diagnostic instrument
COVID-19	**Co**rona**vi**rus **D**isease 20**19**
CPS	Centralised & Point of Care (CPS) is the largest business area of Roche Diagnostics. It is a leading supplier of solutions, instruments, tests, software and services for small- to mid-size and large-size commercial and hospital labs and laboratory networks.
CSF	Cerebro Spinal Fluid is a clear, colourless body fluid found in the brain and spinal cord.
CSR	Chemical Safety Report
DIG	Digoxigenin
DJSI	Dow Jones Sustainability Indices. Indices evaluating the sustainability performance of thousands of companies trading publicly and a strategic partner. This is based on an analysis of economic, social and environmental performance of the company. The DJSI family of indices serves as a benchmark for investors who integrate sustainability considerations into their portfolios
DM	Drug Monitoring, that is included in Clinical Chemistry, specializes in the measurements of levels of therapeutic drugs or narcotic drugs.
DNA	Deoxyribonucleic acid (contains the genetic code of organisms)
DNP	Dinitrophenyl
EBITA	Earnings Before Interest, Taxes, Depreciation, and Amortisation It is an accounting measure calculated using a company's net earnings, before interest expenses, taxes, depreciation, and amortisation 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

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

Term	Explanation
ICU	Intensive care units
IHC	Immunohistochemistry
Ig	Immunoglobulin
IPC	In-Process Control
ISH	*In situ* hybridisation which is a technique for identifying specific DNA or RNA sequence or portion within individual cells in tissue sections, providing insights into physiological processes and disease pathogenesis
IT	Information technology
IVD	*In vitro* diagnostic medical devices. IVD products are regulated and defined by the UK Medical Devices Regulations 2002 (as amended) (S.I. 618 of 2002) as a medical device which is a reagent, reagent product, calibrator, control material, kit, instrument, apparatus, equipment, or system, whether used alone or in combination, and intended by the manufacturer to be used in-vitro for the examination of specimens, including blood and tissue donations derived from the human body, solely or principally for the purpose of providing information: ▪ concerning a physiological or pathological state, or ▪ concerning a congenital abnormality, or ▪ to determine the safety and compatibility of donations, including blood and tissue donations with potential recipients, or ▪ to monitor therapeutic measures; and includes a specimen receptacle but not a product for general laboratory use, unless that product, in view of its characteristics, is specifically intended by its manufacturer to be used for in vitro diagnostic examination.
IW	Industrial worker
LAD	Latest Application Date
LDLC	Low density lipoprotein cholesterol, commonly referred to as “bad cholesterol”
log Koc	Organic Carbon-Water Partitioning Coefficient
MAC-EQS	Maximum allowable concentration environmental quality standard

Term	Explanation
MD	Molecular Diagnostic
MDR	Medical Device Regulations
MDROs	Multidrug-resistant organisms
MHRA	Medicines and Healthcare products Regulatory Agency in UK which regulates medicines, medical devices and blood components for transfusion. It is an executive agency, sponsored by the Department of Health and Social Care
MLS	Managed Laboratory Services
NAD	Nicotinamide Adenine Dinucleotide
NHS	National Health Service
NICE	National Institute of Health and Care Excellence
NOEC	No Observed Effect Concentration
Non-EEA	All countries outside the European Economic Area (EEA).
NP	4-nonylphenol, branched and linear
NP1EC	4-nonylphenoxyacetic acid
NP1EO	Nonylphenolmonoethoxylate
NP2EC	4-nonylphenoxyethoxyacetic acid
NP2EO	Nonylphenoldiethoxylate
$NP_{equiv.}$	4-nonylphenol Equivalent
NPnEO	4-nonylphenol, branched and linear, ethoxylated (substances with a linear and / or branched alkyl chain with a carbon number of 9 covalently bound in position 4 to phenol, ethoxylated covering UVCB- and well-defined substances, polymers and homologues, which include any of the individual isomers and / or combinations thereof), 4-NPnEO [Corresponding to entry 43 of Annex XIV of the REACH regulation as defined in regulation 2017/999/EU and entry 43 of Annex 14 of the UK REACH regulation]

Term	Explanation
NPV	Net Present Value It is a measurement of profit calculated by subtracting the present values (PV) of cash outflows (including initial cost) from the present values of cash inflows over a period of time. Incoming and outgoing cash flows can also be described as benefit and cost cash flows, respectively.
OC	Operational conditions
OEM	Original Equipment Manufacturer
OP	4-(1,1,3,3-tetramethylbutyl)phenol (4-tert-OP)
OP1EC	4-octylphenoxyacetic acid (4-tert-OP1EC)
OP2EC	4-octylphenoxyethoxyacetic acid (4-tert-OP2EC)
$OP_{equiv.}$	4-(1,1,3,3-tetramethylbutyl)phenol Equivalent
OPnEO	4-(1,1,3,3-tetramethylbutyl) phenol, ethoxylated (covering well-defined substances and UVCB substances, polymers and homologues), 4-tert OPnEO [Corresponding to entry 42 of Annex XIV of the REACH regulation as defined in regulation 2017/999/EU and entry 42 of Annex 14 of the UK REACH regulation]
OSH	Occupational safety and health
PBT	Persistent, Bioaccumulative and Toxic
PC	Article categories
PCR	Polymerase Chain Reaction It is a technique used in molecular biology to amplify a single copy or a few copies of a segment of DNA across several orders of magnitude, generating thousands to millions of copies of a particular DNA sequence.
PEC	Predicted environmental concentration
PMA	Pre-Market Approval
PNEC	Predicted no-effect concentrations
PP	Protein production processes
PPE	Professional protective equipment
PRO	Test-strips containing one field

Term	Explanation
PROC	Process category
PVDF	Polyvinylidene fluoride
PW	Professional worker
Q1, Q2, etc.	Quartal 1, Quartal 2, etc.
QALY	Quality adjusted life year
QC	Quality Control
QSAR	Quantitative structure activity relationship
R&D	Research and Development
RAC	Committee for Risk Assessment
RDG - Roche Diagnostics GmbH	Part of the Diagnostic Division of F. Hoffmann-La Roche Ltd. Roche Diagnostics GmbH (RDG) has an extensive portfolio, one aspect of which is the manufacturing of instrument platforms and reagents for the different Roche affiliates worldwide. It is located in Germany (Mannheim and Penzberg).
RDL	Roche Diagnostics Limited (RDL) is the Roche affiliate in the UK selling Roche's IVDs in the UK.
RDUK	All Roche affiliates in the UK.
REACH	Regulation on Registration Evaluation, Authorisation and Restriction of Chemicals European Regulation (EC) No 1907/2006 The EU regulation as amended is reflected in the UK REACH under the SI 758 of 2019. UK REACH is a regulation that applies to the majority of chemical substances that are manufactured in or imported into Great Britain (GB) (England, Scotland, Wales).
RMMs	Risk Management measures
RNA	Ribonucleic acid (contains the genetic code of some viruses, for example HIV)
Roche	F. Hoffmann-La Roche Ltd. and its affiliates are collectively referred to as 'Roche'
RTD	Roche Tissue Diagnostics is a business area of Roche Diagnostics. It is the world's leading supplier of tissue-based cancer diagnostics. Its instruments and reagent systems are used in histology, cytology and drug discovery laboratories worldwide.

Term	Explanation
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 UK REACH
SWA	Serum work area is a segment of Centralized & Point of Care (CPS), which is characterised by modular instruments. This includes immunoassays, Clinical Chemistry, and Drug Monitoring.
TMPA	Total Mycophenolic Acid
TPA	Tripropylamine
UK RP	UK Responsible Person
UN	United Nations
UVCB	Substance of Unknown or Variable composition, Complex reaction products or Biological materials
US	United States
VLDL	very low-density lipoproteins
VOLY	Value of a Life Year Lost
vPvB	very Persistent very Bioaccumulative
VSCC	Value of a Statistical Case of Cancer
VSL	Value of a Statistical Life

Term	Explanation
WCS	Worker Contributing Scenario
WHO	World Health Organisation
£	British pound sterling

DECLARATION

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

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

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

Catherine Pawan, Director of Legal & Compliance

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

Amanda Walker, Director of Quality & Regulatory Affairs

1. SUMMARY OF SOCIO-ECONOMIC ANALYSIS (SEA)

The applicant for authorisation application is Roche Diagnostics Limited (RDL), a UK-based affiliate company of F. Hoffmann-La Roche Ltd. (collectively hereinafter referred to as "Roche"), which is the leading company in the *in vitro* diagnostic (IVD) market in Europe and worldwide. The current SEA was developed to support RDL's application for authorisation to continue the use of two groups of substances octylphenolethoxylates (OPnEO) and nonylphenolethoxylates (NPnEO) in the UK after the sunset date until complete substitution.

UK Registration, Evaluation, Authorisation and Restriction of Chemicals (UK REACH) has been implemented based on the European Regulation on Registration Evaluation, Authorisation and Restriction of Chemicals (European Regulation (EC) No 1907/2006) (EU REACH) including the Annex XIV entries. The group of substances included in this SEA are therefore also listed in Annex 14 of UK REACH in entries 42 (OPnEO) and 43 (NPnEO). As an European Union (EU) application for authorisation for the same use for these substances was submitted to European Chemical Agency (ECHA) before the latest application date (LAD) of the 4th of July 2019, Article 127GA of UK REACH extends the UK LAD/sunset date to the 30th of June 2022. Since the requirements for authorisation under UK REACH were adopted from the EU, the same approach as for the EU dossier is used in this application. Reference is made where applicable to EU requirements and guidance documents.

RDL, as part of the Roche Group is publicly committed to substituting any Substances of Very High Concern (SVHC) from their products if technically possible. RDL is applying for an authorisation to use OPnEO and NPnEO to maintain its current business in the UK and to be able to continue delivering healthcare services to patients via their customers in a reliable way.

This SEA, as a part of an authorisation application, has analysed all the relevant impacts expected in the 'non-use' scenario both from the applicant's and societal perspective. OPnEO and NPnEO are used in a wide array of IVD assays. For the EU application for authorisation, Roche Diagnostics GmbH (RDG) as an applicant identified three distinct uses within Roche Diagnostics Division and one further use was identified in the Roche Pharmaceuticals Division. For RDL, only Use 3, the use of OPnEO / NPnEO in IVD assays is relevant. Therefore, this application refers only to the 'Use of Octyl- and Nonylphenolethoxylates in in vitro diagnostic (IVD) assays specified in Annex 1 to the Analysis of Alternatives (AoA)'. For easy reference, the nomenclature 'Use 3' is kept in this dossier even though only one use is applied for. Please note that some product groups (Roche Molecular Diagnostics, Urinalysis and Accutrend) that were covered in Use 3 of the EU application for authorisation (AfA) are not covered in this application as OPnEO / NPnEO is replaced or they are not sold anymore. Further, some products of the product groups Clinical Chemistry (CC) and Drug Monitoring (DM) are not covered in this application because they do not fall under obligation for authorisation or because OPnEO or NPnEO have already been replaced. Overview of the uses covered in the EU application of authorisation and the use relevant for this AfA is provided in the table below (Table 1). Please note that the use applied for in this authorisation dossier is depending on RDG receiving the EU authorisation, in particular for Use 2, for actually producing the assays.

Table 1. Uses overview

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** **Only use relevant for RDL in the UK**	**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 (QC) products and other, e.g. analytical applications (processes specified in Annex 1 to the AoA)

In the 'non-use' scenario, RDL will not be able to continue supplying the affected IVD assays to the downstream users in the UK. This means laboratories and hospitals will not be able to use certain IVD assays and will thus **not be able to provide complete healthcare services to patients**. RDL's import into the UK of IVD assays will need to be interrupted until the necessary steps to switch to an alternative surfactant at the production site (in Europe) are completed, including – where required – adapted or new registrations with health authorities. In one case, the switch would need to be made to an alternative product instead of an alternative surfactant. An **interruption of the supply of the products is expected until substitution will be completed.**

The most important impacts will be the social impacts related to the temporary unavailability of IVD assays. This will result in a **temporary lack of healthcare services for patients** and an associated **increase in healthcare costs of >> [redacted] (10 – 50) mio £**. More than one million patients are expected to face a temporary lack of healthcare services over at least 1-2 up to 5.5 years after the sunset date. Not being able to supply the affected products will disrupt services for patients and will be associated with an **important loss of customer trust and reputation.** The loss of Earnings Before Interest, Taxes, Depreciation, and Amortisation (EBITA) for Roche / RDL over the course of the review period is estimated to range between [redacted] and [redacted] (1 – 50) mio £. Additionally, cost for customers (i.e.

laboratories and hospitals) and therefore ultimately the healthcare system based on Roche's inability to supply assays could amount as a minimum to an estimated [redacted] (1 – 200) mio £ depending on the scenario. Especially large investment will be needed under Scenario 1 when all customers would switch to competitor systems. Maximum cost cannot be quantified, but cost are in any case expected to represent a high burden to the healthcare system. In some cases, RDL may be liable to indemnify customers for the financial losses, or customers may be able to claim for breach of contract from RDL. The cost for mitigation measures would then represent an additional economic loss to RDL.

As shown in the Chemical Safety Reports (CSR), emissions will be reduced by **completion of substitution projects** over the course of the review period and will be fully eliminated by the end of the review period. It should be emphasized that in the past 6 years a large substitution effort has already been made and emissions of OPnEO / NPnEO have already been substantially reduced. For example, the number of assays containing OPnEO / NPnEO has already been reduced from 19 in 2019 (when the EU dossier was prepared) to 10 in the current dossier. Considering the implemented Risk Management measures (RMMs) and depending on the completion of substitution (i.e. on time or delayed until the end of the review period), total releases will range from 20.4 – 44.8 kg 4-(1,1,3,3-tetramethylbutyl)phenol Equivalent ($OP_{equiv.}$) and 0.04 – 0.06 kg 4-nonylphenol Equivalent ($NP_{equiv.}$) for surface water and 17.0 – 37.3 kg $OP_{equiv.}$ and 0.12 – 0.17 kg $NP_{equiv.}$ as a maximum for soil over the 5.5 years of the review period. As it is highly unlikely that all substitutions are delayed until the end of the review period, the risk that releases will reach the maximum is very low.

Any further RMMs are not technically and practically feasible. At laboratories and hospitals additional RMMs are not feasible within a reasonable time frame to effectively reduce emissions. The majority of emissions is likely to be already eliminated within 3 years after the UK sunset date.

Based on the combined impacts assessment, **the ratio of minimal societal cost** (in terms of increased healthcare costs) per kg 4-(1,1,3,3-tetramethylbutyl)phenol (OP) or $NP_{equiv.}$ emitted are expected to be **much larger than 0.3 – 1.3 mio £ / kg.**

Consequently, it can be concluded with high certainty that the socio-economic benefits of continued use of OPnEO / NPnEO associated with Use 3 outweigh the remaining risks to the environment.

The environmental risks cannot be monetised, but emissions of OPnEO / NPnEO are minimised as far as technically and practically feasible.

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

A **5.5-year review period** will allow Roche to complete the evaluation of alternatives, validate and assure performance of the affected products, and if necessary, submit change notifications as a regulatory requirement for *in vitro* diagnostic assays. More than one million patients in the UK

depend on the accurate, reproducible and reliable results of these assays. Roche and RDL are committed to **substitute OPnEO / NPnEO as fast as possible for each individual product**. However, Roche and RDL have concluded **that any review period shorter than 5.5 years** would not be sufficiently long for completing the substitution of OPnEO and NPnEO in all products.

In summary, RDL is applying for an authorisation to continue the use of OPnEO and NPnEO in accordance with Article 127GA of UK REACH for the following reasons:

1) The **releases of OPnEO and NPnEO are minimised as far as technically and practically feasible**,

2) RDL's IVD assays containing OPnEO / NPnEO have an **unquestionable social value** and

3) **5.5 years** are needed for replacement of OPnEO / NPnEO in all products due to high quality and regulatory requirements for IVD assays.

2. GENERAL INTRODUCTION

The aim of this section is to introduce the applicant and illustrate the principle of *in vitro* diagnostics (IVD).

2.1. Presentation of the Company

- ⇨ **F. Hoffmann-La Roche Ltd. (Roche)** is a Swiss multinational healthcare company.
- ⇨ **Roche Diagnostics Limited (RDL)** is an affiliate of **Roche in UK. RDL is responsible for sales of Roche products in the UK**.
- ⇨ Roche offers the industry's broadest range of *in vitro* diagnostic solutions.

Founded in 1896, Roche is a Swiss multinational healthcare company that, together with its affiliates, works worldwide under three different main divisions: Pharmaceuticals, Diagnostics and Diabetes Care. The Roche group headquarters is located in Basel, Switzerland. In 2021, the Roche group employed 100'920 people[1] worldwide (i.e. number of employees expressed in **full-time equivalents (FTEs)**), invested 11.0 billion British pound sterling (£)[2] in research and development (R&D), and posted sales of 50.2 billion £[2].

The products are produced at different legal entities, among them RDG, the applicant of the submitted EU authorisation dossier.[3] RDG is the producer or importer into the EU of the IVD assays covered in this application. As RDG does not sell its products directly to legal entities (customers) outside of Roche, but has its products sold by its country affiliates dedicated to the sale of Roche's products. RDL is selling Roche's products in the UK. All concerned IVD assays are delivered by RDG to RDL for sales in the UK.

F. Hoffmann-La Roche Ltd. and its **affiliates** are collectively hereinafter referred to as 'Roche', where the term 'Roche', as context requires, may refer to all or some of such affiliates. The use covered in this SEA concerns the Diagnostics Division, which is therefore described in more detail below.

The presence of Roche is worldwide (*Number of employees expressed in full-time equivalents, on 31.12.2021

**Based on headcount, excluding Chugai due to the arm's length alliance agreement between Roche (majority shareholder) and Chugai to retain its autonomy
***Operating Divisional Group

[1] 'Roche Annual Report 2021': https://www.roche.com/investors/annualreport21.htm#welcome
[2] The given financial data are calculated in £ with the exchange rate of 1.00 CHF = 0.8 £. The exchange rate of the first working day of 2022 (the 3rd of January) was used for all conversions from CHF to £. The exchange rate was obtained from https://www.statista.com/statistics/1215222/exchange-rate-pound-swiss-franc
[3] Links to the submitted EU Dossier (both links lead to the same dossier):

Link for OPnEO: https://echa.europa.eu/applications-for-authorisation-previous-consultations/-/substance-rev/45043/del/200/col/synonymDynamicField_1512/type/asc/pre/2/view

Link for NPnEO: https://echa.europa.eu/applications-for-authorisation-previous-consultations/-/substance-rev/45044/del/200/col/synonymDynamicField_1512/type/asc/pre/2/view

Figure 1) with approx. 40% of its FTEs being located in Europe including the UK. In 2017, RDL contributed 1.2 billion £ in UK gross domestic product (GDP) and supported 16'600 jobs in UK.[4]

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 a leading provider of clinically differentiated medicines and personalised healthcare[5]. Personalised healthcare is based on the separation of patients into different sub-groups according to biological differences such as genetic make-up or disease subtype. Using this information, physicians can treat patients more precisely.

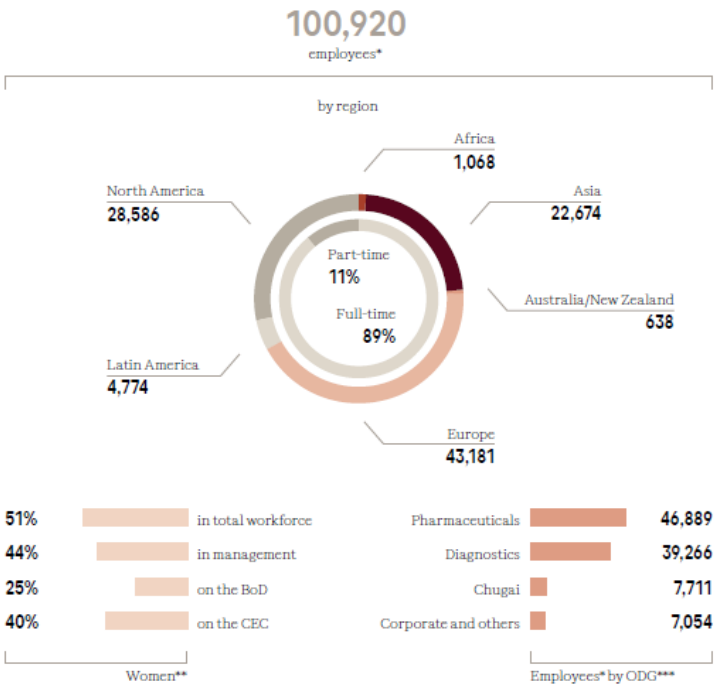
Roche is the world leader in IVD and tissue-based cancer diagnostics and offers the industry's broadest range of *in vitro* diagnostic solutions including the launch of several IVD tests during the **Co**rona**vi**rus **D**isease 20**19 (**COVID-19) pandemic. In fact, as a leading healthcare company, Roche is supporting countries in their fight against COVID-19 and minimising its impact. Roche has developed a growing number of diagnostic solutions that help to detect and diagnose the infection, as well as providing digital support to healthcare systems. Roche is also continuing to identify, develop, and support therapies which can play a role in treating the disease[6]. Moreover, Roche is 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. Roche has been making important contributions to global health for more than a century. More than thirty medicines developed by Roche are included in the World Health Organisation (WHO) Model Lists of Essential Medicines[7], among them life-saving antibiotics and chemotherapy.

[4] Roche Website, 'Roche in the UK', 2018: https://www.roche.co.uk/en/roche-in-the-uk/roche-in-the-uk.html

[5] 'Roche Annual Report 2021': https://www.roche.com/investors/annualreport21.htm#welcome

[6] Roche Media Release,' Roche has rapidly developed additional testing options to differentiate mutations in the Omicron SARS-CoV-2 variant', 2021: https://www.roche.com/de/media/releases/med-cor-2021-12-03.htm

[7] WHO Website, 'WHO Model Lists of Essential Medicines', 2021: https://www.who.int/publications/i/item/WHO-MHP-HPS-EML-2021.02



*Number of employees expressed in full-time equivalents, on 31.12.2021
**Based on headcount, excluding Chugai due to the arm's length alliance agreement between Roche (majority shareholder) and Chugai to retain its autonomy
***Operating Divisional Group

Figure 1. Roche's global presence (data from 2021)[8].

2.2. Roche and the Principle of *in vitro* Diagnostics

- ⇨ Roche Diagnostics manufactures equipment and reagents for **research** and **medical diagnostic applications.**
- ⇨ IVDs are intended to be used for **diagnosis, prevention and monitoring.**
- ⇨ IVDs add **significant value** to treatment processes and medical diagnosis, enhancing the general public and patient health.
- ⇨ A change in the specification of an IVD, depending on the extent of the change, can trigger a renewal or an update of **regulatory approval / authorisation** from health authorities.

Roche Diagnostics manufactures equipment and reagents for **research** and **medical diagnostic applications**.

IVD belong to the category of **medical devices**, i.e. any apparatus, appliance, software, material, or other article intended by the manufacturer to be used for human beings for the purpose of **diagnosis, prevention** and **monitoring** of disease. In contrast to other groups of medical devices, IVDs do not come into direct contact with patients but serve to derive information on the patient's state by analysis of specific sample types such as blood or tissue. Due to the usage of IVDs in healthcare, they can

[8] 'Roche Annual Report 2021': https://www.roche.com/investors/annualreport21.htm#welcome

only be placed on the market with a regulatory approval / market authorisation by the respective health authorities.

According to the UK Medical Devices Regulations 2002 (SI 2002 No 618, as amended) (UK MDR 2002)[9], '*in vitro diagnostic medical device* (or as referred to herein: *in vitro* Diagnostics) means a medical device which

(a) is a reagent, reagent product, calibrator, control material, kit, instrument, apparatus, equipment or system, whether used alone or in combination; and
(b) is intended by the manufacturer to be used in vitro for the examination of specimens, including blood and tissue donations, derived from the human body, solely or principally for the purpose of providing information:

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

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

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. IVDs influence health outcomes at multiple points along the care continuum providing information to the patient (see Figure 2). In fact, IVDs can provide **information** concerning a **physiological state** or to diagnose a **pathological process or state**. In medical terms, prognosis refers to a forecasting or prediction about the likely outcome or course of a disease. It may also refer to the prediction related to the likelihood of recovery from a disease. On the other hand, diagnosis refers to the identification and recognition of a possible disease or disorder. Furthermore, the stratification (i.e. grouping) of the patients (who might need to be similarly treated) can be ideally achieved with IVDs. Moreover, as stated above, IVDs can provide information to predict treatment response or reactions and to monitoring therapeutic measures.

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

Figure 2. IVDs influence better health outcomes at multiple points along the care continuum.

IVDs add significant value to treatment processes and medical diagnosis, enhancing the general public and patient health. It was reported that in Germany and US, IVDs influence over 60% of clinical decision-making, while accounting for only about 1 – 2% of total healthcare spending [21]. The British In Vitro Diagnostics Association (BIVDA) estimated that 70% of clinical decisions are influenced by the use of IVDs and states that approx. less than 1% of the NHS' budget is dedicated to the uptake of new and innovative IVD products [3].

IVDs play an important role for global healthcare. From a worldwide perspective, IVD is the largest sector in the medical technology market. There is a continuous growth of IVD products available for patients. Every year, Roche develops new IVD products with a continuous improvement of their features such as technological advancements, better diagnostic tools, improved treatment monitoring, and increased availability of new tests. Roche is a leader in this segment and is trying to make healthcare spending smarter and more sustainable, through providing diagnostics that drive efficiencies, enable physicians to act earlier and eliminate unnecessary treatments and procedures.

2.3. Roche in UK

- ⇨ RDL is an **affiliate** of Roche located in UK.
- ⇨ RDL supported **more than 21'260 jobs** in the UK in 2020.
- ⇨ **820 million Roche Diagnostic tests** were performed in the UK in 2020.

RDL is an **affiliate** of Roche located in UK. RDL is the UK Responsible Person (UK RP) as required by UK legislation to place Roche's IVD products on the UK market. RDL imports affected IVD assays from RDG into the UK and sells and delivers them to the final customers (laboratories, hospitals and universities) within the UK.

RDL operates in diagnostics, providing a broad and cutting-edge portfolio of tests and technology to prevent, diagnose and manage diseases.

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

In 2020 all Roche affiliates in the UK (RDUK) generated more than 882 million £ of UK revenue and invested more than 400 million £ in UK-based R&D.

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

820 million Roche Diagnostic tests were used to confirm, rule out or manage health conditions in the UK in 2020 - including 11 million tests for COVID-19 - and more than 712'000 patients benefited from Roche medicines, diabetes monitoring and insulin delivery system. At the start of the pandemic RDL brought the first COVID-19 test to the National Health Service (NHS) and continues to play a key role in the UK's pandemic response through its broad portfolio of diagnostic tests and two Roche medicines for treating COVID-19.

[10] Roche website: 'Roche in the UK', 2018: https://www.roche.co.uk/en/roche-in-the-uk/roche-in-the-uk.html

2.4. Roche - a Group Leader in Sustainability

- ⇨ Roche's public commitment: **to substitute any SVHC 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 (UN) Sustainable Development Goals.
- ⇨ Roche ranked the **most sustainable healthcare company** in the Dow Jones Sustainability Indices for the **eleventh times**.
- ⇨ Roche's **five sustainability pillars** are: innovating for patients, providing a great workplace, being a trustworthy partner, protecting the environment, delivering continued growth.

Since 2015, RDL, as part of the Roche group, has a **public company-wide commitment** [1] which has been approved by the Corporate Executive Committee (CEC) to **substitute any SVHC** used in its products or processes. This public commitment states that the company will stop the use of SVHC 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[1] where it is recommended to avoid substances on this list already in the development of new products and processes. Roche engages to avoid regrettable substitutes 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 the AoA of this application and the AoA 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 **Sustainable Development Goals (SDGs)** in line with the business strategy; in particular SDG3, which aims at ensuring healthy lives and promoting wellbeing for all[11].

In 2020, for the eleventh time, **Roche has been recognised as Group Leader in sustainability within the Pharmaceuticals**[12], 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. The DJSI family of indices serves as a benchmark for investors who integrate sustainability considerations into their portfolios.

[11] Roche Website: 'Sustainable development goals', 2022: https://www.roche.com/sustainability/un-sdgs.htm
[12] Roche Website: 'Media Release', 2020: https://www.roche.com/media/releases/med-cor-2020-11-16.htm

The Roche **five sustainability pillars** (Figure 3) are the following:

1) **Innovating for patients**: Meet the patients' needs for high-quality products and services. Investment in R&D (11.0 billion £ in 2021) is the major expression of the company's willingness to bring new innovative medicines and diagnostics to the market, which will influence the patients' lives.

2) **Providing a great workplace**: Provide a work environment where the Roche's employees are encouraged to build their careers and pursue their passions providing to everyone a career development opportunity.

3) **Being a trustworthy partner**: Keep an open and constructive dialogue with the stakeholders to improve Roche's ability to create sustainable value and growth. This is crucial to better understand how to serve patients, their caretakers and physicians and to focus the company activities to create value for both the company and society.

4) **Protecting the environment and supporting communities**: Seek new ways to minimise the impact on the environment. Roche has been committed to mitigating environmental impact and climate change for many years, proactively looking for new and more sustainable technologies and processes to achieve this goal. The purpose of Roche activities is to make a lasting impact by building stronger and healthier communities.

5) **Delivering continued growth**: Create value for Roche's stakeholders and achieve sustainable high profitability. This is an important goal to maintain Roche's commitment to research, to ensure the company's growth and independence, to provide employment opportunities, to cover risks and to pay an attractive return on invested capital.

Figure 3. Sustainability at Roche.

Roche is committed to improve global healthcare with several projects. One example of this commitment is Roche's collaboration with private insurance companies to create private funding solutions in countries where public coverage is lacking.

For over 120 years, sustainability has been an integral part of Roche's business. Roche follows a holistic approach when managing sustainability. In addition to improving access to products, the company's strategy also focuses on achieving continuous progress in areas such as social responsibility, environmental protection, supply chain sustainability, people attraction and retention.

2.5. Aims and Scope of SEA

- ⇨ The current SEA was developed to support application of RDL for an authorisation to **continue the use of OPnEO / NPnEO in the UK after the UK sunset date** until complete substitution.
- ⇨ This dossier covers the use of OPnEO and NPnEO in IVD assays (Use 3). Both groups of substances have been included on UK REACH Annex XIV due to the same property (endocrine disrupting properties of the degradation products).
- ⇨ Due to the uncertainties associated with endocrine disrupting properties the applicant assumes that **no threshold applies** for this endpoint as the safest option. This decision was accepted in the opinion of EU Committee for Risk Assessment (RAC) on the EU dossier.
- ⇨ **OPnEO and NPnEO are addressed in the same dossier** since they are identified as 'close analogues' and are employed for the same or similar uses.
- ⇨ The geographical scope of this SEA is Great Britain.
- ⇨ This SEA examines impacts of the non-use scenario starting from the **30th of June 2022** until the end of the applied for review period (the 4th of January 2028).

The current SEA was developed to support RDL's application for authorisation **to continue the use of two groups of substances OPnEO / NPnEO after the sunset date until complete substitution in the UK to meet the requirements of UK REACH.** It is based on the SEA developed for a similar application that has previously been submitted by RDG in the EU. RDG is the producer or importer into the EU of the IVD assays covered in this application. All concerned IVD assays are delivered by RDG to RDL for sales in the UK.

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

In its note from December 2017[13], the EU RAC left the decision to the industry to define if a threshold can be derived for the endpoint 'endocrine disrupting properties for the environment' for OPnEO / NPnEO. This was also confirmed by the EU Socio-economic analysis committee (SEAC) note on 'SEA-related considerations in AfAs for **endocrine disrupting substances for the environment**,

[13] RAC, Risk-related considerations in applications for authorisation for endocrine disrupting substances for the environment, specifically OPnEO and NPnEO: https://echa.europa.eu/documents/10162/13637/npneo_and_opneo_for_agreement_final_en.pdf/026cbafc-6580-1726-27f3-476d05fbeef0

specifically OPnEO and NPnEO'[14]. Because of the uncertainties associated with these specific properties, in the AfA submitted by RDG in the EU it was assumed that **no threshold applies** for this endpoint as the safest option. This decision was accepted in the opinion of RAC on the EU dossier. Therefore, the applicant of this AfA (RDL) will also assume that no threshold applies and demonstrate 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 the guidance on the preparation of an application for authorisation, Annex I [2], concludes that if the substances were treated as a group or category or a read-across was conducted in the Annex XV dossier of the substances, a reference to the Annex XV dossier in the AfA is sufficient for the substances being regarded as a group or category. In the Annex XV dossier for OPnEO, in many instances data on NPnEO are referenced (e.g. degradation, endocrine effects of the degradation product (4-(1,1,3,3-tetramethylbutyl)phenol (OP) and 4-nonylphenol, branched and linear (NP) 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 covered in this AfA and benefits from the use of the two groups of substances overlap so that benefits in this SEA cannot easily be assigned separately to OPnEO or NPnEO. 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. The same approach was used for the EU Dossier.

OPnEO and NPnEO are used in a wide array of IVD assays. In accordance with the provisions of the UK REACH regulation, the substances cannot be used and placed on the market after the sunset date, unless an authorisation has been granted or the uses fall under an exemption. For RDG's EU application for authorisation, three distinct uses were identified within the Diagnostics Division and one further use was identified in the Roche Pharmaceuticals Division (see Table 2). For RDL, only Use 3, the use of the IVD assays is relevant. Therefore, this application refers only to the 'Use of Octyl- and Nonylphenolethoxylates in IVD assays specified in Annex 1 to the AoA'. Please note that some product groups (Roche Molecular Diagnostics, Urinalysis and Accutrend®) that were covered in Use 3 of the EU AfA are not covered in this application as OPnEO / NPnEO is replaced or they are not sold anymore. Further, some products of the product groups Clinical chemistry and DM are not covered in this application because they do not fall under obligation for authorisatrion or because OPnEO or NPnEO have already been replaced. Please note that the use applied for in this authorisation dossier is depending on RDG receiving the EU authorisation, in particular for Use 2, for actually producing the assays.

Table 2. Uses overview of the EU AfA and relevant use for this application.

Use	Division	User	Short name	Use Name
1	Pharmaceuticals	RDG	Pharma	Use of Octylphenolethoxylates as emulsifier in the siliconisation of glass containers used as primary packaging for medicinal products (NeoRecormon® and MIRCERA®)
2	Diagnostics	RDG	Formulation	Use of Octyl- and Nonylphenolethoxylates in the formulation and filling of *in vitro*

[14] SEAC note (SEAC/37/2017/03): https://echa.europa.eu/documents/10162/13637/seac_ed_approach_opneo_npneo_en.pdf/26c7779a-7228-2670-ad41-085d10ca056b

Use	Division	User	Short name	Use Name
				diagnostic (IVD) assays specified in Appendix 1 to the AoA
3	**Diagnostics** **The only use relevant for RDL in the UK**	**Downstream Users (e.g. laboratories)**	**Products**	**Use of Octyl- and Nonylphenolethoxylates in *in vitro* diagnostic (IVD) assays specified in Appendix 1 to the AoA**
4	Diagnostics	RDG	Processes	Use of Octyl- and Nonylphenolethoxylates in the production of proteins and the conjugation of latex beads, both being used as components or for the production of components of *in vitro* diagnostic (IVD) assays, research or QC products and other, e.g. analytical applications (processes specified in Appendix 1 to the AoA)

RDL is applying for an authorisation for the use of IVD assays containing OPnEO and NPnEO by its customers, i.e. mainly laboratories and hospitals, that are distributed throughout the entire UK. Concurrently, this will allow RDL to **maintain its current business in selling IVD assays and instruments** in the UK including **potential growth**.

The expected impacts based on the described 'non-use' scenario were considered for the UK. The geographical scope of this SEA is consequently the UK.

As outlined in the AoA, RDL is applying for an authorisation for a **review period of 5.5 years** due to quality and regulatory requirements for the replacement of OPnEO and NPnEO in all products.

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

2.6. Roche Diagnostics Products and Business Model

⇨ Roche Diagnostics **Business Areas affected by this AfA include**:

- **SWA as part of Centralised & Point of Care (CPS):** CPS is a leading supplier of solutions, instruments, tests, software and services for small- to mid-size and large-size commercial and hospital laboratory and laboratory networks. This business area includes the SWA, which is characterised by modular instruments that are solutions for small to large-size laboratories with a wide range of immunoassays, Clinical Chemistry assays and Drug Monitoring.
- **Roche Tissue Diagnostics (RTD) as part of Molecular Solutions:** Is the world's leading supplier of tissue-based cancer diagnostics.

As described before, Roche Diagnostics is the diagnostic division of Roche, which manufactures equipment and reagents for research and medical diagnostic applications. Internally, Roche Diagnostics is organized into various Business Areas. The Roche Diagnostics **Business Areas** are set up according to the **fields of activities** of **Roche customers**, and these areas are responsible for R&D, product portfolio management, global strategic direction and marketing, along with business development in their area of expertise. In Figure 4 these units are graphically displayed.

Figure 4. Overview of Roche Diagnostics Business Areas.

In the following section, the focus is on the Business Area, segments and products which are affected by this authorisation (Figure 5):

1) **Serum work area (SWA) as part of Centralised and Point of Care (CPS) Solutions**: CPS is the largest business area and it is a leading supplier of solutions, instruments, tests, software and services for small- to mid-size and large-size commercial, hospital laboratory and laboratory networks. The products made by CPS help physicians make clinical decisions based on numerous indications in areas such as oncology and virology, as well as in cases of cardiovascular, inflammatory and infectious diseases. They provide healthcare specialists with critical information at the right time and in the right place. CPS is also at the forefront of the growing market for rapid diagnostic products, and thus supports clinical decision-making close to patients in emergency rooms and other primary and specialty care settings. The CPS headquarters is in Rotkreuz (Switzerland). In the portfolio, there are approx. 115 Clinical Chemistry assays, 111 immunoassays and more than 450 instrument configurations. CPS includes a variety of business

segments and among them the **Serum Work area**, which is the affected business segments by this AfA. The SWA segment is characterised by modular instruments (Figure 5). These instruments (**cobas**® 4000, 6000, or 8000 as well as the newer generation instruments **cobas**® **pro** integrated solutions or **cobas**® **pure** integrated solutions) are solutions for small to mid-size and large-size laboratories with a wide range of **immunoassays, Clinical Chemistry assays and Drug Monitoring**. In fact, with their scalable modular design, they can be customized to meet any laboratory's needs. The reagents and assays are the basis for high quality results, combined with proven workflow convenience. In general, the customers (hospitals and laboratories) of these modular instruments have **supply contracts** with Roche for **5 – 7 years**.

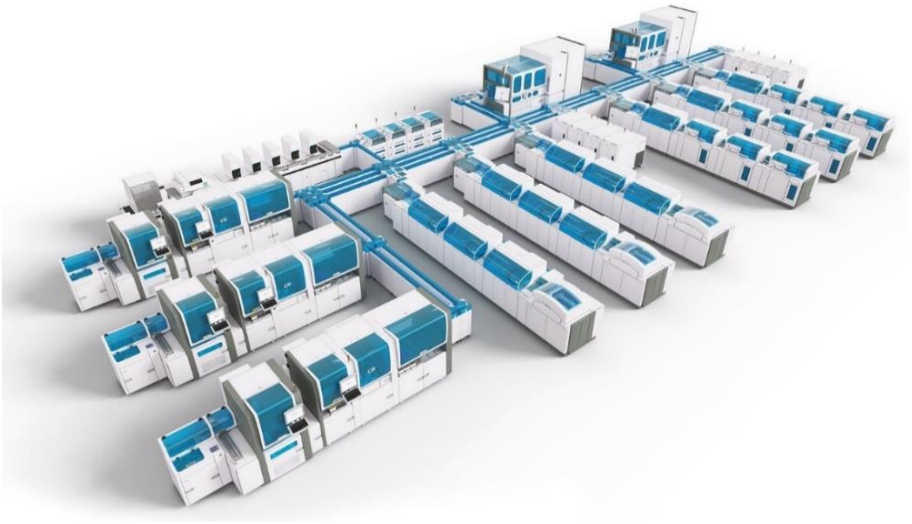


Figure 5. Example of a **cobas**®: the modular instrument of Roche[15].

2) **Roche Tissue Diagnostics (RTD) as part of Molecular Solutions: RTD** 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.

Roche Diagnostics' vision is to empower laboratories to manage the future by streamlining how they are designed and by simplifying their equipment and processes. With the innovative integration of Clinical Chemistry and immunochemistry, creating the concept of the 'Serum Work Area' Roche has already made a big step forward. **Within a single automated system, it is possible to test a vast array of parameters**. With the arrival of the fully automated system, less samples need to be taken from patients and these can simply be investigated in one place. This provides healthcare professionals with faster results, reduces errors and increases efficiency.

[15] Roche Service Website 'cobas connection modules', 2022: https://diagnostics.roche.com/ch/de/products/instruments/cobas-connection-module-ccm.html

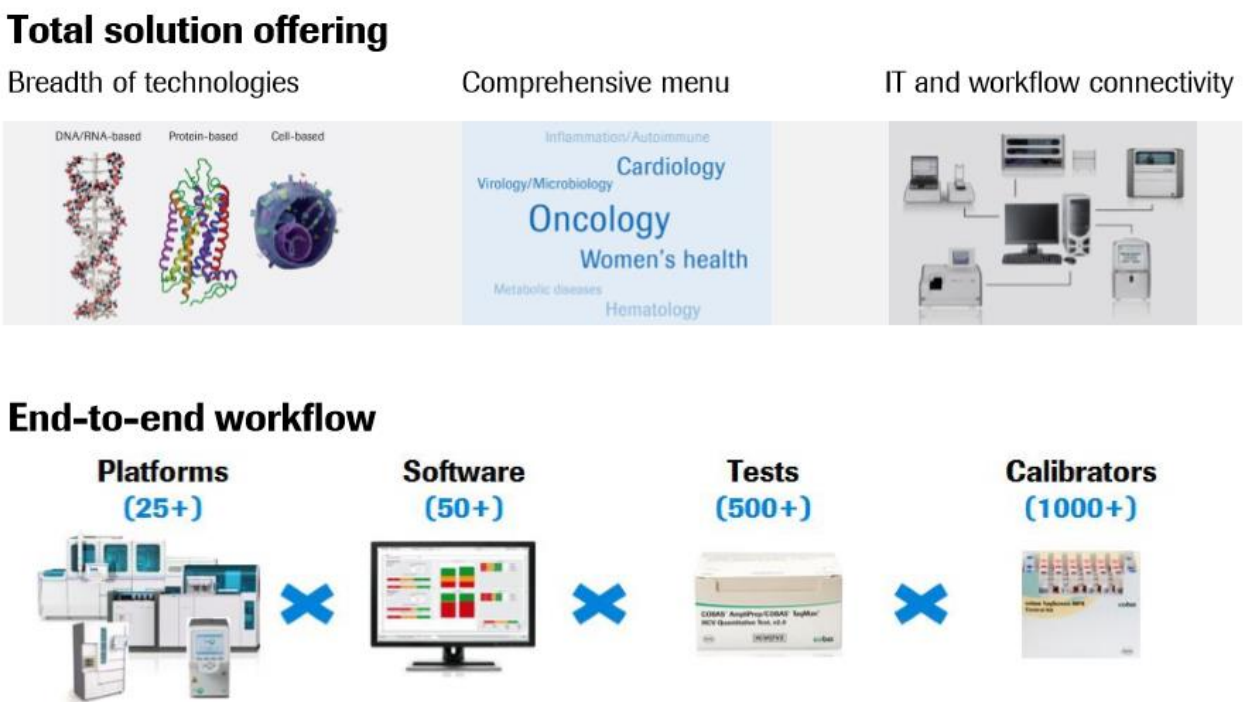


Figure 6. Roche total solution offer.

Roche's automated pre- and post-analytical solutions are integral to providing complete flexibility and process optimisation (see Figure 6). The integrated solution combining IVD and Information technology (IT) reduces risk and complexity for the laboratory. Roche does not provide only the automated systems like **cobas**®, but also ready to use reagents and advanced assay technologies (e.g. **Elecsys**® ECL) as well as IT solutions (see Figure 6).

2.7. Overview of Products

- ⇨ **OPnEO and NPnEO** are **used in wide array of IVD assays** of Roche.
- ⇨ Four different product groups (CC, DM, HIV, RTD) are in scope of this AfA.
- ⇨ IVD assays function based on different principles, but all have in common that **a target** (health) **marker** in patient samples (e.g. blood or urine) shall be qualitatively or quantitatively determined.
- ⇨ In IVD assays, OPnEO and NPnEO are used in **reagents** and **calibration mixtures** to
  - **Improve assay performance** (specificity, linearity etc.).
  - Lower the surface tension to allow a fluid to coat a surface (**wetting agent).**
  - **Lyse cells.**
- ⇨ Measurements are performed with dedicated Roche-specific instruments and are calibrated using Roche reagents.

OPnEO and NPnEO are **used in wide array of IVD assays of Roche**. In Table 3 an **overview** of **affected products**[16] is provided.

Table 3. Overview of uses and affected product groups.

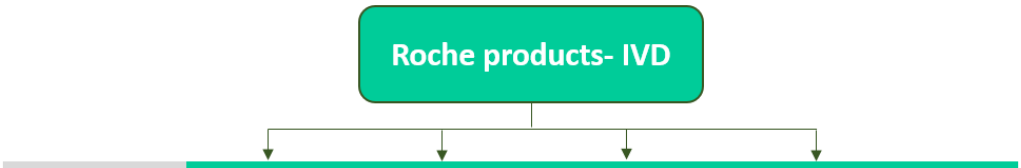
Product Group	Abbreviation	Business area concerned*
Clinical Chemistry	CC	SWA Core reagents
Drug Monitoring	DM	
HIV	HIV	SWA Infectious diseases and oncology
Roche Tissue Diagnostics	RTD	RTD

*SWA: Serum Work Area; RTD: Roche Tissue Diagnostics.

IVD assays function based on different principles, but they all have in common that **a target** (health) **marker** in patient samples (e.g. 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**. Measurements of signals are performed with a dedicated **Roche-specific instruments** using an IVD kit containing **Roche reagents** including any calibrators and auxiliary substances used for the measurements. An overview of the IVD assays per product group is covered by the AoA of this dossier. It includes occurrence and function of OPnEO and NPnEO in the assays, principles of the measurement and parameters measured. Here, a description of the affected products is given (see Figure 7) and the relevance of these assays for healthcare is highlighted.

In IVD assays, OPnEO and NPnEO are used in **reagents** and **calibration mixtures** to improve assay performance (specificity, linearity etc.), as **wetting agents** lowering the surface tension to allow a fluid to coat a surface, or as **cell lysis** agent.

[16] Throughout this document, products containing OPnEO or NPnEO and covered in this AfA will be referred to as 'affected' products



Product group	CC	DM	HIV	RTD
Product type	Reagent	Reagent	Reagent	Wash buffer
Analyzers	Integra 400+ cobas® c 311* cobas® 6000** cobas®8000*** cobas® c 111 cobas® pro cobas® pure	Integra 400+ cobas® c 311* cobas ®6000** cobas®8000*** cobas® c 111 cobas® pro cobas® pure	cobas® e 411* cobas® e 601 cobas® e 602	BenchMark® GX, BenchMark® XT, BenchMark® ULTRA
Assays or reagents containingO PnEO / NPnEO	CC3, CC7	DM5, DM6, DM7, DM8, DM9, DM11	Elecsys® HIV combi PT	Wash buffer for ISH assays

* cobas® c 311 analyzer and cobas® e 411 analyzer are combined in the cobas® 4000 system.
**cobas® 6000: Various combinations of modules c501/502 together with Elecsys® modules.
***cobas® 8000: Various combinations of modules c701/702 together with Elecsys® modules.

Figure 7. An overview of the different product types containing OPnEO / NPnEO, including their associated analysers and assays

2.7.1 Clinical Chemistry and Drug Monitoring

- ⇨ **CC** is a field of IVD which comprises tests for **determining components of blood and urine** and enables healthcare professionals to check for abnormal values.
- ⇨ **DM**, that is included in CC, specialises in **the measurements of levels of therapeutic drugs or drugs of abuse**.
- ⇨ The CC and DM portfolios include approx. **120 tests** and **220 applications** i.e. the measurement of a specific analyte in a specific sample type.
- ⇨ The OPnEO / NPnEO present in the **reagents** ensure adequate performance of the **assay,** promote stabilisation, prevent aggregations, improve solubilisation and are necessary for cell lysis.

CC is a field of IVD which comprises **tests** for determining various components of **blood and urine** and enable healthcare professionals **to check for abnormal values**. **Typical CC tests** may include, e.g. electrolytes (e.g. indication of certain metabolic and kidney disorders), lipids (evaluation of heart and liver disease), other metabolic substances and proteins (e.g. assessment of metabolic or nutritional disorder)[17]. DM, that is included in CC, specialises in the measurements of **levels** of **therapeutic drugs** or **drugs of abuse**. Figure 8 gives an overview of the assays in scope.

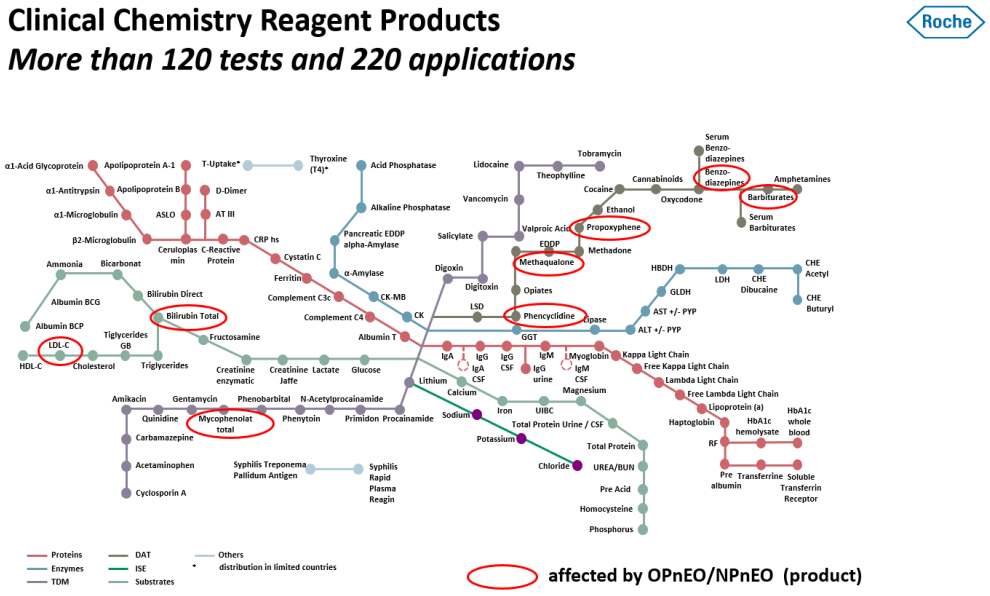


Figure 8. Affected assays from the CC and DM portfolio.

The OPnEO / NPnEO in the **reagents** lead to improvement of the **assays' performance** (specificity, linearity etc.), promote stabilisation, prevent aggregations and improve solubilisation.

Within the **CC portfolio** OPnEO and NPnEO are used for assays such as cholesterol, and bilirubin, that are included in the basic metabolic panel physicians commonly order for each patient seen at a

[17] Roche Website, 'Clinical chemistry & immunochemistry', 2022: https://diagnostics.roche.com/gb/en/products/product-category/clinical-chemistry-and-immunochemistry.html

general physician or a hospital (including emergency room). These tests, among others, give information e.g. about **the kidney functions** of the patient and can help in the prognosis of e.g. metabolic risk.

Within the **DM portfolio** OPnEO and NPnEO are used in assays distinguished between:

- DM assays, which are used in the **detection of drugs** such as depressants, hallucinogens and to check the adherence to substitution drug therapy in urine. Laboratory testing of urine for **drug abuse** plays a central role not only in **health facilities**, but also **workplaces** and **legal settings**. Urine is the preferred and most often used specimen for drug testing because urine specimens are easy to provide (non-invasive) and may contain detectable levels of drug over an extended period (window of detection) and at much higher concentrations than in blood, e.g., providing further evidence of drug use [15].

- DM assays, which are used in the monitoring of **therapeutic drugs** with a narrow therapeutic range. The DM parameter is the measurements of the serum or plasma level of a drug to ensure that its concentration in blood is within the therapeutic range (the concentration range in which the drug is known to be effective while causing little or no toxic effects to the patient). Levels of certain prescription medications (e.g. antibiotics) in the bloodstream can be a serious health concern for patients when they are not within the therapeutic range / window. By testing **levels of medications** in a patient's bloodstream, physicians can monitor and adjust the prescribed dosage to help ensure a drug's safety and efficacy.

In centralised laboratories, typically, a range of different parameters from the CC / DM and / or the immunoassay portfolio (including the HIV assay see Table 3 and Section 2.7.2) are measured in one single sample. Measurement is performed on dedicated **analyser** instruments with **modules** for immunoassays (**Elecsys**® instruments like e601, e602, e801) and modules for CC / DM (**cobas**® instruments like c311, c501, c502, c701, c702) (Figure 9). The different modules can be connected in various combinations to address the different throughput needs of the different customer segments. The resulting analyser combinations are then referred to as e.g. **cobas**® 6000 for the mid-throughput segment (combining e.g. 1x **Elecsys**® e601 and 1x **cobas**® c501) or the new generation **cobas**® **pure** integrated solutions (combining e.g. 1x **Elecsys**® e402 and 1x **cobas**® c303) and e.g. **cobas**® 8000 for the high-throughput segment (combining e.g. 1x e801 and 2x **cobas**® c702) or the new generation **cobas**® **pro** integrated solutions (combining e.g. 1x e801 and 1x c503). More than **100 different combinations** are feasible. For the low throughput segment, Roche offers also stand-alone modules like e411 for immunoassays and **Cobas Integra**® 400+ or **cobas**® c311 for CC / DM.

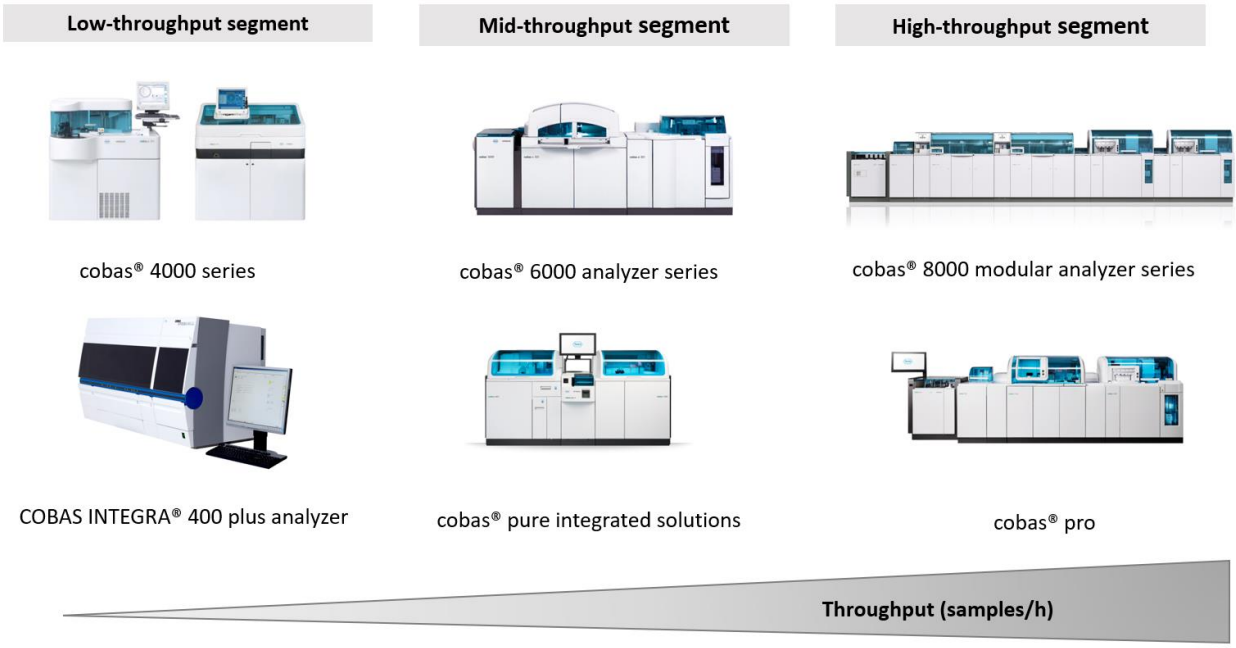


Figure 9. CC / DM analysers.

2.7.2 HIV

- ⇨ **NPnEO** is **used in two reagents** of the HIV combi PT assay to **improve the assay performance**, enhancing sensitivity and guaranteeing early recognition of HIV infection.
- ⇨ The affected assay HIV combi PT runs on **cobas® e** 411 and **cobas® e** 601/ e 602 analysers.
- ⇨ These analysers are used in various fields such as for **infectious diseases**, **fertility / hormones, thyroid function, oncology**, etc.

The **HIV** portfolio is included in the Elecsys® immunoassay portfolio and is intended for centralised private or hospital laboratories.

In the affected assay**, NPnEO is used to improve the assay performance**, enhancing sensitivity guaranteeing early recognition of HIV infection.

The human immunodeficiency virus is the causative agent of Acquired Immunodeficiency Syndrome (**AIDS**). Reliable screening and diagnosis represent a crucial aspect of the global strategy for reducing the human and financial burden of HIV transmission. For instance, in the case of blood transfusion, which remains a lifesaving intervention in almost all healthcare facilities worldwide, the blood **screening** before the transfusion is essential to prevent transmission of infections. With the Elecsys® HIV combi PT assay (using NPnEO) the HIV-1 p24 antigen and antibodies to the distinct types HIV-1 and HIV-2 (i.e. two distinct type of HIV) can be detected simultaneously within one determination, improving sensitivity and shortening the diagnostic window.

The affected assay HIV combi PT is run on **cobas**® e 411 and **cobas**® e 601/ e 602 analysers which include not only tests for **infectious diseases** but also **fertility hormones, thyroid function and oncology** tests among others. Figure 10 shows the **cobas**® e411, which has high analytical sensitivity enabling low sample volumes (only 10 – 50 µL per test) for fewer samples in the laboratories.

Figure 10. cobas® e411 instrument.

2.7.3 Roche Tissue Diagnostics

- ⇨ RTD is a supplier of **tissue-based cancer diagnostics**.
- ⇨ Affected product: Stringency **wash buffer** which contains the OPnEO / NPnEO used in the washing steps for all in situ hybridisation (ISH) probes used in the diagnostic of different types of cancer.
- ⇨ OPnEO / NPnEO is used as a **wetting agent** to reduce surface tension and to unbound molecular probes on tissue specimen slides.

Roche Tissue Diagnostics 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. Diagnosis based on examination of tissue stained with diagnostic tests, such as those provided by RTD, help inform the physician on **tumor presence, exact tumor type, degree of malignancy** and helps to identify potential causes and consequences. In the past, many steps were performed manually, and this was time consuming and less accurate. Nowadays, automation has standardised many of these specialised tests, allowing accurate and quicker delivery of results to the physician. This ultimately enables the physician to start treatment earlier.

Affected products in the RTD portfolio include **in situ hybridisation** products. **In situ hybridisation** is a type of hybridisation that uses a labelled complementary Deoxyribonucleic acid (DNA), RNA or modified nucleic acids strand (i.e., probe) to localise a specific DNA or RNA sequence in a portion or section of tissue (in situ). The products are used to assess presence, absence and / or level of expression for nucleic acid targets with the platforms **VENTANA BenchMark XT, GX and ULTRA** (Figure 11). In situ hybridisation (ISH) probes are used to aid in the **diagnosis** of different types of **cancer**, such as cervical cancer. The INFORM HER2 Dual ISH DNA Probe Cocktail Assay, a RTD product, is a good example of a cancer diagnostic that helps inform therapy

decisions. The assay is used to assess amplification status (level of gene expression) of the HER2 gene. Patients who have cancer with HER2 amplification are candidates for Herceptin (trastuzumab) treatment, this is an example of a Roche drug helping deliver personalised medicine to patients who can benefit based on the results of a Roche diagnostic test. In fact, the aim of the personalised medicine is to deliver the right treatment, meeting the exact need of the patient.

All these assays use a stringency **wash buffer containing OPnEO / NPnEO** which is used to reduce surface tension and to unbound molecular probes on tissue specimen slides. For more information on the principle of the measurements please refer to the AoA.

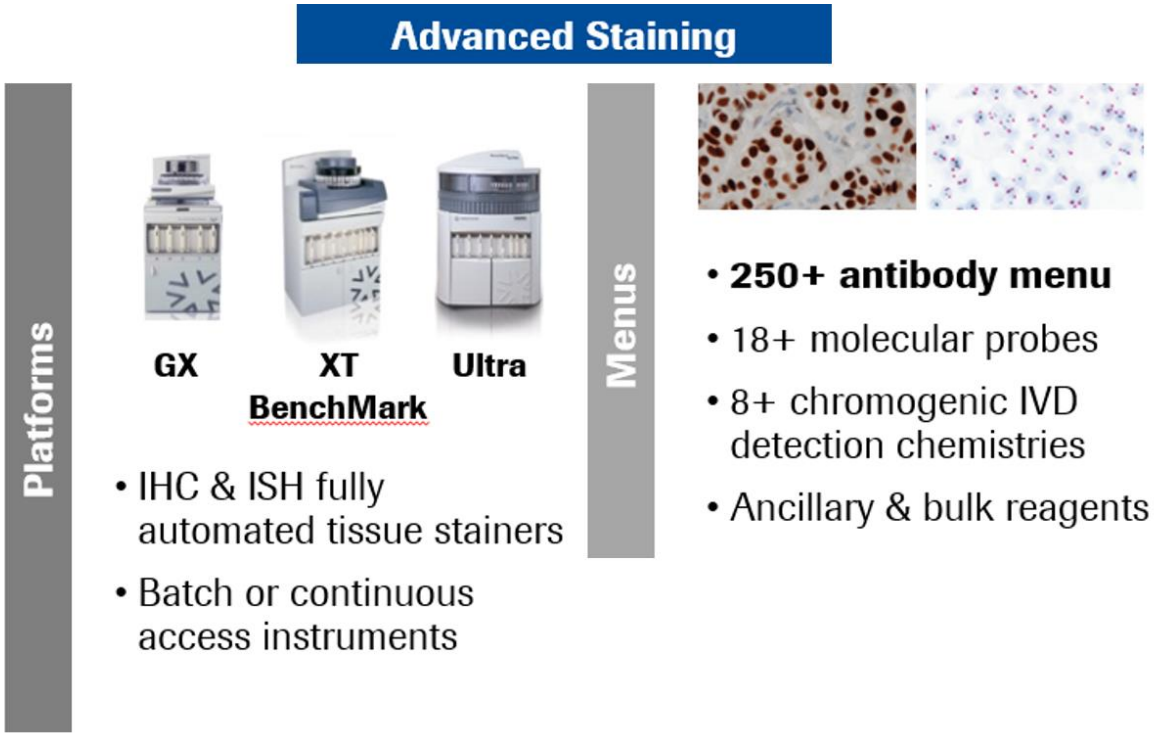


Figure 11. **VENTANA**® BenchMark GX, XT and ULTRA.

2.8. Definition of 'Applied for Use' Scenario

- ⇨ In the **'applied for use' scenario**, RDL continues to sell products containing OPnEO / NPnEO until substitution is completed.
- ⇨ This scenario is **used as baseline to evaluate the impact for RDL** under the 'non-use scenario'.

In the '**applied for use**' scenario, **RDL continues to sell products containing OPnEO / NPnEO** until substitutions are completed. This description is a projection assuming a continued use of OPnEO / NPnEO for the use applied for under the conditions described in the CSR taking into account the continued efforts to complete substitutions.

This scenario is used as baseline to evaluate the impact for RDL under the 'non-use scenario' which is described in Section 2.9.

In this scenario RDL will continue to sell products, i.e. IVDs, containing OPnEO and NPnEO. **Substitution projects to replace these substances in all assays will continue** in order to achieve substitution as fast as possible (see further information in the AoA). RDL's customers will continue to use the IVD assays with OPnEO / NPnEO until the OPnEO / NPnEO-free assays are available.

Furthermore, **RDL will be able to continue to supply the entire portfolio to existing customers and consequently comply with contracts**. Roche's customers (laboratories / hospitals) will continue to use Roche's IVD assays to provide healthcare services to patients. From an economic point of view, RDL expects to be able to continue to expand the business (as given in Section 2.8.1) and to offer a complete portfolio to new customers thus being able to compete on the market.

2.8.1 Economic Figures: Market Share, Competitors, Sales and EBITA

- ⇨ Roche is a **one of the key player of the European Economic Area (EEA) and EMEA IVD market**.
- ⇨ Roche is a key player in the UK pharmaceutical and diagnostics industries

The aim of this section is to illustrate the economic significance for RDL of the product groups depending on the use of OPnEO / NPnEO. Please note that the economic figures, sales and EBITA, including their predicted development over the review period, are based on the figures given in the AfA submitted by RDG in the EU (note that the figures were adapted to only represent the product groups and assays in scope of this UK AfA). The figures were verified and represent a reasonable estimate since the business for the assays covered in this AfA has not substantially changed since the preparation of the EU dossier. The figures, that were originally converted from Swiss Francs (CHF) to Euro (EUR), are converted to British Pounds (based on an CHF/ £ exchange rate of 0.8 (the 3rd of January 2022). They are further scaled to the UK market using the percentage of the total number of instruments (EEA and UK) installed in the UK. This is a reasonable approximation since turnover is mainly generated by the sales of assays (see Figure 12) and the need for (and therefore purchase of) assays per instrument can be assumed to be on average the same. In addition, average EU prices are slightly below UK prices so that scaling average EU sales or EBITA figures to the UK without further adjustment represents a conservative approach. Please note that this is applicable with the exception of HIV. Current figures were collected and assessed for HIV since the situation on the UK market regarding the replacement of instruments with new generation instruments for HIV differed substantially from what was described for the EU market.

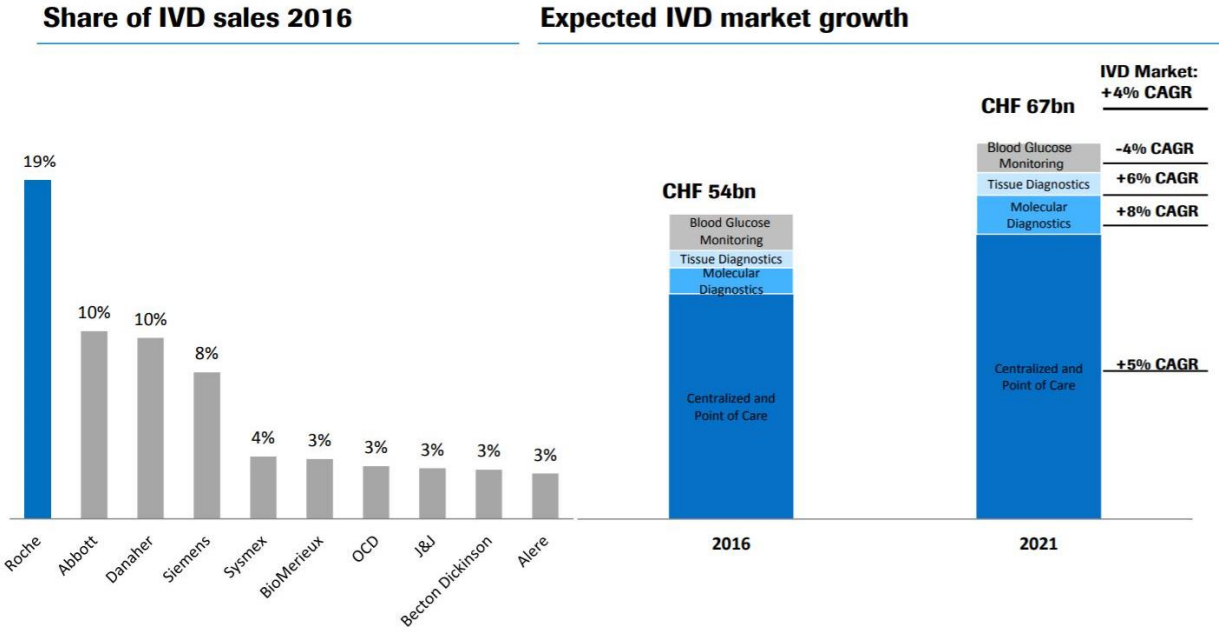


Figure 12. Share of global IVD sales and expected IVD market growth in 2016[18].

As illustrated in Figure 12, Roche is a leader of the global IVD market and has the largest market share in CC and DM. In 2016, Roche had, with **19%**, the highest market share in the IVD market.

[18] Roche's presentation, 'Committed to innovation and growth', August 2017

RDL is **expecting growth on** the UK IVD market in the next years. The main competitors of RDL are Becton, Dickinson Ltd, Siemens Healthcare Ltd Abbott Diagnostics Ltd and Agilent Ltd.

Roche's market share as well as key competitors' market shares differ between the product groups. In Table 4, UK and Europe, the Middle East and Africa (EMEA) market share versus competitors per product group / portfolio or business is given (reference year: 2021).

Table 4. Roche's Market share in the UK and EMEA versus competitors per product group / portfolio or business (reference year: 2021).

Group name	**Market share 2021 in UK**	**Market share 2021 in the EMEA region**	**Competitors and their market share 2021 in the EMEA region***
CC	[redacted]	[redacted]	Competitor 1 21.0% Competitor 2 13.6%
DM	[redacted]	[redacted]	Competitor 1 25.9% Competitor 2 21.4% Competitor 3 25.5%
HIV	[redacted]	[redacted]	Competitor 1 29.8% Competitor 2 18.0%
RTD	[redacted]	[redacted]	Competitor 1 25% Competitor 2 27% Others 3%

°Clinical Chemistry excl. Rapid Test.
°° This information is valid for the whole portfolio.
*Note that the term 'competitor 1, 2, or 3' is not nominative of a specific company but rather indicate the first or next in line in the competition for a specific business line.

Table 5 shows the sales per affected group for UK in mio £ for the year 2021 (reference year for the baseline). The aggregated EBITA was [redacted] mio £ for the affected products (Use 3) for the same year.

Table 5. UK sales of the affected products per product group for 2021.

Group name	**UK sales 2021** **mio £***
CC**	[redacted]°
DM**	[redacted]°°
HIV***	[redacted]°°°
RTD**	[redacted]
TOTAL****	[redacted]

°This only reflects the sales figures for CC3 and CC7 assays.
°°This only reflects the sales figures for DM5, DM6, DM7, DM8, DM9, DM11 assays.
°°°This only reflects the sales figures for HIV combi PT assays.
*For the conversion CHF/ £ an exchange rate of 0.8 (03.01.2022) was used.
**The UK sales figures for CC, DM and RTD shown are not based on survey data but were estimated by scaling EU sales figures using the percentage of instruments installed in the UK.
***The sales figures for HIV were calculated using the number of test kits sold in the UK (168.9. £ per test kit).
****Totals are rounded figures from the exact sum. rounding of the figures might lead to some inconsistencies.

Figure 13 shows the historical, but also predicted sales for the different portfolios demonstrating the expected development assuming the continued use of OPnEO / NPnEO. Figures are based on affected products per product group and are scaled based on data from the EU dossier except for HIV. For HIV (i.e. HIV combi PT) a decrease is predicted after 2020 due to the continuous replacement of HIV combiPT and the respective analysers with the newly developed HIV Duo assay and their analysers.

Figure 13. Historical and predicted sales development in the UK for the affected products per product group. The UK sales for CC, DM and RTD portfolio shown are not based on survey data but were estimated by scaling EU sales using the percentage of instruments installed in the UK (for HIV see note here below).

For CC and DM the entire portfolio may be affected, not only the individual affected products. Figure 14 therefore shows the historical, but also predicted sales for the entire portfolios for CC and DM. Please note that RTD is not shown since the affected products and the portfolio are identical. HIV is not shown as the portfolio is not affected due to the new analyzers with the NPnEO-free HIV Duo assay being available on the market.

Figure 14. Historical and predicted sales development for the entire product portfolios for CC and DM for the UK. RTD is not shown since the affected products and the portfolio are identical. HIV is not shown as the portfolio is not affected due to the new analyzers being available. The UK sales shown are not based on survey data but were estimated by scaling EU sales using the percentage of instruments installed in the UK.

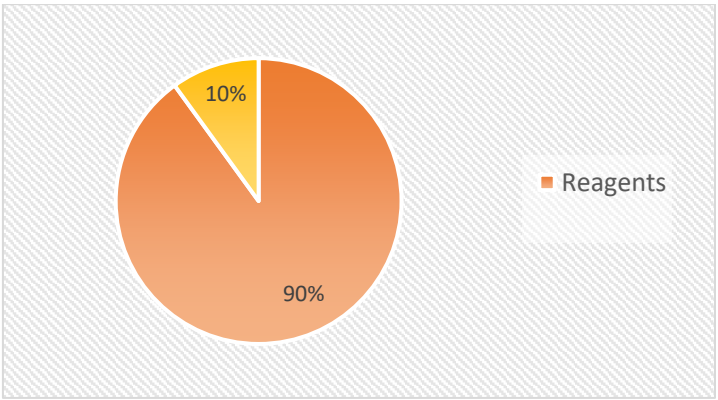


Figure 15 Assays - Contribution of reagents and instruments to the turnover.

As described in Section 2.7, Roche provides, in addition to the diagnostic assays, the required instruments to run the assays, as well as several related services. However, sales in diagnostics are predominately generated by the reagents (90% of sales is based on reagents, see Figure 15). Therefore, the core of Roche's business is indeed the sales of the assays.

2.8.2 Employment

- ⇨ A total of **730 employees** are dedicated to the RDL businesses affected by this authorisation.
- ⇨ Under the 'applied for use scenario', RDL will continue to be an employer in UK and support further jobs in the UK through it's business activities.

RDL has estimated that a total of **730 employees** in UK are direct employment by Roche supporting headquarters, field technical services and sales-based activities nationwide. However, in 2020, more than 21'260 jobs[19] in the UK were supported through Roche's business activities and supply chain.. Under the applied for use scenario, RDL will therefore continue to be an **employer in the UK**.

2.8.3 Customers

- ⇨ Roche offers different types of solutions to a variety of customers such as hospital laboratories, commercial laboratories or blood banks. Under the 'applied for use scenario' they will be able to continue to provide health services to patients.
- ⇨ Roche sells its products via country **affiliates such as RDL**. In the UK, more than >1000 instruments are installed.

RDL provides IVDs to UK hospitals, laboratories and universities. It also provides Managed Laboratory Services (MLS) to public sector entities via Framework Agreements, whereby a full laboratory package is provided to individual laboratories and hospitals under different NHS Trusts. MLS provides customers with a full package of IVDs and supporting third party products that have been validated for use with Roche products, together with technical maintenance and support services.

Roche offers different types of solutions as described in Section 2.5, targeted at **different kinds of customers** such as hospital laboratories, commercial laboratories or blood banks. Roche sells its products via country **affiliates such as RDL in the UK**. Table 6 provides an estimate of number of instruments in UK per each product group. In the UK **> 1000 instruments** are currently installed (for details on instruments per instrument type see supporting document 1 'SD1_SEA_Nr_Instruments_RDL_Use3_CONFIDENTIAL'). Please note that the data refers to the year 2017 for CC/DM and RTD. As the sales figures (see Figure 13) increased between 2017 and 2021, this is a conservative estimate. For HIV, the latest numbers available were those from 2021. Depending on the customers, one customer may use a **single** instrument or have **2 to 15** instruments installed (e.g. for centralised laboratories).

Under the 'applied for use scenario', **RDL will be able to continue to supply the market** (hospital laboratories and commercial laboratories), with CC and other IVD assays and consequently, hospital

[19] Roche website: 'Roche in the UK', 2021: https://www.roche.co.uk/en/roche-in-the-uk/roche-in-the-uk.html

laboratories, commercial laboratories and blood banks will be able to operate '**as usual**' and **provide health services** to patients.

Table 6. Estimation of number of instruments in UK per each product group.

Group name	**Type of customer**	**Estimation of number of instruments in UK*/****
CC DM	Hospital laboratories Commercial laboratories	[redacted]
HIV	Hospital laboratories Commercial laboratories Blood banks	[redacted]
RTD	Reference laboratory*** Hospital laboratories Commercial laboratories	[redacted]
TOTAL	-	[redacted] (> 1000)

°This only reflects the number of affected instruments within the HIV portofolio (cobas® e 411 and cobas® e 601/ e 602 analysers).
* Figures for CC, DM and RTD are provided from 2017 as given in the EU AfA. Overall number of instruments will have mostly increased or remained stable since then so that the figures can be considered as a minimum. However, number of individual instruments may have changed since new instruments have been introduced to the market in the meantime.
** The figures for HIV are based on 2021 figures.
***Reference laboratories: is a large laboratory that performs staining for other clinical sites who do not have the infrastructure to do so themselves.

2.8.4 Patients

- ⇨ The overall number of affected tests provided by RDL performed in UK ranges roughly between **10-50 mio tests** per year.
- ⇨ This leads to a **benefit for an estimated 1-5 mio patients per year**.

As specified before, under the 'applied for use' laboratories and hospitals will be able to operate 'as usual' and provide health services to patients. These **health services** provided by laboratories / hospitals will be available to patients reliably (i.e. without any interruption). In fact, the availability of such services is overall expected to remain the same or even increase.

Regarding specifically the IVD segment there is a range of different **benefits for patients**. The different assay features and benefits are discussed in Section 3.3.1 and 3.3.2 Overview affected products. These affected assays are run up **10 – 50 mio tests per year** (see Table 7). Therefore, assuming on average 10 tests per patient annually, this would result in [redacted] **(1 – 5) mio patients per year** that benefit from these tests in UK. In UK there is a population of 67.3 mio of inhabitants (data of 2021[20]). This corresponds to [redacted] (1 – 5)% of the UK population. Please note that the affected assays are estimated based on data from 2017 (except for HIV, see note below). This is a conservative

[20] Statista website with statistical Information on the total population of the UK information, 'Großbritannien: Gesamtbevölkerung von 1980 bis 2021 und Prognosen bis 2027', 2022: https://de.statista.com/statistik/daten/studie/19319/umfrage/gesamtbevoelkerung-in-grossbritannien/

estimate, since sales and therefore use of assays have remained stable or increased since 2017 (see Figure 13).

Table 7. Current number of tests (directly affected assays only) performed per year.

Product group	**Affected assays – estimated number of tests in UK [mio tests/ a] (in 2021)**
CC°	[redacted]*
DM°°	[redacted]*/**
HIV°°°	[redacted]
RTD	[redacted]*
TOTAL	[redacted](10 – 50)

°Only reflects the number of CC3 and CC7 affected assays.
°°Only reflects the number of DM5, DM6, DM7, DM8, DM9, DM11 affected assays.
°°°Only reflects the number ov HIV combi PT assays.
*The number of tests were estimated by scaling EU numbers from 2017 using the percentage of instruments installed in the UK.
**As only the number of tests for the entire DM portofolio were available, the number of tests affected was estimated using the share of the corresponding sales figures of the total DM portofolio.

Table 8. Overview of the health benefits for each product group.

Product group	**Function**	**Benefits to society**
CC	• Provides a **wide array of tests** that give an **indication on the general health status** of patients. • Provides parameters for screening and **early or predictive markers** of disease onset. • Includes many markers that are used in **emergency settings**.	• Signals of potentially worrying health conditions that need further investigation are picked up and lead to early diagnosis and start-up of treatment or change of lifestyle, improving patient outcome and life expectation. • Therapy efficacy can be monitored and therapeutic intervention adjusted, resulting in the most appropriate treatment. • Quick diagnosis in life-threatening conditions.
DM	• Used to **confirm suspected drug abuse or overdose** status for patients in emergency departments.	• Quick diagnosis in life-threatening conditions involving drug abuse. • Workplace drug testing greatly enhances health and safety in the workplace.

Product group	Function	Benefits to society
	• Used in **screening for drug abuse** in a **working place** or **legal context**. • Used for confirming **adherence to replacement drugs**. • Used to **fine-tune therapeutic drug use** in patients.	• Screening for drug abuse in a legal context contributes to the reduction of costs to society related to drug abuse. • Follow-up of adherence to replacement drugs is essential in the process of reintegration drug abusers in society and reducing costs to society related to drug abuse. • For selected drugs, therapeutic Drug Monitoring aims to enhance drug efficacy, reduce toxicity or assist with diagnosis, all improving patient outcome and quality of life.
HIV	• Used in the **diagnosis of HIV infections**. • Used for **screening for HIV in blood banks**.	• Early diagnosis improves patient outcome and reduces spreading of HIV through sexual transmission. • Screening in blood banks avoids transmission of HIV via transfusions. • Diagnosis of HIV infections and preventing/avoiding the spreading of HIV through the population substantially decreases healthcare expenditure related to HIV suppression and AIDS treatment.
RTD	• Aids in **diagnosis** of **several types of cancer**	• Aids in cancer diagnosis and identification and allows start-up of personalised treatment and therefore improved patient outcome.

2.8.5 Investment into R&D and Planned Substitution

⇨ Substitution projects are already ongoing and OPnEO / NPnEO have already been replaced in several products.

⇨ **Total investment cost** for the likely scenario is **ca. [redacted] mio £** for the products covered under **Use 2&3 of the EU dossier in the product groups where substitution is not yet complete**.

⇨ A **review period of 5.5 years** is needed from the **sunset date to complete substitutions** taking into account **risks associated with the timelines**.

Roche's R&D department is currently **working on the complete substitution of OPnEO / NPnEO** in all affected IVD assays. As described in the AoA substitution projects are already ongoing and OPnEO / NPnEO have already been replaced in several products. In the applied for use scenario, Roche will continue this process until substitution is completed. Roche is and will be investing a large amount of resources into this change process. The estimated **investment costs** for the substitution are given in Table 9 considering the likely and worst-case scenario regarding regulatory requirements for substitution which are an important driver for cost.

Since RDL is only an affilitate of Roche, no direct investment costs are covered by RDL. The investments cost as given in Table 9 are the total cost for all uses applied for in the EU in the product groups where substitution is not yet completed and thus reflect the total of Roche's investment into substitution of OPnEO / NPnEO in these product groups. Part of this cost are related to the tests covered by this AfA. The cost related only to the tests covered in this AfA are not shown since such a selection would not be meaningful at the level of Roche as a company. For Roche, the total investment costs for the likely scenario are ca. [redacted] **mio £**[21] for the product groups where substitution is not yet completed (Use 2&3 and 4 (where relevant for DM), for an overview of the Uses of the EU dossier, please consult the Table in the Summary Section). The main cost driver in the worst-case scenario are the additional regulatory requirements in case of a re-registration. These requirements directly translate in additional experiments that need to be performed to provide the requested data. R&D efforts to generate this data are more than double if a **re-registration is needed**. If the **worst-case scenario** applied for all products and processes, cost could reach ca. [redacted] **mio £**. The cost includes cost for the required personnel to perform the projects or the clinical studies (e.g. for HIV). Please note that in case assays in the product group DM would need to undergo a re-registraton, [redacted]

Table 9. Substitution: investment costs including cost for required personnel.

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

* Re-registration to obtain market authorisation.
[a] Scenario for a development of an HIV assay on all instruments.
[b] Scenario if there are two developments. [redacted]

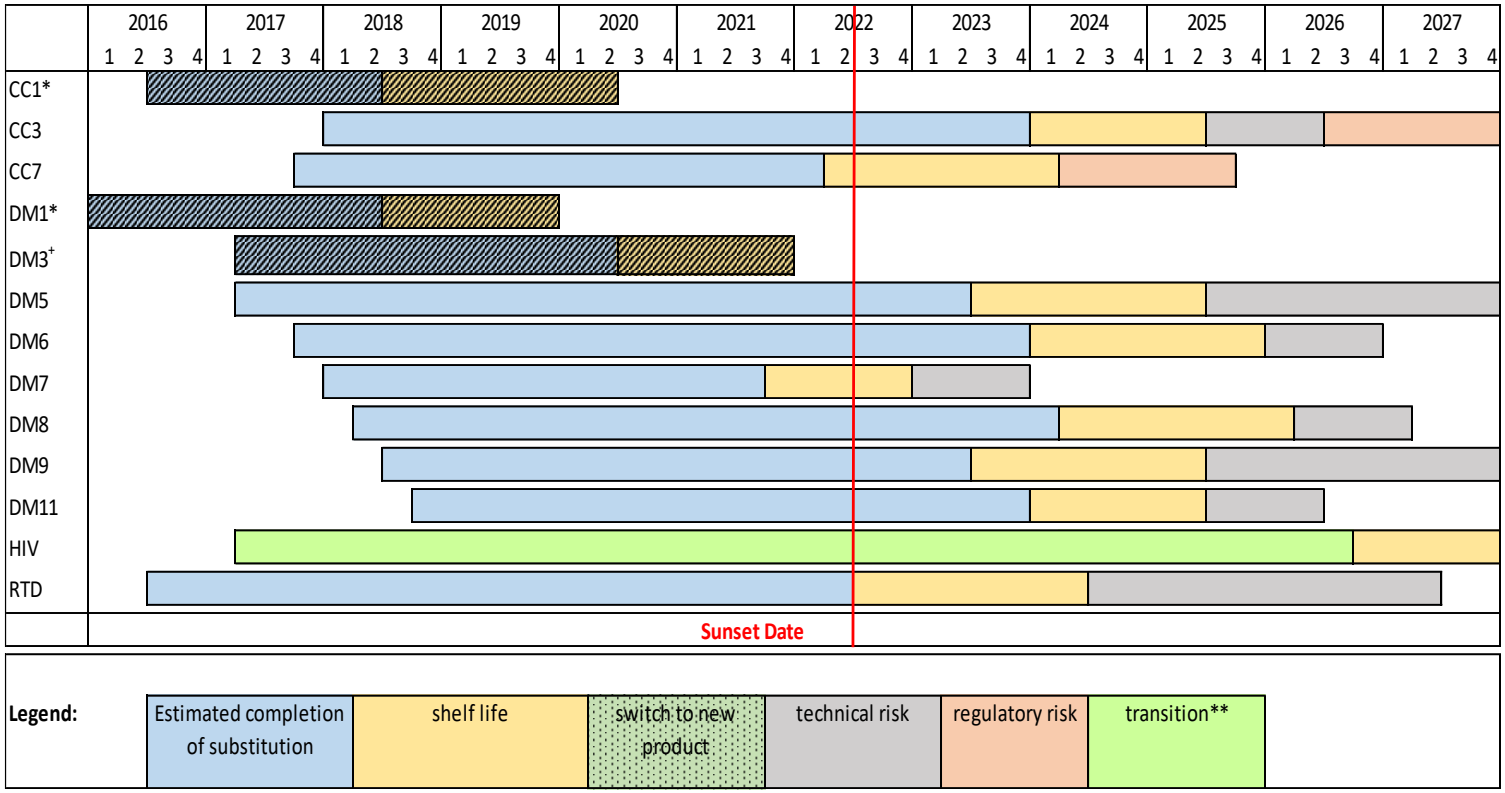
The Figure 16 summarises the planned time line following (for more details please consult the AoA).

The timelines include planned substitution dates as well as **technical and regulatory risks** associated with the substitution projects.

In conclusion, the AoA explains the unique technical and regulatory challenges associated with validating alternatives for products (Use 3). A **5.5-year review period** will allow Roche to complete the evaluation of alternatives, validate and assure performance of the affected products and if necessary, submit change notifications to health authorities, including the Medicines and Healthcare products Regulatory Agency (MHRA) via the UK RP, as a regulatory requirement for *in vitro* diagnostic assays. Roche is committed to **substitute OPnEO / NPnEO as fast as possible for each individual product**. However, Roche has concluded **that any review period shorter than 5.5 years**

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

would not be sufficiently long for completing the substitution of OPnEO and NPnEO in all products taking into account the associated risks in the timelines.



* Product is not in the scope of this AfA Dossier as substitutionn was completed before the Sunset Date, and replacement of all stock containing OPnEO / NPnEO will have been completed before the Sunset Date. The inclusion of this products in this timeline is to illustrate succesfully completed replacement projects and it is marked with a striped shading.

+ Product that has been already replaced before the submission of the AoA document for the UK Dossier. No longer in scope for UK Dossier. It is marked with a striped shading.

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

Figure 16. Planned timelines for Use 3.

2.8.6 Emissions and RMMs

⇨ Under the 'applied for use scenario', RDL will sell products, which are produced by Roche containing OPnEO and NPnEO **until substitutions are completed.**

⇨ The maximum yearly used amount and therefore amount applied for is:
- **48.65 kg/a OPnEO and 0.39 kg/a NPnEO** at the downstream users

In the 'applied for use scenario', RDL will sell products, which are produced by Roche containing OPnEO and NPnEO until substitutions are completed. Substitution projects to replace these substances in all assays will continue in order to achieve substitution as fast as possible (see further information in the AoAs for Use 3 and Section 6). RDL's customers will continue to use the IVD assays with OPnEO / NPnEO until the OPnEO / NPnEO-free assays are received from RDL. In Table 10 the **maximum used amount of OPnEO and NPnEO after the UK sunset date** at downstream user sites is given. This corresponds to the **amount applied for**.

Table 10. Maximum yearly amount of OPnEO and NPnEO used for downstream uses (Use 3).

Maximum used amount in kg/a after the UK sunset date	**OPnEO**	**NPnEO**
Use 3	48.65	0.39

If the substitutions are delayed, a **maximum total annual amount of 48.65 kg/a OPnEO by the end of 2027 could potentially be reached** based on sales development and usage could continue until the end of the review period (the 4th of January 2028). **For NPnEO the usage (0.39 kg/a NPnEO) will constantly decrease after the UK sunset date,** even if the substitutions are delayed (see Table 12 and Table 13). An **overview of releases of $OP_{equiv.}$ and $NP_{equiv.}$ to surface water** and **soil** at the sunset date and over the course of the review period is given Section 3.1.3. Additionally, an overview of the RMMs in order to minimise the releases of OPnEO and NPnEO to wastewater is provided also in Section 3.1.3.

2.9. Definition of 'Non-Use' Scenario

⇨ Under Use 3, in case of refusal of authorisation RDL will **not be able to continue the supply of the affected products.**

⇨ The following alternatives were analysed:

- **Bridging the period of non-use by stock-building** is not possible for all products due to concentrations ≥ 0.1% w/w.
- **Replacement by assays from a third party** is considered unrealistic for compatibility reasons (competitors' products are not suitable for Roche's closed systems).
- **Replacement by other Roche assays** (e.g. new-generation product or entirely new formulation) is not feasible on short notice due to long development times and times for regulatory approval.
- **Replacement with Roche products containing alternative surfactants** is not yet feasible due to time required for substitution including validation and regulatory approval.

⇨ Supply to the UK market will need to be interrupted **until substitutions are completed**.

The purpose of this section is to describe the reaction of RDL in case of refusal of authorisation after the UK sunset date of the 30th of June 2022. In Table 11 an **overview of the non-use scenarios** and their **feasibility** is given.

Table 11. Overview of the feasibility of the non-use scenarios considered in this AfA.

Option	Feasibility	Justification for the feasibility claim
Stock-building	No	- Not possible due to OPnEO / NPnEO concentration in products of ≥ 0.1% w/w **=> not feasible for the assays covered in this AfA**
Replacement by product from a third party	No	- Compatibility problem - Production capacity limitations of third parties - Time constraints - Availability - Possible price increase - No certainty to acquire OPnEO / NPnEO free products - Market authorisation required => **not feasible for compatibility and technical reasons**
Replacement by other Roche product / assays	No	- Time constraints - High developmental costs - Market authorisation required - Approach taken for one assay but cannot be completed before the sunset date => **not (yet) feasible option due to time constraints and costs**
Replacement with Roche products with an alternative surfactant	No	- The substitution is ongoing but cannot be completed before the sunset date for all products => **not yet feasible due to time requirements for the assays covered in this AfA**

Upon refusal of authorisation and after the sunset date, RDL will **not be able to continue the supply of the affected IVD products** (i.e. the products containing OPnEO / NPnEO). The supply will need to be interrupted until the necessary steps to switch to reformulated products (i.e. products with an alternative surfactant) or in one case a new-generation product (i.e. completely new product) are completed at Roche. This includes successful changes to existing registrations or successful finalisation of entirely new registrations with health authorities for the UK market as well as different markets worldwide (please note that for Roche to switch to an alternative surfactant, the IVD assay needs to be approved worldwide, see AoA). It is expected that this process will extend beyond the UK sunset date of the 30th of June 2022 (see timelines described in the AoA for the products under consideration). An authorisation refusal would therefore imply that there will be a period during which RDL will not be able to deliver products to the market, triggering responses of the impacted customers that may slightly differ depending on the affected product under consideration, but in all cases, would lead to loss of business, a lack in the provision of healthcare services. Alternative non-

use scenarios were evaluated for their potential to enable Roche to continue supply of the affected products to the market. However, it was concluded that RDL will have to interrupt supply.

Bridging the period of non-use by stock-building could be considered as a possibility for some products with OPnEO / NPnEO concentration below 0.1% w/w, in case stocks for such products could be built before the sunset date. However, all the products in scope of this AfA contain ≥ 0.1% w/w OPnEO / NPnEO. Therefore stock-building is not an option for the UK customers as the use of affected products would not be allowed after the sunset date.

Replacement by material from a third party is also considered unrealistic for compatibility and capacity reasons. In fact, competitors' products are not suitable for Roche's closed systems. 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. Due to the high competitiveness in the IVD market, there is also a probability of refusal from third parties to sell to Roche or the risk for third parties to provide their reagents only at very high transfer prices. Moreover, in the unlikely case that the product could be acquired from a third party, there is no certainty that it would be OPnEO / NPnEO free (or, in case manufactured outside the UK or EEA, contain <0.1% w/w OPnEO / NPnEO) and that it would meet Roche quality / performance standards.

Replacement by other Roche assays (e.g. new-generation product or entirely new formulation) is not a suitable option either. In most cases, re-formulation of the current product is considered first (i.e. replacement of OPnEO / NPnEO by an alternative surfactant), since it has the advantage to reduce registration efforts. A new-generation product or entirely new formulation will only be considered if the current performance cannot be maintained with re-formulation and in this case the new-generation product must be registered and substitution will take from 5-7 years to more than 10 years depending on the regulatory requirements. An overview for the different product types is given here below:

- For **DM assays, CC assays** (included in large systems such as **cobas**® 6000 or **cobas**® 8000) and RTD assays no new-generation products are available and the focus is on re-formulation. The cost for development of new-generation products is disproportionally high when considering it for several assays at the same time and would then likely require more than the 5-10 years estimated for one assay depending on R&D resources.
- For **HIV combi PT**, the analysers on which the assay is running (**cobas**® e 602 **cobas**® e 601 and **cobas**® e 411) are being stepwise replaced worldwide by new generation instruments. The re-development costs of HIV combi PT including a worldwide re-registration are [redacted]. This will make a new development of HIV combi PT running on analysers which will be outphased within a short timeframe highly uneconomical. A newer generation assay (HIV Duo) which is OPnEO / NPnEO free has already been developed to run on the new-generation instruments and has been introduced to the UK market. The two successor instruments on which the HIV Duo is running (**cobas**® e801 and **cobas**® e 402) have already been launched in the UK in 2016 and 2020, respectively. Customers are progressively being switched to the alternative **cobas**® e801 **cobas**® e 402 (and thus HIV Duo). The time frame for the switch will depend on the capacity of the analyser manufacturer (i.e. HITACHI high Technologies). In addition, after the introduction of the new generation instruments, an average of at least five years of support for the old instruments (that includes providing the HIV combi PT assay) is required. Therefore, despite the ongoing activities regarding alternative products, a switch of all customers to an NPnEO-free HIV assay in case of refusal of authorisation is not feasible. These assays need to be on the market (including shelflife) until ca. end of 2027, which corresponds to the estimated time necessary for replacing the old instruments with the new generation instruments in the UK.

A **replacement with RDG products with alternative surfactants** is the chosen approach for most assays, but not feasible within a short timeframe. Projects to substitute OPnEO / NPnEO by alternative surfactants in the different products started in 2016 or 2017 and are ongoing. However, only replacement in some of the products in scope of this AfA may be completed by the UK sunset date (the 30th of June 2022) for the reasons as outlined in the AoA.

Under Use 3 upon refusal of authorisation and after the sunset date, RDL will **not be able to continue the supply of the affected products including their downstream applications**. The supply to the market will need to be interrupted until the necessary steps to switch to an alternative surfactant - or in one case a new generation product - are completed. This includes adapted or new registrations for the different markets for IVD assays that currently contain OPnEO or NPnEO. Therefore, an interruption of the supply of the products is expected until substitution will be completed.

2.10. Information for the Length of the Review Period

- ⇨ RDL is applying for an authorisation to use OPnEO / NPnEO until the **end of 2027**.
- ⇨ For a change of the affected assays, **performance and stability testing** needs to be performed, and in some cases, change of specific IVD **market authorisations** or re-registration is required.
- ⇨ As a worst-case, the last of the substitutions will be completed by end of 2027. However, it is highly unlikely that the full review period will be needed for substitution in all assays.
- ⇨ **Any review period shorter than approx. 5.5 years** would not be sufficiently long for completing the substitution of OPnEO and NPnEO in **all products** taking into account the associated risks in the timelines.

RDL is applying for an authorisation to use OPnEO / NPnEO for a period of (approx.) 5.5 years starting from the UK sunset date: the 30th of June 2022. This period of time is justified in detail in the AoA.

A large number of alternative substances to replace the OPnEO / NPnEO in the IVD assays is available. It is expected that **feasibility studies** will identify one or more suitable alternatives. Due to the complexity of requirements for the *in vitro* diagnostic assays a **considerable effort** is needed for performance and stability testing. Please note that these testings need to be done for each assay; in fact the experience has shown that there is **no single surfactant that can be used for all assays**. 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 R&D 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 and substutiton has already been successfully completed in a number of assays.

The estimated timelines for replacement are depicted in Figure 16. The estimated completion of substitution is the **date when production of the corresponding assay is planned to be started with the alternative surfactant** (end of blue bars). From that moment on, old products will be used by the customers, as a maximum, until the end of shelf life (yellow bars). In one case (HIV), the affected product will not be produced anymore and the clients will be switched to a new system during a transition period (green bar), detailed information on this can be found in Sections 6.3 of the AoA document.

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

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

For **one assay** that employs a small portion of the overall amount of OPnEO / NPnEO, a **different alternative is being implemented**. The new HIV generation Elecsys® HIV Duo which was launched April 2017 in the EU, including UK, already reflects the REACH regulation aspect and uses a detergent with no concerns. Despite the ongoing activities regarding introduction of the new generation instruments, the HIV Duo is not a suitable alternative that can be implemented before the sunset date for all of Roche's customers. Authorisation is therefore needed to allow for the continued use of HIV combi PT on the older-generation instruments until all customers have been provided with new-generation analysers (using HIV DUO assays) and trained on their use. Due to contractual obligations and the long time required to replace all older systems, the replacement process of HIV combi PT is estimated to be completed only by the end of the review period, i.e. the 4th of January 2028.

In conclusion, the AoA explains the unique technical and regulatory challenges associated with validating alternatives for the IVD products. A **review period until the end of 2027** will allow Roche to complete the evaluation of alternatives, validate and assure performance of the affected products and if necessary, submit change notifications as a regulatory requirement for *in vitro* diagnostic assays. Roche is committed to **substitute OPnEO / NPnEO as fast as possible for each individual product**. However, Roche has concluded **that any review period shorter than 5.5 years** would not be sufficiently long for completing the substitution of OPnEO and NPnEO in all products taking into account the associated risks in the timelines.

3. ANALYSIS OF IMPACTS

3.1. Environmental and Human Health Impacts

3.1.1 General Introduction

⇨ As part of the process of application for authorisation for endocrine disrupting substances for the environment, the applicant is to conclude that the **benefits of continued use outweigh the remaining risk to the environment** by presenting an assessment containing:
- A monetised estimate of the benefits of continued use.
- A quantified release estimate accompanied with a qualitative description of where the releases occur.
- A qualitative description of the potential impacts.

⇨ The applicant should **minimise releases to the environment** as far as technically and practically possible, to guarantee minimisation of the likelihood of adverse effects.

In its note on 'risk-related considerations in applications for authorisation for endocrine disrupting substances for the environment, specifically OPnEO and NPnEO', the EU RAC indicates that in case the applicant does not propose a dose-response relationship under the socio-economic route for applying for authorisation, the application will be evaluated on the same basis as an application for a Persistent, Bioaccumulative and Toxic (PBT) / very Persistent very Bioaccumulative (vPvB) substance. As for the latter type of substances, the **releases to the environment can be considered as a proxy for the environmental impacts**, the **applicant should minimise releases to the environment as far as technically and practically possible**, to guarantee minimisation of the likelihood of adverse effects. Since the requirements for authorisation under UK REACH were adopted from the EU REACH, the same approach as for the EU dossier is considered applicable for this application.

Further, in the note published by the EU SEAC on 'SEA-related considerations in applications for authorisation for endocrine disrupting substances for the environment, specifically OPnEO and NPnEO', it is if further stated that **for the applicant to conclude that the benefits of continued use outweigh the remaining risk to the environment**, it is necessary to **provide as part of the assessment**:

- A monetised estimate of the benefits of continued use.

- A quantified release estimate accompanied with a qualitative description of where the releases occur (e.g. dilution capacity of a river and number of release sources and their temporal and geographical distribution).

- A qualitative description of the potential impacts (e.g. on fish populations).

In case abovementioned information is not sufficient to conclude, based on qualitative comparison, that the benefits of the use under consideration outweigh the risk, the applicant may provide further contextual information on the likelihood and significance of potential impacts (e.g. the margin of safety between predicted or measured environmental concentrations and relevant thresholds of exposure / adverse effect in biota or quality standards from other legislation) or illustrative

quantitative assessments (e.g. based on worst-case scenarios or break-even analysis) to support the case.

Considering the abovementioned recommendations of the EU RAC and the EU SEAC, the **following information will be summarised / discussed** in the following subsections:

- Total annual use of OPnEO / NPnEO at downstream user sites over time, taking into account expected sales development as well as planned substitutions.
- Releases of OPnEO / NPnEO over time, taking into account expected sales development, planned substitution, and RMMs.
- Comparison of predicted environmental concentrations with concentrations of monitoring campaigns.
- Geographical and temporal considerations.
- Qualitative description of impacts.
- Margin of safety when comparing predicted environmental concentrations with existing environmental quality criteria.

Part of the information discussed below is taken from the CSR submitted in view of this AfA. Where this is the case, reference to the respective parts in the CSRs is made for more detailed discussion.

3.1.2 Use of OPnEO / NPnEO at Downstream User Sites Over Time

- ⇨ **Downstream sites such as laboratories and hospitals** purchase IVD assays with reagents containing OPnEO / NPnEO from RDL for diagnostic purposes in healthcare.
- ⇨ The **maximum annual usage** at the UK sunset date for Use 3 was estimated to be **40.19 kg/a OPnEO and 0.39 kg/a NPnEO.**
- ⇨ However, the total annual usage of OPnEO and NPnEO is expected to change over time due to **completed substitutions** of OPnEO and NPnEO in the formulation and in the corresponding downstream products and due to sales development. Two cases were considered:
  - 'All substitutions completed as planned': If the substitutions in the formulated reagents are completed as planned, the total annual amount of OPnEO will be 1.4 g/a on 1st of June 2025 (0 g/a on 1st of April 2026) and NPnEO will reach 0 g/a by the end of 2027 for the use applied for.
  - 'All substitutions delayed': If the substitutions are delayed, a maximum total annual amount of 48.65 kg/a OPnEO by the end of 2027 could potentially be reached based on sales development and usage could continue until the end of the review period (the 4th of January 2028). For NPnEO the usage will constantly decrease after the UK sunset date, even if the substitutions are delayed.
- ⇨ RDL therefore applies for a **maximum annual amount of 48.65 kg/a of OPnEO and 0.39 kg/a NPnEO for Use 3.**

For the CSR, the maximum annual usage for Use 3 at the end of 2027 (OPnEO) and at the UK sunset date (NPnEO), respectively, assuming that all substitutions are delayed, serves as a basis for the exposure assessment as this represents a worst-case of the used amounts. The total annual usage in the UK, including the predicted development over the review period, are based on the figures given in the AfA submitted by RDG in the EU. For the EU dossier, the sales figures for the different IVD assays for 2016-2017 sold to the different EEA downstream users i.e. laboratories / hospitals were collected. Note that for the present dossier the figures were adapted to only represent the product groups and assays in scope of this UK AfA and were scaled to the UK (see CSR for further information). The figures were verified and represent a reasonable estimate since the business for the assays covered in this AfA has not substantially changed since the preparation of the EU dossier. Further, the situation on the UK market is comparable to the situation in the EU (including the UK) as described in the EU dossier.

At the time of preparing the EU dossier, the expected sales development between 2017 and 2022 translated into corresponding amounts and/or direct volume predictions was considered in the estimates. They are further scaled to the UK market using the percentage of the total number of instruments considered in the EU dossier (EEA including the UK) that are installed in the UK. This is a reasonable approximation since (liquid and solid) waste generation mainly depends on the use of assays and the use of assays per instrument can be assumed to be on average the same.

These data were then aggregated per exposure scenario and served as a basis for the estimation of the total annual usage at the downstream users at the UK sunset date considering the expected development until the 30th of June 2022 based on 2016/1017 data. This estimation was further

extrapolated to the end of the review period (the 4th of January 2028) considering the development in the sales figures and/or volume predictions as forecasted until the end of 2027.

The total annual usage of OPnEO for the downstream sites will further increase after the UK sunset date due to growth in the sales figures. However, total annual usage of OPnEO is expected to decrease from 2024 to reach 0 at the latest at the end of the review period due to completed substitutions of OPnEO in the IVD assays. For NPnEO, the total annual usage for the downstream sites is expected to decrease overtime from the UK sunset date to reach 0 at the latest at the end of the review period due to completed substitutions of NPnEO in the IVD assays and replacement with new generation instruments for HIV.

Since the possibility exists that the ongoing substitution projects run into delays, two cases were considered in the CSR:

- **'All substitutions completed as planned':** If the substitutions in the formulated reagents are completed as planned, the total annual amount of OPnEO will be 1.4 g/a on 1st of June 2025 (0 g/a on 1st of April 2026) and NPnEO will reach 0 g/a by the end of 2027 for the use applied for.

- **'All substitutions delayed':** If the substitutions are delayed, a maximum total annual amount of 48.65 kg/a OPnEO by the end of 2027 could potentially be reached based on sales development and usage could continue until the end of the review period (the 4th of January 2028). For NPnEO the usage will constantly decrease after the UK sunset date, even if the substitutions are delayed.

Figure 17 and Figure 18 provide an overview of the expected **evolution** in the total used amount of OPnEO and NPnEO (respectively) over time resulting from the **use of the affected IVD assays at downstream user sites**. The evolution expected under the two cases (substitutions delayed or substitutions as planned) are shown in each figure.

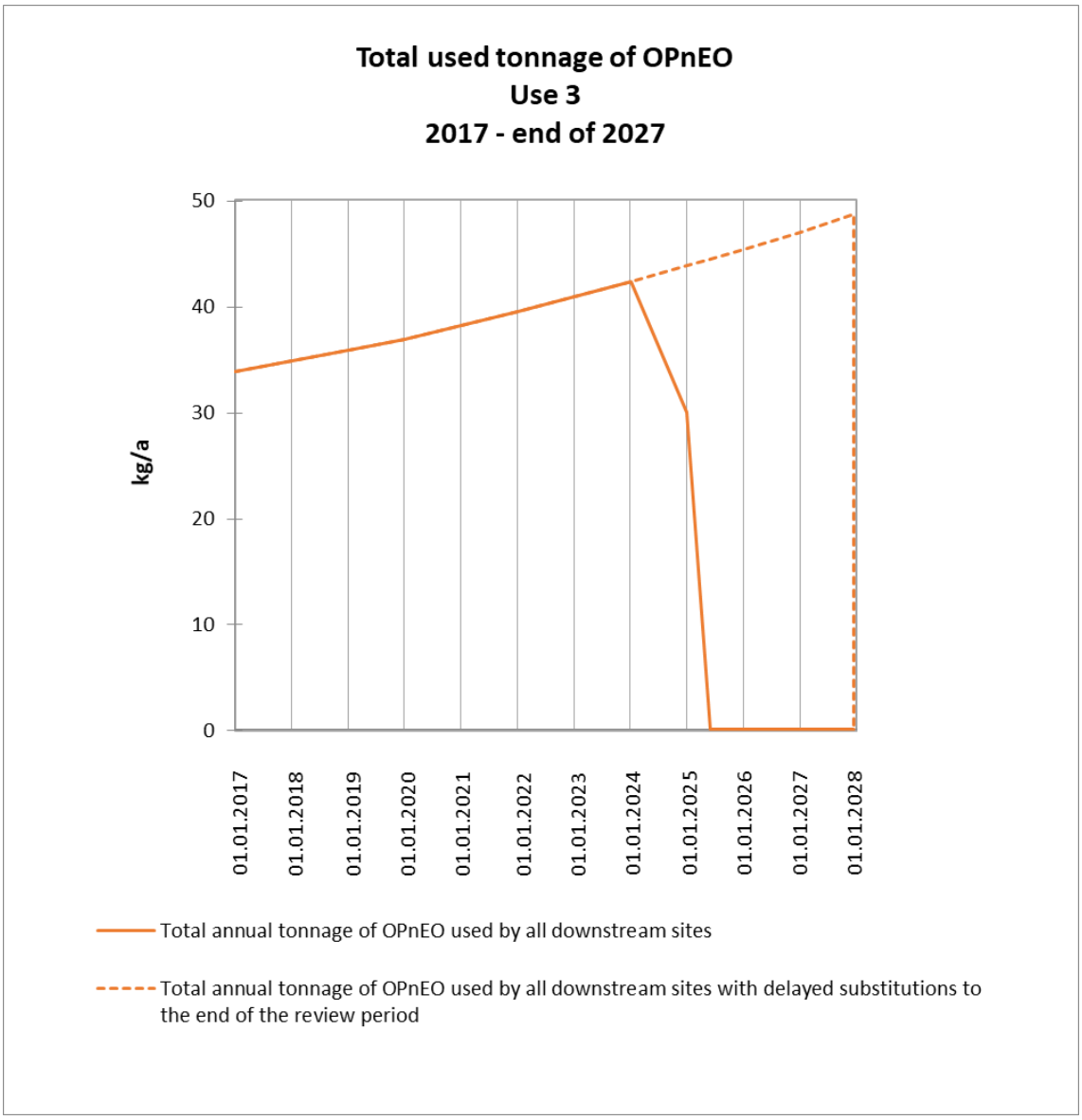


Figure 17. Evolution of the total annual use of OPnEO between 2017 and end of 2027 for the downstream users' sites considering planned substitutions and sales development.

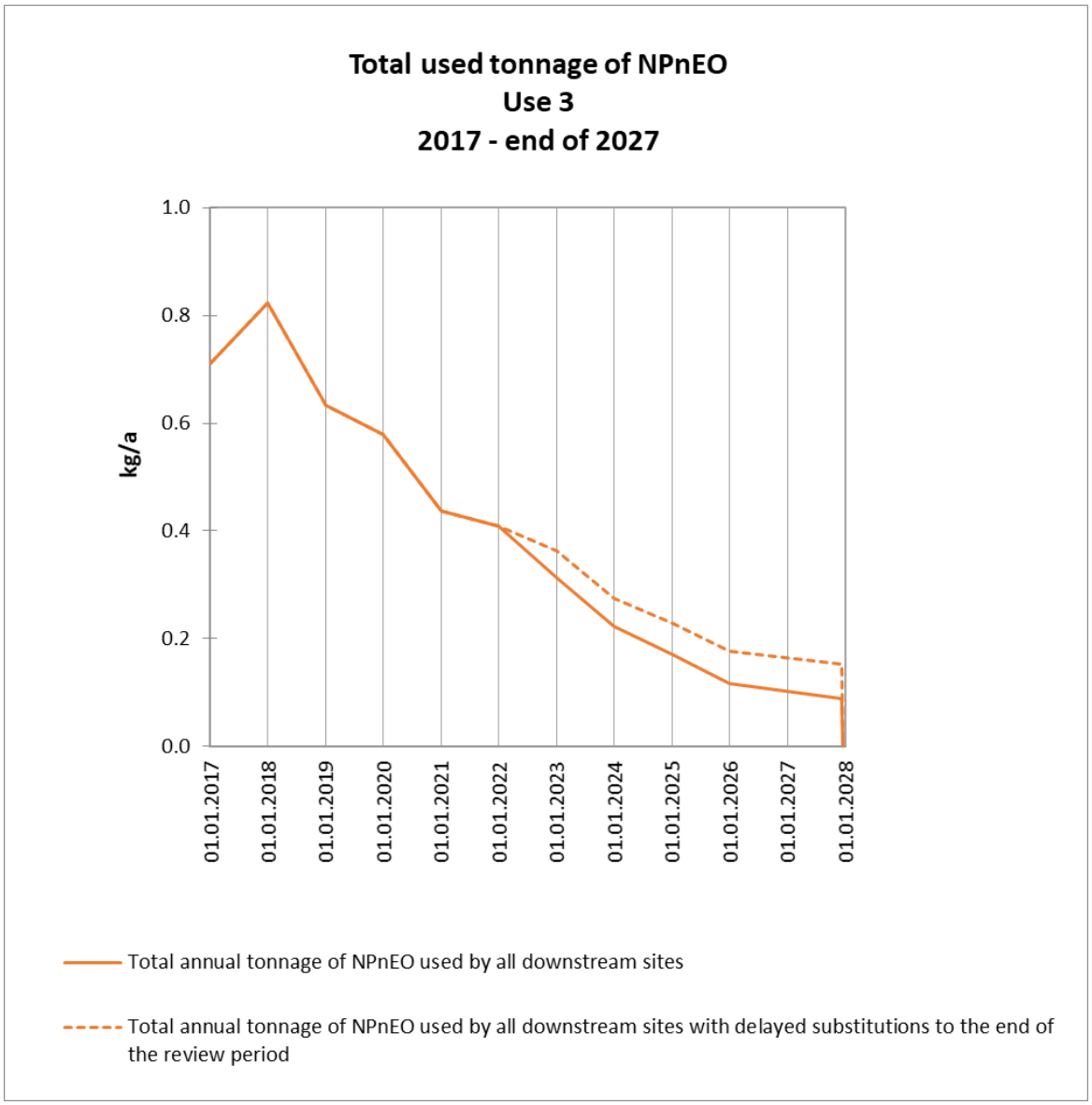


Figure 18. Evolution of the total annual used of NPnEO between 2017 and end of 2027 for the downstream user's sites considering planned substitutions and sales development.

The **total annual use at different times** and predicted for the **two cases** (substitution as planned or delayed) for **Use 3** are also displayed below in Table 12 for OPnEO and in Table 13 for NPnEO.

Table 12. Overview of evolution of amounts over time for OPnEO for Use 3 (downstream uses) under the two cases (substitutions as planned or delayed).

	Case 1	**Case 2**
	(substitution as planned)	**(all substitution projects delayed)**
Total annual tonnage at UK sunset date (kg/a)	40.19	40.19
Maximum annual tonnage after sunset date	42.28	48.65
Year when usage reaches 0	2026*	4th. of Jan. 2028

*1.4 g/a on 1st of June 2025 (0 g/a on 01.04.2026).

From the information presented above, it is clear that thanks to the planned substitutions, provided no substantial delays occur, the total annual amount of OPnEO will initially increase from 40.19 kg/a at the UK sunset date to 42.28 kg/a on the 1st of January 2024 due to growth in the sales figures. After this date, the used amount will start to decrease and reach 1.4 g/a on the 1st of June 2025 (0 g/a on the 1st of April 2026) if the substitutions are completed in time in the formulated reagents. This is in-line with the delay due to the shelf life of the products. However, if the substitutions are delayed towards the end of the review period for all formulation activities, a maximum annual usage of 48.65 kg/a from all uses at the downstream sites could potentially be reached as a worst-case until the end of the review period (the 4th of January 2028).

Table 13. Overview of evolution of amounts over time for NPnEO for Use 3 (downstream uses) under the two cases (substitutions as planned or delayed).

	Case 1	**Case 2**
	(substitution as planned)	**(all substitution projects delayed)**
Total annual tonnage at UK sunset date (kg/a)	0.36	0.39
Maximum annual tonnage after sunset date	n.a.	n.a.
Year when usage reaches 0	4th. of Jan. 2028	4th. of Jan. 2028

n.a.: not applicable

For NPnEO, the total annual amount should decrease from 0.36 kg/a at the UK sunset date to cease until the end of 2027 if the substitutions are completed in time in the formulated reagents. This is in-line with the delay due to the shelf life of the products. However, if the substitutions are delayed towards the end of the review period for all formulation activities, a total annual usage of 0.39 kg/a from all uses at the downstream sites could potentially be reached as a worst-case. The maximum usage of 0.39 kg/a would be reached at the UK sunset date in case of delayed substitutions.

For further details on this topic, refer to Section ‘Mass Balances and Evolution of used Amounts over Time’ in the CSR (Section 9.2.2.2 for OPnEO and Section 9.2.3.2 for NPnEO, respectively).

3.1.3 Releases of OPnEO / NPnEO at Downstream User Sites Over Time in OP / NPequiv., and Discussion on RMMs

- The releases of OPnEO and NPnEO occur via the release to wastewater from the laboratories or hospitals to municipal STPs. The predominant receiving compartments considered in this assessment are **surface water** and **agricultural soil,** the latter due to sludge application to soil from STPs.

- The two cases considered for the calculation of releases are:
  - Case 1 – Expected development in the total release of OP / $NP_{equiv.}$ over time considering the **planned substitutions**.
  - Case 2 - Expected development in the total release of OP / $NP_{equiv.}$ over time considering that all **substitutions are delayed** until the end of the review period.

⇨ In both cases the same level of **RMMs** are in place (e.g. **disposal of solid waste** containing OPnEO / NPnEO from downstream uses as if it was 'hazardous waste').

⇨ Considering the RMMs in place, the total release to wastewater is 33.33 kg/a OPnEO and 0.18 kg/a NPnEO at the downstream sites for the use applied for at the UK sunset date (worst-case).

⇨ **For OPnEO, the maximum annual release to wastewater** potentially reached over the review period at the end of 2027**, assuming that all substitutions are delayed (worst-case), is 40.77 kg/a** at the downstream sites. **For NPnEO, the maximum annual release** over the course of the review period **of 0.18 kg/a is reached at the UK sunset date**, assuming that all substitutions are delayed (worst-case). After this date, the release of NPnEO will constantly decrease, even if the substitutions are delayed.

Release pathways

- **Wastewater**: For downstream uses, direct release is occurring to wastewater.

- **Soil**: Direct release to soil is not considered relevant. Releases to soil are only indirect via application of sewage sludge to agricultural land. Releases to soil after STP via the air by way of deposition can occur even if those are expected to be very small.

- **Air**: Direct release is set to zero due to the very low vapour pressures of OPnEO and NPnEO. Releases to air during the removal process taking place in the sewage treatment plant (STP) are not set to zero but are minimal.

Main releases to the environment are releases to surface water via STP and releases to agricultural land via application of sludge. Releases to the environment can also occur from waste assumed to be landfilled. As estimated releases to the environment through landfilled waste are minimal in comparison to modelled direct releases from Use 3, these are not discussed further. Similarly, releases to air and direct releases to soil are not discussed further as they are minimal.

Overview of releases of OPnEO / NPnEO to surface water and soil in OP / NP equivalents

Two cases have to be considered regarding the expected development in the total release to the environment in OP / $NP_{equiv.}$ by the activities covered in Use 3 over time until the end of the review period. In both cases expected sales development, the shelf life of the reagents and the implemented RMMs at the downstream user sites are considered:

- '**All substitutions completed as planned'**: Expected development of the total release to surface water and soil in OP / $NP_{equiv.}$ over time considering that substitutions are completed as planned.

- '**All substitutions delayed'**: Expected development of the total release to surface water and soil in OP / $NP_{equiv.}$ over time considering that all planned substitutions are delayed until the end of the review period as a worst-case.

In the following only release to surface water is discussed in more detail. However, the same trend as for release to surface water over the course of the review period is also applicable to release to soil via application of sludge to agricultural soil.

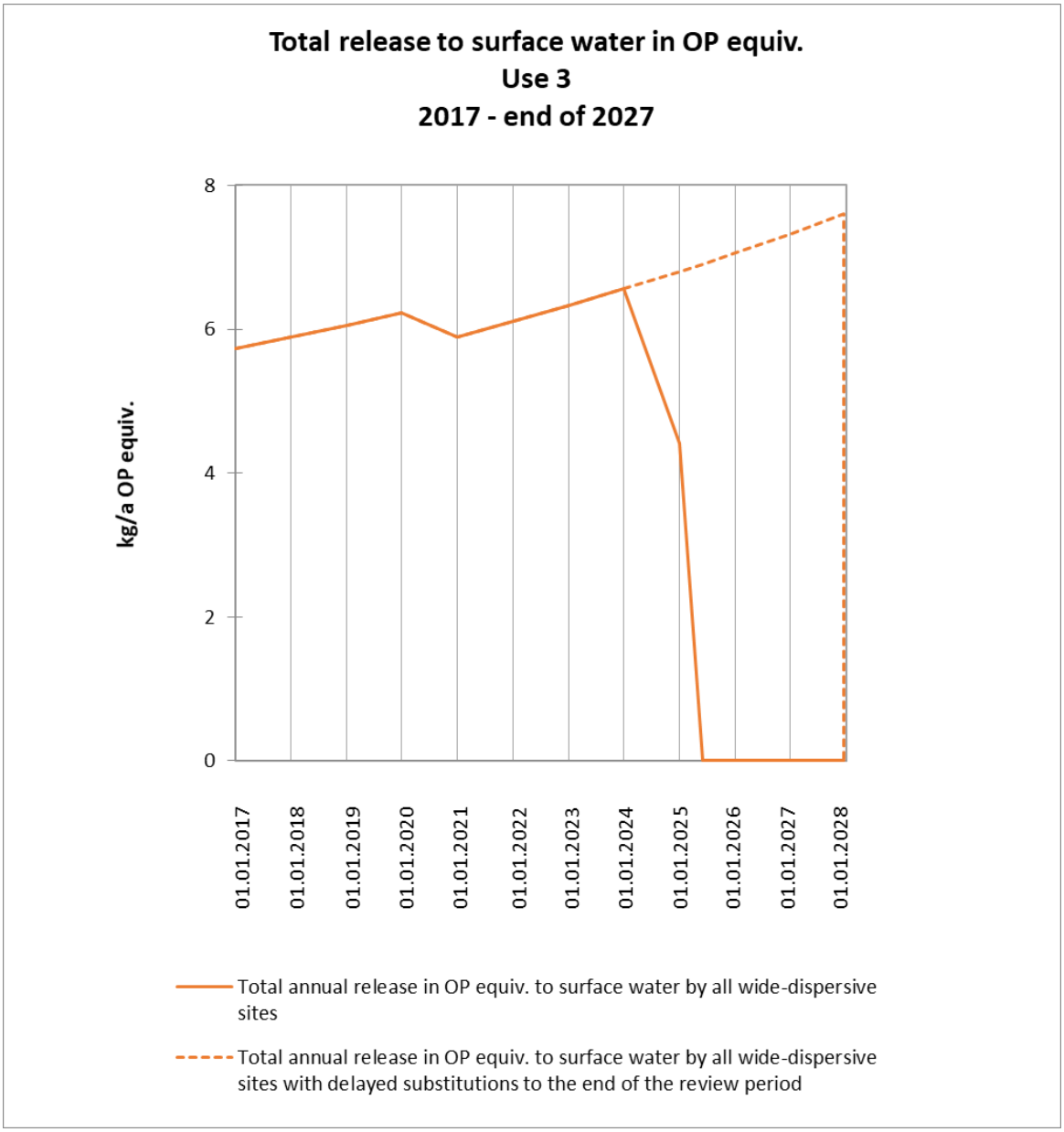


Figure 19. Evolution of the total annual release to surface water in $OP_{equiv.}$ from 2017 until the end of 2027 for the downstream sites considering planned substitutions, sales development, and the shelf life of the reagents.

As shown in Figure 19, if the substitutions are completed as planned in the formulated reagents, the total release to surface water in $OP_{equiv.}$ at the downstream user sites would initially further increase from **6.22 kg/a $OP_{equiv.}$** at the UK sunset date to reach a maximum of **6.56 kg/a in 2024** due to growth in the sales figures. After that, the release will decrease and will be **0.19 g/a on the 1st of June 2025** (0 g/a on the 1st of April 2026) in-line with the delay due to the shelf life of the products. However, if the substitutions are delayed towards the end of the review period for all formulation activities, a maximum total annual release of **7.61 kg/a $OP_{equiv.}$** to surface water from all wide-dispersive uses could potentially be reached as a worst-case until the end of the review period. Even though there is a certain risk of delay of substitution projects due to potential technical or regulatory difficulties and some delays have already occurred (see AoA), a delay of all projects until the end of the review period is highly unlikely.

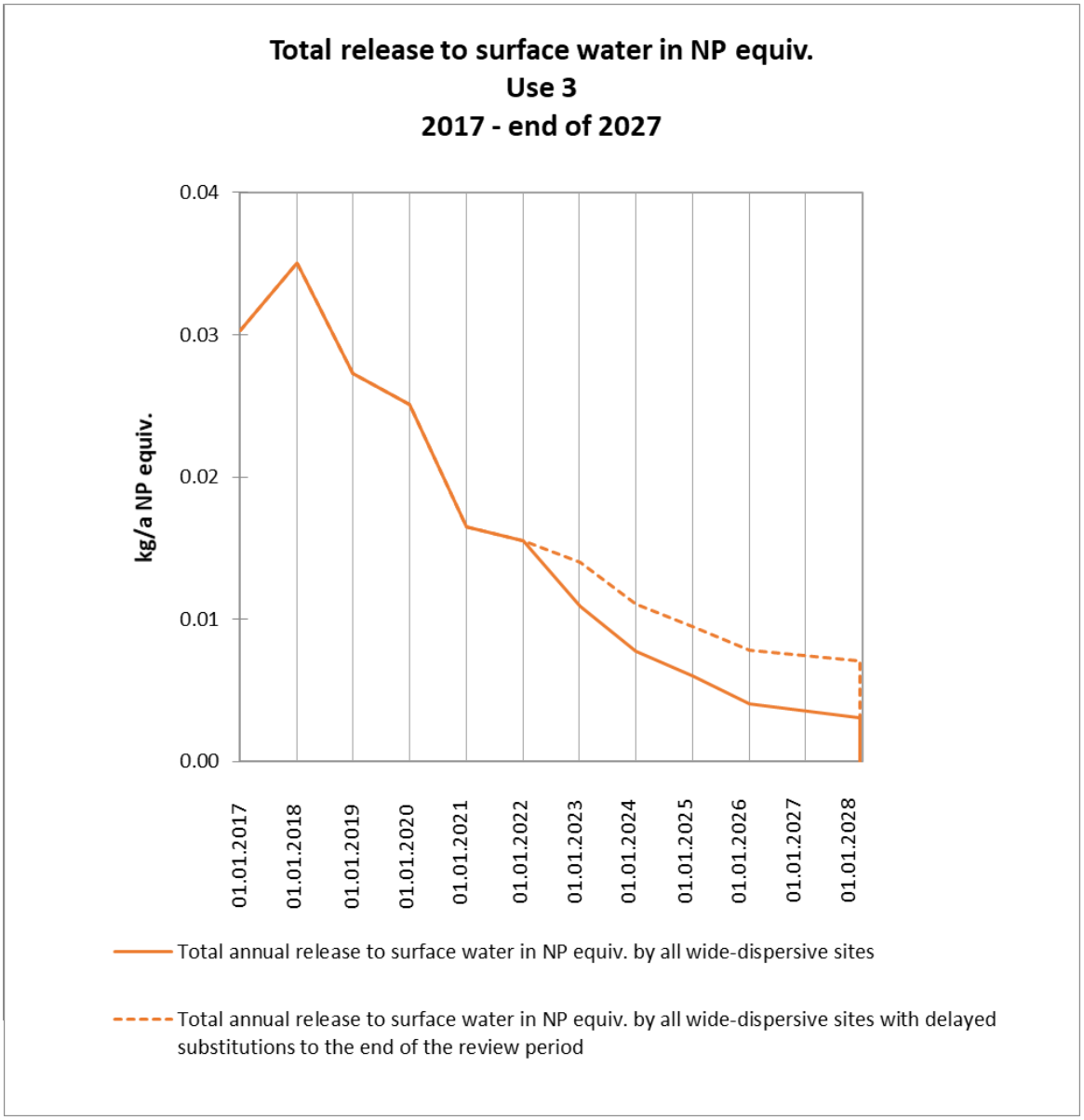


Figure 20. Evolution of the total annual release to surface water in $NP_{equiv.}$ from 2017 until the end of 2027 for the downstream sites considering planned substitutions, sales development, and the shelf life of the products.

As shown in Figure 20, if the substitutions are completed in time, the total release to surface water in $NP_{equiv.}$ at the downstream sites should decrease from **0.013 kg/a $NP_{equiv.}$** at the UK sunset date to cease at the end of the review period in-line with the delay due to the shelf life of the products. However, if the substitutions are delayed towards the end of the review period for all formulation activities, a maximum total annual release of **0.015 kg/a $NP_{equiv.}$** to surface water from all wide-dispersive uses could potentially be reached as a worst-case at the UK sunset date. Even though there is a certain risk of delay of substitution projects due to potential technical or regulatory difficulties and some delays have already occurred (see AoA), a delay of all projects until the end of the review period is highly unlikely.

Table 14 and Table 15 respectively give an overview of the total annual release of $OP_{equiv.}$ and $NP_{equiv.}$ to surface water and soil at the sunset date and by the end of the review period, for both cases (substitutions completed as planned or delayed), as well as the total (integrated) release of $OP_{equiv.}$

and $NP_{equiv.}$ to surface water over the review period (2022 to end of 2027). In the following only release to surface water is discussed in more detail. However, the discussed trends for release to surface water from downstream uses are also applicable for release to soil.

Table 14. Expected and worst-case releases to surface water after STP and soil (from application of sewage sludge) per year in kg/a $OP_{equiv.}$ from 2022 until the end of 2027 considering RMMs implemented at the EU sunset date.

USE 3	Scenario	Unit	Downstream uses release to surface water	Downstream uses release to soil*
Release to surface water / soil after STP at sunset date (the 30th of June 2022)	**Expected release considering substitutions**	kg/a $OP_{equiv.}$	6.22	5.19
	Max total releases with delayed substitutions	kg/a $OP_{equiv.}$	6.22	5.19
Release to surface water / soil after STP at the end of review period (end of 2027)	**Expected release considering substitutions**	kg/a $OP_{equiv.}$	0	0
	Max total releases with delayed substitutions	kg/a $OP_{equiv.}$	7.61	6.35
Total release to surface water / soil after STP over the review period (2022-end of 2027)	**Expected release considering substitutions**	kg/5.5a $OP_{equiv.}$	20.41	17.0
	Max total releases with delayed substitutions	kg/5.5a $OP_{equiv.}$	44.79	37.3

* Releases to soil are worst-case as 100% of sludge is assumed to be applied to soil (see CSR Use 3 Section 9.3.2.1).

Towards the end of the review period (end of 2027), the release to surface water in $OP_{equiv.}$ will have already ceased if substitutions are completed as planned (see Table 14). If all substitutions are delayed, a maximum of **7.61 kg/a $OP_{equiv.}$** (**6.35 kg/a $OP_{equiv.}$** for release to soil) could be reached at this time. In this case, an overall maximum amount of $OP_{equiv.}$ 2.2 times higher than if the substitutions would be completed as planned, would be released over the 5.5 years of the review period (i.e. **44.79 kg $OP_{equiv.}$** for surface water; **37.3 kg $OP_{equiv.}$** for soil). Although there is a certain risk of delay of substitution projects due to potential technical or regulatory difficulties and some delays have already occurred (see AoA), **a delay of all projects until the end of the review period is highly unlikely.** Therefore, this total amount can be considered as a worst-case that is highly unlikely to occur. Also,

as it was assumed that 100% of sewage sludge is applied to soil for Use 3 and this is only the case on average for 80% in the UK, the release to soil is likely lower [5].

Table 15. Expected and worst-case releases to surface water after STP and soil (from application of sewage sludge) per year in kg/a $NP_{equiv.}$ from 2022 until the end of 2027 considering RMMs implemented at the EU sunset date.

Use 3	Scenario	Unit	Downstream uses release to surface water	Downstream uses release to soil*
Release to surface water / soil after STP at sunset date (the 30th of June 2022)	**Expected release considering substitutions**	kg/a $NP_{equiv.}$	0.013	0.040
	Max total releases with delayed substitutions	kg/a $NP_{equiv.}$	0.015	0.046
Release to surface water / soil after STP at the end of review period (end of 2027)	**Expected release considering substitutions**	kg/a $NP_{equiv.}$	0.0031	0.009
	Max total releases with delayed substitutions	kg/a $NP_{equiv.}$	0.0071	0.022
Total release to surface water / soil after STP over the review period (2022-end of 2027)	**Expected release considering substitutions**	kg/5.5a $NP_{equiv.}$	0.0385	0.117
	Max total releases with delayed substitutions	kg/5.5a $NP_{equiv.}$	0.0568	0.173

* Releases to soil are worst-case as 100% of sludge is assumed to be applied to soil (see CSR Use 3 Section 9.3.2.1).

The release to surface water in $NP_{equiv.}$ is expected to decrease by about 75% towards the end of the review period in comparison with the emission at the UK sunset date if the substitutions are completed as planned (i.e. 0.013 kg/a $NP_{equiv.}$ at the UK sunset date compared to 0.0031 kg/a $NP_{equiv.}$ towards the end of 2027). The release to surface water will be 0 kg/a $NP_{equiv.}$ on the 4th of January 2028 (all substitutions completed). If all substitutions are delayed, a maximum of **0.0071 kg/a $NP_{equiv.}$ (0.022 kg/a $NP_{equiv.}$** for release to soil) could be reached towards the end of the review period. In this case, an overall maximum amount of $NP_{equiv.}$ about 1.5 times higher than if the substitutions would be completed as planned, would be released over the 5.5 years of the review period (i.e. **0.0568 kg $NP_{equiv.}$** for surface water; **0.173 kg $NP_{equiv.}$** for soil). Although there is a certain risk of delay of substitution projects due to potential technical or regulatory difficulties and some delays have already occurred (see AoA), **a delay of all projects until the end of the review period is highly unlikely**. Therefore, this total amount can be considered as a worst-case that is highly unlikely to occur. Also, as it was assumed that 100% of sewage sludge is applied to soil for Use 3 and this is only the case on average for 80% in the UK, the release to soil is likely lower [5].

Overview of RMMs and discussion on additional RMMs

As discussed above, the decrease over time in the releases of OPnEO and NPnEO to wastewater and thus to surface water and soil is the **result of the progressive substitution** (for which two cases are considered in the CSRs – one assuming substitutions as planned and one assuming delay in substitution until the end of the review period) as well as **RMMs** already in place at the downstream user sites. In the CSRs it is demonstrated that emissions and releases to the environment to and after STP from the activities covered in the Use 3 **are minimised as far as practically and technically feasible** by implementation of the RMMs as discussed below.

Downstream uses

The downstream uses take place in medicinal laboratories and hospitals. The generation of liquid and solid waste streams from these uses, and potential RMMs to avoid / reduce releases of OPnEO and / or NPnEO from these waste streams, are further discussed below.

All unused reagents in cartridges are disposed of as if they were hazardous solid waste. Note that most of these reagents are actually not classified as hazardous waste according to the waste regulations. However, instructions for waste disposal in communication to customers were adapted to indicate to dispose of this waste 'as if it was hazardous'.

Releases to wastewater mainly take place via liquid waste streams from the IVD modules, which may be directly connected to the sewer system. In the UK laboratory wastewater is considered as trade effluent and a trade effluent consent is needed from the local water authority prior to commencing any trade effluent discharge. Collection and/or pretreatment of liquid waste is not performed as a standard in UK laboratories, as there is no general legal requirement for this in the UK. In conclusion, OPnEO- and NPnEO-containing liquid waste is usually directly released to wastewater. A removal of these compounds by pretreatment or collection and subsequent incineration of liquid waste from the instruments is not implemented as a standard in UK laboratories. Therefore, no further removal of OPnEO / NPnEO was assumed. Instead, it was assumed as a worst-case that the entire volume of liquid sold minus the volume of liquid waste in empty cartridges and minus waste from specific instruments / assays (which are collected and disposed of as described above) ends up in the sewer. With respect to the total amount used for all assays covered in this AfA, this is ca. 84% for OPnEO and 47% for NPnEO. Implementation of further RMMs at downstream users to reduce release to the environment via liquid waste streams is not considered technically and practically feasible as further discussed below.

For instance, for the cobas® instruments, the adaptation of modules to selectively collect waste containing OPnEO and / or NPnEO would require development of new hardware components and new software by Roche's instrument partner. The adaptation of the module setup would require in-house verification and validation of instrument function, re-registration as new instrument in most countries, re-registration of the entire assay portfolio, etc. The efforts to be made for adaptation of the IVD modules would be comparable with those needed when developing and introducing a new analyser generation. This would require at least 5 years for the development phase, which is also associated with a high cost (> [redacted]). In addition, the implementation phase would easily take another 5 – 7 years in order to replace all instruments on the market. Note that the cost for the implementation phase is not yet included in the figure given above (which represents the cost for development only). Altogether, **all substitutions are expected to be completed in a much shorter time frame** than that needed for the development and introduction of adjusted instrument modules on the market.

In principle, another option would be to **collect all liquid waste from the instruments**. However, facilities for liquid waste collection (i.e. containers and logistic facilities for the waste to be collected by a waste management company) are not foreseen during installation of laboratories, as this is not required by UK regulations. Space is identified as the most important limitation for the installation of large liquid waste containers (e.g., two tanks of 1'000 L) (see Section 9.6 in the CSR for Use 3). Therefore, **modifications of the laboratory building would typically be needed**. This could result in high costs as well as a long time needed for implementation of the risk management measure. The use of available small containers (e.g. 5-L containers for cobas® 8000) on the other hand would require too frequent manual emptying and therefore disrupt normal operation of and throughput in laboratories. Moreover, larger waste storage tanks and accompanying facilities would be needed on-site anyhow to store the liquid waste before collection by a waste management company.

The collection of liquid waste would need to be followed by incineration. Based on incineration cost in the UK (ca. 3'000 £ per ton), incineration of concentrated liquid waste would lead to **total cost of ca. 4.8 to 27.6 mio £ per year.** Moreover, incineration of the generated liquid waste would also be unfavorable with respect to the high energy need as well as the increased emission of CO_2 to the environment.

Alternative to collection and disposal of liquid waste, liquid waste could theoretically be pre-treated before release into the sewer system. Online pre-treatment devices have been installed in France, as a result of the legal requirement to disinfect biological wastewaters. Although some degradation of OPnEO and NPnEO may occur in such devices, no complete degradation could be expected, and in addition, generation of OP or NP or other degradation products may occur during treatment. An efficient method for removal of OPnEO / NPnEO in liquid waste from IVD instruments is currently not available. The cost of pre-treatment devices as installed in France range roughly from 13'000 to 26'000 £. Several hundred devices would be required. Further, space constraints would also pose an important problem. Altogether, **it will be difficult to identify a method or device having a high and reliable efficiency for complete OPnEO and NPnEO degradation** for all kinds of IVD waste compositions. If such a method or device was identified, installation would require a large amount of time and would be associated with high cost.

In conclusion, separate collection of concentrated liquid waste (followed by incineration) or pre-treatment of waste is **not considered feasible to be implemented within a reasonable timeframe and at reasonable cost**. If such cost was not claimed from Roche, the customers themselves – and thus ultimately insurance schemes and the healthcare system – would have to cover the additional cost.

Monitoring

No monitoring campaign was conducted at a laboratory / hospital or an associated STP since the exact source of OPnEO and NPnEO in such effluents would be difficult to trace. Measurements would not only reflect emissions from the downstream user site but likely be a mixture of several sources.

Regarding liquid waste streams from IVD instruments, amounts of OPnEO and NPnEO contained in the assays and the fractions that are released are known. Measurements from one study [6] are available and are in good agreement with calculated values. Therefore, there would be **no or limited added value of routine monitoring of OPnEO and NPnEO in liquid waste streams** and such monitoring is not performed.

3.1.4 Geographical and Temporal Considerations and Comparison with Monitoring Data

- ⇨ Releases are generally **well-spread over the year**. The releases are **spread throughout the UK** as RDL's instruments are installed throughout the UK.
- ⇨ The demonstrated **broad margin of safety** at most times and locations when comparing local PECs with reference values such as Environment Quality Standard from the EU Water Framework Directive (EQS) and / or predicted no-effect concentration (PNEC) can serve as an indication that the overall releases from RDL's downstream uses to the environment **are not expected to cause issues** in the receiving environmental compartments.

Geographical and temporal considerations

Downstream user sites

The downstream users are medicinal laboratories and hospital laboratories. The number of instruments currently installed in the UK is > 1'000 giving an indication of the number of customers in the UK (See supporting document SD1_SEA_Nr_Instruments_RDL_Use3_CONFIDENTIAL). These **customers are well-spread across the UK**. As explained in the CSR (Use 3) as well as above, the exposure scenario had to be developed using a worst-case assumption that all liquid waste (except the fraction disposed of as solid waste, see above) is introduced to the wastewater and treated in a municipal wastewater treatment plant. Similarly, it was assumed that all sewage sludge is used in agriculture. At the same time, it was considered not feasible nor cost-efficient (taking into account the timeline of planned substitutions) to install additional RMMs to collect and incinerate or pre-treat liquid waste at downstream user sites. The overall release of OP and $NP_{equiv.}$ to surface water from Use 3 was estimated to be 6.22 and 0.015 kg/a respectively at the UK sunset date (assuming that all substitutions are delayed) and will evolve to 0 kg/a at the end of the review period (or earlier for OPnEO in case all substitutions are completed as planned). Release from STP can be assumed to be mostly to freshwater systems, although it can be assumed that the STPs to which some laboratories are connected release to the marine environment. **Temporal variation in releases is expected to be minimal**. The maximum emission days for the exposure scenarios is assumed to be 360 days/year. Fluctuations may however be expected between weekends (lower releases) compared to working days. Predicted environmental concentrations (PECs) are given for the maximum usage at the end of 2027 for OPnEO and at the UK sunset date for NPnEO, assuming that all substitutions are delayed as a worst-case and will be further discussed below. The development of the emissions as shown in Figure 19 and Figure 20 of OPnEO / NPnEO are expected to vary mainly due to:

- Change in quantities of OPnEO / NPnEO required for the IVD-assays due to evolution in the sales of assays thereby influencing the quantities of OPnEO / NPnEO used and released to wastewater by the downstream users (laboratories / hospitals).
- Planned substitutions of OPnEO / NPnEO in the IVD assays leading to a decrease of OPnEO / NPnEO used and released to wastewater.

Similar considerations apply for releases to soil. The maximum overall release to soil via application of sewage sludge from Use 3 was estimated to be 5.19 kg/a $OP_{equiv.}$ and 0.045 kg/a $NP_{equiv.}$ (assuming that all substitutions are delayed).

Comparison of predicted environmental concentrations with available measurements, measurements from monitoring campaigns, existing reference values

Before **comparing modelled / measured concentrations with EQS / PNEC** values [30] it should be noted that this comparison is **only for illustration**. Ideally, OP / $NP_{equiv.}$ concentrations should be compared with EQS / PNEC values. All modelling results presented in this dossier are given as OP / $NP_{equiv.}$, but often only OP / NP concentrations are available in case of measured background concentrations. This should be kept in mind when drawing conclusions. Further, in this application for authorisation it is assumed that currently, no reliable threshold values for endocrine disruptive effects in aquatic organisms can be assigned for the substances under consideration. Moreover, the EQS values for OP and NP under the Water Environment (Water Framework Directive) (England and Wales) Regulations 2015 [30] are currently under revision and will be prone to change. Altogether, only indicative conclusions can be drawn from the comparisons made below. In the following paragraphs, PECs for the different sites and both substances are discussed. For soil, a PNEC is only available for OP. The PEC / PNEC ratio for $OP_{equiv.}$ in soil based on maximum releases from Use 3 was 0.0082, i.e. well below 1 (see Section 10.1.2.1.3.2. CSR Use 3).

An overview is provided below of the comparison of $OP_{equiv.}$ (Table 16) and $NP_{equiv.}$ (Table 17) in surface water with background and EQS values, and in the case of $OP_{equiv.}$ a PNEC value, for the different scenarios. The different sites and scenarios are discussed in more detail for surface water in the following sections.

Table 16. Comparison of combined local and regional PECs (in $OP_{equiv.}$) with available background and reference values for fresh waters.

Sites / Region	**Combined Freshwater PEC** [µg/L]	**Background values** [µg/L]	**EQS** [µg/L]	**PNEC**** [µg/L]	**Ratio PEC / EQS**	**Ratio PEC / PNEC**
Average-size laboratory	0.00597	0.02 – 0.7*	0.1	0.034	0.060	0.18
Big laboratory	0.000225	0.02 – 0.7*	0.1	0.034	0.0023	0.0066
Regional	$6.19 \cdot 10^{-6}$	0.02 – 0.7*	0.1	0.034	$6.2 \cdot 10^{-5}$	0.00018

* Range for surface and groundwaters.

** PNEC value as determined in the hazard assessment of this CSR ('Derivation of the PNEC or dose-response-relationship for endocrine disrupting properties of 4-(1,1,3,3-tetramethylbutyl) phenol, ethoxylated (OPNEO)', February 28, 2019, Patricia Janz, Christiane Brandt). See supporting document to the CSR 'SD1_CSR_Hazard_assessment_OPnEO_RDL_Use3'.

Table 17. Comparison of combined local and regional PECs (in $NP_{equiv.}$) with available reference values for fresh waters.

Sites/Region	Unit	Combined Freshwater PEC [µg/L]	Background values (range)* [µg/L]	EQS [µg/L]	Ratio PEC / EQS
Wide-dispersive uses					
Average-size laboratory	µg/L	$4.76 \cdot 10^{-5}$	0.05 – 0.1	0.043	0.0011
Big blood bank	µg/L	$1.75 \cdot 10^{-3}$	0.05 – 0.1	0.043	0.041
Regional	µg/L	$5.27 \cdot 10^{-11}$	0.05 – 0.1	0.043	$1.22 \cdot 10^{-9}$

*Range for surface and groundwaters.

Wide-dispersive uses - OP

The local PEC in surface water for wide-dispersive uses was calculated to be 0.00597 µg/L for an average-size laboratory to 0.000225 µg/L for a large laboratory, i.e. 5.97 ng/L to 0.225 ng/L (Use 3 + regional; $OP_{equiv.}$; see Table 16), respectively. This concentration is lower than measured environmental concentrations (rivers and groundwaters show concentrations across the EU and the UK in the range of 20 – 700 ng/L).

Local $OP_{equiv.}$ in soil porewater of 0.044 pg/L, i.e. 0.000000044 µg/L (which, according to the guidance document, are assumed to be identical to groundwater concentrations) are by a factor of 100'000 lower than calculated surface water concentrations of 0.00597 µg/L due to wide-dispersive uses (obtained by summation of the PEC obtained for Use 3 at an average-size laboratory and the local concentration in surface water resulting from the release of treated leachate from a landfill site as well as the regional concentration). Consequently, the modelled local soil porewater concentrations are not assumed to contribute to $OP_{equiv.}$ in surface water.

The local PEC for wide-dispersive uses in surface water (0.225 – 5.97 ng/L, see above) is also approx. 16 – 440 times lower than the AA-EQS of 100 ng/L for OP, resulting in a PEC / EQS ratio of $6\ 10^{-5}$ – 0.06 (Table 16). Furthermore, the local PEC for wide-dispersive uses in surface water is also approx. 5 times lower than the PNEC of 34 ng/L for OP, resulting in a PEC / PNEC ratio of 0.18 (Table 16). Since the modelling assumptions were demonstrated to be very conservative, it can be assumed that the **'true' contribution of wide-dispersive uses** to environmental OP concentrations **will likely be much lower than the EQS / PNEC value**.

Wide-dispersive uses – NP

The local PEC in surface water for wide-dispersive uses was calculated to be 0.0000476 µg/L for an average size laboratory and 0.00175 µg/L for a big blood bank, i.e. 0.0476 – 1.75 ng/L (Use 3 + regional; $NP_{equiv.}$; see Table 17). These concentrations are a factor of 30 – 2'100 lower than the measured concentration of NP in surface waters of 50 – 100 ng/L.

Local $NP_{equiv.}$ in soil porewater of 0.063 pg/L, i.e. 0.000000063 µg/L (which, according to the guidance document, are assumed to be identical to groundwater concentrations) are by orders of magnitude lower than calculated surface water concentrations of 0.0000476 µg/L due to wide-dispersive uses (obtained by summation of the PEC obtained for Use 3 at an average-size laboratory

and the local concentration in surface water resulting from the release of treated leachate from a landfill site as well as the regional concentration). Consequently, the modelled local soil porewater concentrations are not assumed to contribute to $NP_{equiv.}$ in surface water.

The local PEC for wide-dispersive uses in surface water (0. 476 – 1.75 ng/L, see above) is also approx. 25 – 90 times lower than the AA-EQS of 43 ng/L for NP, resulting in a PEC / EQS ratio of 0.0011 – 0.041 (Table 17). Since the modelling assumptions were demonstrated to be very conservative, it can be assumed that the **'true' contribution of wide-dispersive uses** to environmental NP concentrations **will likely be much lower than the EQS value**.

Wide-dispersive uses – OP and NP

The relative contribution of wide-dispersive uses (as quantified and described above) to OP / NP concentrations in surface waters will be lower than the values depicted above as the modelled PEC values are OP / $NP_{equiv.}$(i.e. the sum of OP / NP and all of its precursors) and the measured concentrations are OP / NP concentrations only. Despite these conservative assumptions, the comparison of modelled OP / $NP_{equiv.}$ with measured OP / NP concentrations already shows that the **wide-dispersive PEC is smaller than the measured values**.

Regional exposure

The contribution of regional versus local exposure to combined PEC values is discussed below. For this comparison, it should be kept in mind that regional exposure was calculated with the 'Multifate' model based on the wide-dispersive uses under the assumption that 100% of the total amount are released in the region. Release from waste (as was estimated for Use 3) also contributes to regional exposure, however, as is shown in the CSR for Use 3, the contribution was small.

Total local exposure is calculated by summing up exposure from local uses and regional exposure for each site. The contribution of regional and local exposures to combined local exposure were evaluated by comparing the respective predicted environmental concentrations for each site as depicted below. For OP, in summary, the respective local sources contributed to a greater extent than regional exposure to total exposure of surface waters with $OP_{equiv.}$ for local wide-dispersive use. For NP, the respective local sources contributed to a greater extent than regional exposure to total exposure of surface waters with $NP_{equiv.}$.

Regional exposure – OP

Total local exposure is calculated by summing up exposure from local uses and regional exposure for each site. The contribution of regional and local exposures to combined local exposure were evaluated by comparing the respective predicted environmental concentrations for each site as (Table 16). In summary, the respective local sources contributed to a greater extent than regional exposure to total exposure of surface waters with $OP_{equiv.}$ for local wide-dispersive use.

Regional $OP_{equiv.}$ in soil porewater (which, according to the guidance document, are assumed to be identical to groundwater concentrations) are by a factor of approx. 650 lower than calculated surface water concentrations and hence, are not assumed to contribute to $OP_{equiv.}$in surface water

Regional exposure – NP

Total local exposure is calculated by summing up exposure from local uses and regional exposure for each site. The contribution of regional and local exposures to total local exposure were evaluated by

comparing the respective predicted environmental concentrations for each site (Table 17). In summary, the respective local sources contributed to a greater extent than regional exposure to total exposure of surface waters with $NP_{equiv.}$.

Overall conclusion

Comparison of modelled and measured concentrations in surface water and modelled concentrations in soil with **current EQS / PNEC** values for OP and NP further demonstrated that **concentrations were well below the EQS / PNEC values.** The **broad margin of safety** can serve as an indication that the overall releases from RDL's downstream uses to the environment are not expected to cause issues in the receiving surface waters or agricultural soil.

The comparison with environmental concentrations from large surface water monitoring campaigns indicated that modelled concentrations are in most cases lower than recently observed 'background' concentrations in the receiving surface waters. This demonstrates that **the contribution of the releases from RDL's downstream uses is small**.

Qualitative description of impacts

Taking all abovementioned information into account, the **impacts** of the releases from RDL's downstream uses **are considered to be very low**. Taking into account the timeline of the planned substitutions, the releases and the associated potential impacts **will be further gradually reduced**, reaching zero by latest by the end of the review period (the 4th of January 2028).

The predominant receiving compartments are surface water and agricultural soil, and both OPnEO and NPnEO are included in the authorisation list because of their degradation to OP and NP, which are considered as potential endocrine disruptors in the environment. The evidence for OP and NP's endocrine disruptive properties mainly stems from studies in fish. Evidence for other types of organisms is more limited, less clear or experimentally still further being explored. Therefore, **fish populations are currently the most important endpoint** in the assessment of potential risks / impacts to the environment. However, it cannot be excluded that other organisms may also be potentially impacted.

3.2. Description of Economic Impacts

3.2.1 Overview

⇨ There is a range of possible impact scenarios resulting from a non-authorisation with the following two extremes:

- **Scenario 1: Competitors** will either **receive an authorisation** or will not be dependent on OPnEO or NPnEO for their assays and are able to continue business as usual and have the capacity to take over Roche's market share.
- **Scenario 2**: Most Roche's **competitors** are also **not able to supply** the market with a complete portfolio of IVD products. This could be due to the fact that they also use OPnEO / NPnEO in their products, also do not receive an authorisation and / or are not able to take over Roche's market share due to capacity constraints.

⇨ In all cases, an **impact on health** services to patients is expected to occur. This is due to factors complicating the replacement of lacking IVD assays by competitor assays / systems, if at all possible and limited alternative options to obtain missing IVD test results.

As described in the non-use scenario, RDL will not be able to continue to import and deliver the affected IVD assays to their customers in the UK. At the same time, Roche's customers, i.e. laboratories and hospitals in the UK will not be able to perform the full portfolio of IVD assays with immediate effect.

To **evaluate the impacts** in case of the non-use scenario, it is important to consider possible assumptions regarding the situation of RDL's competitors, i.e. the situation on the UK IVD market. There is a **range of possible scenarios** with the following two extremes:

- **Scenario 1**: **Competitors** will either **receive an authorisation** or will **not be dependent on OPnEO or NPnEO** for their assays so that they could deliver the market with IVDs as usual and may increase their market share depending on production capacities and thus take over Roche's market share.

- **Scenario 2**: Most **Roche's competitors are also not able to supply the market** with IVD products. This is expected under the assumption that competitors also use OPnEO / NPnEO in their products and none of them receives an authorisation. Due to the constraints of the IVD business (see non-use scenario), it is expected that for at least some competitors, the non-use scenario will be like RDL's, meaning that the products will not be available on the market anymore.

For each of these scenarios, minimum and maximum impacts depend on whether substitutions are completed as planned (minimum) or all are delayed until the end of the review period (maximum) (see Figure 21).

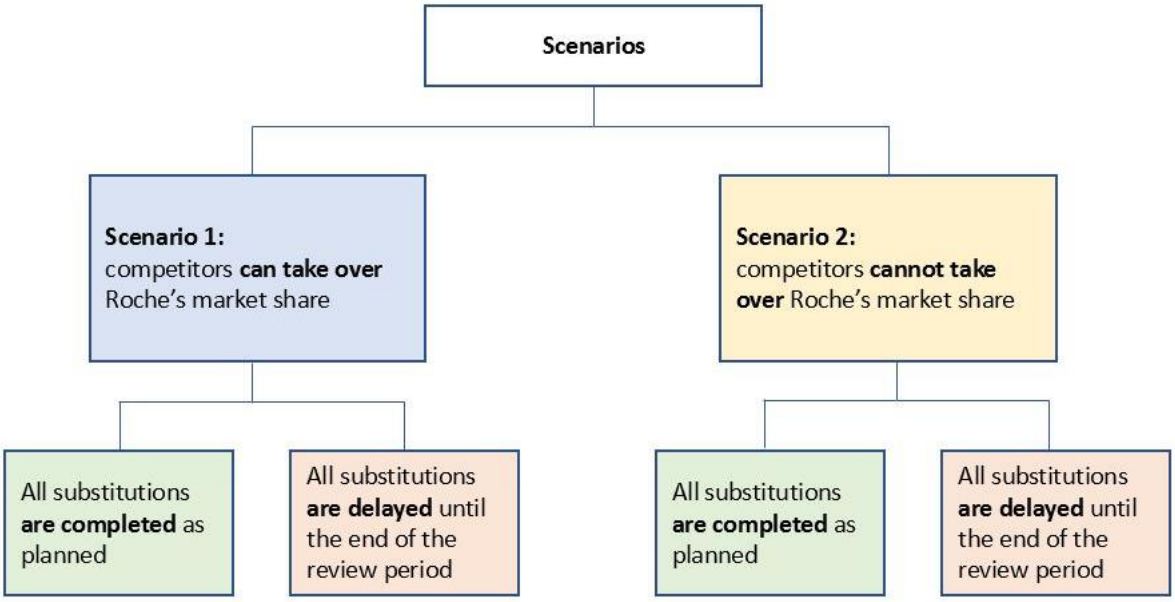


Figure 21. Overview of the two scenarios considered in the impacts assessment with two sub-scenarios depending on the completion of substitution projects.

As indicated, Scenario 1 and 2 are extremes and the likely impacts are expected to be in-between. It is expected that at least **some competitor systems** that are not affected (or for which a UK authorisation is already available) **will be available to replace a part of RDL's systems** considering the worldwide market of IVD manufactures. On the other hand, it is **unlikely that competitors can fully take over Roche's market share** as it is known from EU applications for authorisation and some UK applications that have already been submitted that other IVD manufactures are using OPnEO, and to a lesser degree NPnEO, in their assays. Competitors may in particular not be able to fully take over Roche's market share if authorisation was also not obtained in the EU and competitor's would have to take over Roche's entire market share in the EU and the UK. The use of OPnEO in competitor assays was not further analyzed since – even with further information on such usage – it will not be possible to predict more precisely the likely impacts as the latter will be influenced by several factors. It should be further noted, that some customers may not switch to competitor systems if RDL could guarantee re-supply of the missing assays within 12 – 24 months. Even though this is unlikely, this would be covered under Scenario 2. Therefore, in the following analysis of impacts the influence of the two extreme scenarios is considered to define the possible range for the likely case.

In all cases, an impact on health services to patients is expected to occur due to factors complicating the replacement of lacking IVD assays by competitor assays. These include limited production capacities of competitors and time required for laboratories to switch to a competitor system, if available on the market, including validation of the systems. As a consequence of **Scenario 1**, **competitors are expected to gain from Roche's loss**, but this cannot easily be quantified. In addition, a large investment will be needed for all customers to switch to competitor systems.

The most important direct consequences and the occurrence of **impacts on healthcare services in the two scenarios** over the course of the review period are summarised in Figure 22 based on the assumption that all substitutions are delayed. Note that not all impacts are shown.

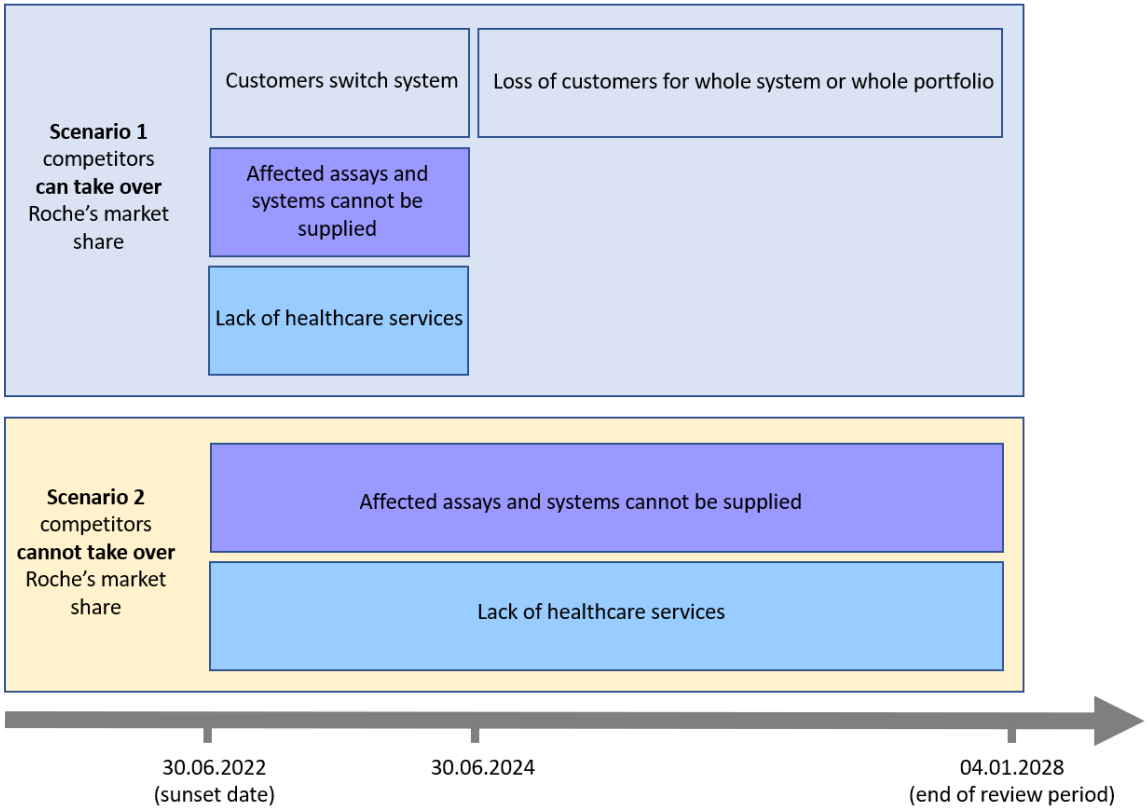


Figure 22. Most important direct consequences and the occurrence of impacts on healthcare services in the two scenarios over the course of the review period if all substitutions are delayed. (Not all impacts are shown).

In the following sections, the **details of these impacts are first described for the four product groups**. The four product groups are discussed together since they are all assays used in centralised laboratories with similar consequences in the non-use scenario.

Subsequently, impacts are quantified and summarised for the different actors in the supply chain (Roche and its customers). In a separate section, social impacts are then described.

3.2.2 Description of Impacts for IVD Assays Used in Centralised Laboratories Including RTD

- ⇨ If RDL can no longer supply certain assays, this will lead to **gaps in the parameter portfolio** and RDL will not be able to fulfil **customer contracts**.
- ⇨ From a physician's and patient's perspective, it is not acceptable to **miss one or several pivotal diagnostic markers**. Therefore, gaps in the parameter portfolio would need to be filled instantly.
- ⇨ Filling the gaps with competitors' IVD assays is not feasible due to the '**closed system'** approach of Roche's instruments and assays typical for the IVD industry.
- ⇨ Short-term solutions such as backup systems, sending out samples or installing only single instrument units from competitors may only **temporarily alleviate** the issue of lacking parameters and only to a limited extent.
- ⇨ Customers are expected to change to a competitor system if possible. Considering the requirements to setup a full centralised laboratory and the tender process, the switch to the **complete solution** of a competitor will take **12 – 24 months**. Customers and therefore ultimately the healthcare system are expected to face substantial cost for such a switch.
- ⇨ A laboratory changing supplier might need to **validate all assays** (making sure that old results fit new results) and might even risk **losing its accreditation** if this is not possible due to unavailability of the old assays.
- ⇨ Upon refusal of an authorisation, Roche / RDL faces financial **losses** from products not sold, which could extend to the entire market for centralised laboratories for the affected systems or portfolios including the loss of existing customers and inability to gain new ones. Roche also faces **damage in reputation** due to not being able to fulfil contracts.
- ⇨ In any case, a **serious lack of healthcare services** for patients is expected due to the logistical challenges of short-term solutions and time required to switch to a competitor system.

As described in the non-use scenario, RDL will not be able to continue to deliver the affected IVD assays to their customers (hospitals, laboratories, blood banks) in the UK leading to RDL not being able to fulfil their customer contracts. For the product portfolios of CC and DM these customers are mainly large centralised private laboratories or centralised laboratories in hospitals (see further description in Section 2.7.1) and for HIV centralised laboratories and in addition, blood banks. Laboratories for tissue diagnostics (RTD) are also centralised, but the assays are usually not run in the same laboratories as e.g. CC or DM. RTD is discussed at the end of this section.

As illustrated by the **'subway' map** (see Figure 8 in Section 2.7.1), the Roche portfolio of Clinical Chemistry (incl. Drug Monitoring) comprises about 120 parameters, many of which are 'basic' parameters that are routinely ordered by physicians / hospitals to assess the general health status of a patient. If some of these parameters cannot be tested on Roche systems (as in the non-use scenario), Roche's customers could no longer fulfil the requests of their customers completely (i.e. the laboratory result report would **miss some of the requested parameters**, e.g. low-density lipoprotein cholesterol (LDLC3) or Bilirubin Total Gen 3 (BILT3). Similarly, if the HIV parameter cannot be measured within the infectious disease portfolio, a **key parameter for a patient's diagnosis or**

blood-product classification is missing. From a physician's and patient's perspective, it is not acceptable to miss one or several pivotal diagnostic markers as this could lead to wrong diagnosis and ultimately to wrong treatment decisions. Therefore, gaps in the parameter portfolio would need to be filled instantly. This is however not, or only partially, feasible as explained in the following paragraphs:

1) The switch to another provider (a Roche competitor) on a reagent level would not be possible due to the '**closed system'** approach as described in Section 3.3. The competitor's reagents would not work on the Roche instrumentation and are furthermore not registered on Roche instruments and are therefore not approved as IVDs on the Roche systems.

2) In some cases, and to a limited extent (i.e. for few customers), **backup systems** may be available to measure the missing parameters, e.g. in the case of blood banks that cannot operate if the HIV parameter is missing and therefore usually have backup systems in place. In order to fill the gaps of missing assays, the assays of these backup systems must also be 'OPnEO / NPnEO-free' or an authorisation must be available for usage, which may not be the case. As laboratories will not have a fully mirrored system in place, the backup systems may only **temporarily alleviate** the issue of lacking parameters and will likely not cover the complete instrumentation.

3) As mitigation, a laboratory could **send the samples to another laboratory** that uses a different IVD provider's system that is not affected by the usage of OPnEO / NPnEO and pay for the testing leading to additional costs, logistic efforts, data transfer, etc. RDL may be liable to indemnify laboratories for the cost of sending out samples, depending on the terms of the individual Framework Agreement. Apart from the additional costs and efforts, it is questionable whether the additional time needed for testing would be acceptable to the ordering hospital / physician. Furthermore, it is questionable whether the **capacity of laboratories** with competitor systems would be sufficient to fulfil these **additional requests** even if the missing parameters could in principle be measured on competitor systems. This is especially questionable for products where Roche has a large market share, e.g. for CC. Therefore, it can be assumed that this approach may only provide a temporary solution in some specific cases in which the measured parameter is not relevant for fast, potentially lifesaving decisions.

4) In principle, it would be conceivable to provide the single specific reagents of affected parameters (i.e. the affected assays) from a competitor together with the corresponding **competitor's instrument**. This, however, would need **additional laboratory space** (which is often limited, see supplemental document SD5 to the CSR), would result in **increased training efforts** for laboratory personnel, **reduce throughput** while at the same time **increase complexity** and make the system **less reliable** and **efficient**. Furthermore, also the implementation of only a single instrument unit of a different provider can result in considerable efforts and costs while not providing a longer-term solution that meets the requirements of the laboratory. Therefore, this solution may only be accepted by Roche customers in specific circumstances. For example, this may in some cases be feasible for DM assays where it is more common that customers already have a competitor system in place for some complementary parameters. It can therefore be assumed that this approach may only provide a (temporary) solution in some specific cases.

5) The **switch to the complete solution of a competitor** would not be feasible at all in a short timeframe when considering the requirements to setup a centralised laboratory and the tender process (see Section 3.3). The decision for a competitor would take months and then the de-installation of the Roche system, re-building of laboratory infrastructure, delivery and installation of the competitor's system would take another several months. Under normal circumstances,

instruments in a large laboratory would be replaced in a stepwise approach with parallel testing on new and old instruments (comparison via **side-by-side validation**) to validate the new instruments / assays. This is often a regulatory requirement, especially for laboratories with accreditation. One common way to handle this is to place the new instruments at another location close to the laboratory during the verification due to space limitations. Then the old instruments are deinstalled one by one and at the same time the new instruments are moved and replace the old ones. This typically takes one day per instrument. This approach will not be feasible for affected assays as the affected assays will not be allowed to be run anymore. Consequently, accreditation of laboratories, often needed for reimbursement by health insurances, are put at risk. Overall, the process of switching to a competitor solution for the **entire laboratory at one customer is estimated to take 12-24 months** including validation of, and training for the new system. Therefore, as Roche will only be informed of a non-authorisation decision after the sunset date, laboratories (Roche's customers) would not have the possibility for testing of the affected assays for a considerable time and would hence be seriously affected.

For these reasons, even the loss of a few single parameters of the portfolio would jeopardise the entire Roche IVD business with centralised laboratories as well as their customers' operations and specifically, their ability to provide their services to the healthcare system. In the first 12-24 months after a non-authorisation decision, RDL is therefore expected to face **losses** based on affected assays that cannot be sold. Moreover, losses are expected for customers of RDL due to assays not delivered, i.e. assays that cannot be offered to patients or additional costs for testing certain parameters in other laboratories (if at all feasible; see above). Customers would need to switch to the instruments of another supplier if possible. The customers themselves - and thus ultimately insurance schemes and the healthcare system – are expected to have to face financial consequences. RDL has a large market share in providing MLS to NHS hospitals in the UK. Therefore, the NHS would be faced with the cost of changing systems in all the affected hospitals. In some cases, RDL may be liable to indemnify customers for the financial losses or customers may be able to claim financial losses from RDL. This will depend on the individual framework agreements and contracts. The cost for mitigation measures would then represent an additional economic loss to RDL.

Apart from possible financial consequences, Roche's customers, i.e. laboratories and hospitals, will have to deal with the logistical challenges of a short-term solution such as sending samples to different laboratories or, more likely, the fact that they **cannot provide full services for healthcare**. Ultimately this will have consequences for physicians and patients as specific diagnostic results will not be available and some may only be available with substantial delay which is expected to lead to delayed or even wrong treatment decisions. Furthermore, additional financial pressure and disruption of the laboratories' operations could have an impact on the quality of healthcare services beyond the unavailability of the affected assays.

As outlined above, the switch of a laboratory from Roche to a different provider is estimated to take **12-24 months**. Likely Roche will not be able to guarantee re-supply of all assays within this timeframe after a non-authorisation decision. This is explained by the fact that a range of different substitution projects would have to be completed. Even though for all projects the substitution in production based on planned timelines (not considering any additional risks) would be completed within a timeframe of 24 months after the sunset date (see AoA), it is questionable if Roche could guarantee re-supply of all assays within this timeframe due to the remaining risks in the substitution timelines. In addition, for the HIV assay, Roche could not offer a switch to the new instruments and the NPnEO-free HIV DUO assay to all concerned customers in a short timeframe (see below). Assuming Roche is not able to guarantee re-supply of all assays within 24 months, in medium-term, laboratories are expected to switch to a competitor system if competitors are able to offer complete

portfolios (i.e. if they are not themselves affected by the OPnEO / NPnEO ban) and competitors' capacities are sufficient to offer replacements for Roche's large market share (Scenario 1). This is expected for those laboratories whose contracts with Roche will be running out within the timeframe of 12-24 months. Even those laboratories with ongoing contracts will likely choose a switch to a different system, if possible, based on competitors' capacities, as Roche is unlikely to be able to offer an alternative and satisfactory solution (see above). Such a reaction is expected based on statements from laboratories, especially if several assays are not available for a longer timeframe. In the further assessment of Scenario 1, it is assumed that all laboratories could be switched within **24 months** assuming sufficient capacities from competitors. However, under to the current situation due to the COVID pandemic there is a lack of electronic parts and therefore this is not very likely.

From the perspective of Roche's customers, such replacement of instruments or whole systems will require tender exercise, trainings (for thousands of end users), new Standard operating procedure (SOPs), validation etc. all involving considerable efforts. In addition, a laboratory changing supplier might need to **validate all assays** (making sure that old results fit new results). It is also probable that expected result values will change due to different standardisation between competitors' assays, leading to even more resource requirements and to an extended inability of the laboratories to provide services to their customers (i.e. either internally within a hospital or by private laboratories to hospitals). In case a laboratory with accreditation is not able to perform a validation via side-by-side comparisons (see above), the laboratory might even risk **losing its accreditation**.

Based on these considerations and assuming availability of competitor systems on the market, the **entire market for centralised laboratories may be lost at least for the affected systems or portfolios**, in the UK. The case of the HIV assay and the associated infectious disease portfolio differs from the CC/DM portfolio as Roche is offering two new-generation analysers with a new HIV assay for high- and mid-throughput customers which have been introduced to the UK market in 2016 and 2020. High-throughput systems constitute approx. [redacted] of the HIV systems in UK. The second generation for these systems (cobas® e 801) has been on the UK market since 2016, which might have contributed to an accelerated switch from HIV combi PT to HIV Duo. In 2020, ca. [redacted] of instruments on the UK market were second generation instruments and ca. [redacted] of assays sold were HIV DUO. The time frame to switch all customers to the new systems will depend on the capacity of the analyser manufacturer (HITACHI high Technology). Currently the transition to the new instrument family is delayed due to the worldwide shortage of electronic components caused by the pandemic. This situation will continue throughout 2022 at least. It is estimated that 5.5 years after the sunset date, i.e. until end of 2027 will be needed for replacing the old instruments with the new generation instruments in the UK.

Even though new generation HIV assays are available, it remains open, if customers would be willing to invest into a new Roche infectious disease system in the case of the non-use scenario. This is due to remaining gaps in other parts of Roche's portfolio (i.e. in Clinical Chemistry and Drug Monitoring) as these assays are often run in the same laboratory.

Should competitors not be able to cover the demand for systems with complete portfolios, either due to limited production capacities or based on the OPnEO / NPnEO ban (Scenario 2), Roche may lose no or less customers. However, in this case, the lack of services for patients in the healthcare system as described above is expected to continue beyond the timeframe of 12-24 months.

Assays in tissue diagnostics (RTD) are usually run in separate laboratories to the ones described in this section. The options to deal with a lack of assays and **the same impacts** as described above are

however also applicable for these laboratories. They are usually centralised to run these specialised assays.

Specifically, the HER2 ISH testing (test to identify a gene indicating suitability of a specific cancer treatment, see Section 2.7.3) includes a brightfield assay whereas most competitors use a fluorescence assay. This implies a need for a specific microscope and different instruments. If the production of assay HER2 ISH was to be interrupted customers would need to change their entire laboratories to support the darkfield assay. The process of switching to a competitor at one customer is estimated to take **6-12 months** including re-validation of assays / kits with the new instruments. For all customers, a change could take ca. 2 years assuming that competitor systems are available. As mitigation options such as sending samples to other laboratories as outlined above are only expected to provide an **interim solution** in some cases. This could result in **the unavailability of tests** in tissue diagnostics unless substitution of OPnEO / NPnEO in the assays can be completed on-time.

3.2.3 Market Position and Competitiveness for the IVD Business

- ⇨ Not being able to provide core systems (i.e. CC assays) renders **RDL no longer competitive** and may **reduce the sales** of other systems or portfolios (i.e. not affected by this authorisation).
- ⇨ RDL expects to experience **loss of reputation and trust** gained in the past as IVD supplier.

As an IVD supplier, providing all relevant products is a strong sales argument and often a requirement in tenders. Roche's business model (see Section 2.5) is built on the goal to offer a complete portfolio to their customers. Competitors able to provide complete solutions will be favoured in **tenders**. Not being able to provide core systems like Clinical Chemistry assays or more specialised products such as Drug Monitoring assays will render **RDL no longer competitive**. Therefore, the effects described above may go beyond the directly affected products and might even **reduce the sales** of other systems or portfolios (i.e. not affected by this authorisation). It is assumed that, as long as Roche cannot offer a complete portfolio and competitors are able to do so, no new customers could be gained for the affected portfolios or systems (possibly including non-affected portfolios). Therefore, the **predicted increase in sales and EBITA** (see Section 2.8.1) **will be lost** during several years in addition to the possible loss of existing customers both leading to a gain at Roche's competitors. To still **win tenders**, Roche might be forced to reduce prices or include competitor products in tenders to complete the portfolio at a higher cost. This may especially happen if (many) competitors are not in the position to supply the market with (sufficient) complete systems either, e.g. due to the competitors themselves being affected by the OPnEO / NPnEO ban or limited production capacities.

Beside losing competitiveness on the market, RDL expects to experience **loss of reputation and trust** gained in the past as IVD supplier. Losing customer trust can be disastrous for any company but can be even worse for a leading company as Roche. This is particularly true for RDL position as one of the key player for MLS for NHS hospitals in the UK. Due to loss of trust, it is unlikely that the customers lost would continue to do business with Roche in the future. Should a current customer switch supplier, it is likely that the customer would not revert to Roche due to the difficulties associated with changing to a different system. Loss of trust on the market and the high investment associated with changing to a different system (as discussed in Section 3.3.3), will also make it difficult for Roche to win new customers or win back previous customers after substitution is completed.

In conclusion, the **loss of reputation** (Roche's reliability as a supplier) in the market will increase the difficulties to hold the existing customer base for products not affected by the use of OPnEO or NPnEO, winn back customers after completed substitution or get new customers in the future and lead to further economic losses.

3.3. Quantification of Economic Impacts for RDL and RDL's Customers

3.3.1 Approach for Quantification of Impacts

- ⇨ Financial losses are estimated for **Roche / RDL** based on affected assays / systems not sold and existing and new customers that are expected to be lost.
- ⇨ Due to the uncertainties regarding the extent and duration of economic impacts and the situation of Roche's competitors (Scenario 1 and 2), **ranges are estimated for each impact**. In addition, for each Scenario, it is assumed that **substitutions are completed on time (minimum)** or **delayed until the end of the review period (maximum)**.
- ⇨ RDL's customers are expected **to face losses** if they cannot supply full services to patients and / or **additional cost** if they need to change to a competitor system.
- ⇨ This loss / cost is roughly estimated based on affected assays that cannot be supplied to patients and cost for new instruments based on the different Scenarios.

This section provides quantitative estimates of the **economic impacts** over the course of the review period from the 30th of June 2022 until the end of 2027 in case the authorisation was not granted. Due to the uncertainties regarding the extent and duration of economic impacts and the situation of Roche's competitors (**Scenario 1 and 2**), ranges are estimated for each impact. For this purpose, for each scenario, impacts are assessed separately assuming that substitutions are either completed on time (minimum) or delayed until the end of the review period (maximum). This provides an overall range which will comprise the actual impacts.

The economic figures, sales and EBITA, including their predicted development over the review period, are based on the figures given in the AfA submitted by RDG in the EU (note that the figures were adapted to only represent the product groups and assays in scope of this UK AfA). The figures were verified and represent a reasonable estimate since the business for the assays covered in this AfA has not substantially changed since the preparation of the EU dossier. The figures, that were originally converted from Swiss Francs to EUR, are converted to British Pounds (based on an CHF/ £ exchange rate of 0.8 (03rd of January 2022)). They are further scaled to the UK market using the percentage of the total number of instruments (EEA and UK) installed in the UK. This is a reasonable approximation since turnover is mainly generated by the sales of assays (see Section 2.8.1) and the need for (and therefore purchase of) assays per instrument can be assumed to be on average the same. In addition, average EU prices are slightly below UK prices so that scaling average EU sales or EBITA figures to the UK without further adjustment represents a conservative approach. Please note that for HIV current figures were collected and assessed since the situation on the UK market regarding the replacement of instruments with new generation instruments for HIV differed substantially from what was described for the EU market.

As described previously, for **Scenario 1**, i.e. assuming competitors can take over Roche's market share, main impacts occur at the portfolio / system level as e.g. the CC portfolio will not be useful for customers if important parameters cannot be measured. For **Scenario 2**, i.e. assuming that competitors cannot take over Roche's market share, impacts occur at the level of individual assays that cannot be sold.

To assess the impacts in case of the non-use scenario, RDL's economic performance is compared with the situation outlined in the applied for use scenario including predicted developments over the course of the review period (Section 3.4).

In addition to RDL itself, RDL's customers will be directly affected in case of the non-use scenario as described above. RDL will not be able to supply the affected products and the UK customers will not be allowed to use any Roche assays containing at or above 0.1% w/w OPnEO or NPnEO in case of a refusal of authorisation. Customers may need to switch to the instruments of another supplier or send samples to another laboratories for analysis (if at all possible). Any occurring cost that would have to be covered by the customers (see Section 3.3.3) would ultimately need to be covered by the **healthcare system**. In some cases, cost may have to be compensated by Roche and would then represent an additional economic loss to RDL. Such cost is difficult to estimate due to different Scenarios and laboratory-specific situations. As an indication, this cost is roughly estimated based on the cost of the affected assays that cannot be performed by the laboratories (Scenario 1 and 2) and cost for switching to a competitor system based on cost for new instruments (Scenario 1).

In case Roche's competitors are able to take over Roche's market share for the affected product portfolios, these companies are expected to gain market share, but this gain cannot be reliably estimated.

In summary, **financial losses** as listed in Table 18 and indicative cost for customers as listed in Table 19 are expected depending on the scenario. Time when the impact is expected to occur, and maximum duration used for the calculations are indicated in those tables. Result of the calculations are provided in Sections 3.3.2 (financial losses) 3.3.3 (cost for laboratories / hospitals).

RDL is responsible of the distribution of the assays in the UK. Assays are delivered from RDG to the UK for a certain transfer price. The transfer price is arranged so that RDL can cover sales and administration costs and also gains some profit with taxation in UK. While the economic impact of non-authorisation is highly significant for RDL as an affiliate company and market leader, the impact on UK public health presents a more serious and immediate risk. For this dossier the conclusion was drawn that the health impacts are far more important than the economic impacts. For this reason, further differentiation of losses between RDL and the mother company Roche (RDG as well as Roche in the US as producer of RTD assays) was not performed. Indicated losses are therefore the sum of losses for Roche.

See also Figure 22 for a qualitative, general illustration of the timelines in case all substitutions are delayed.

Table 18. Financial losses (sales / value added (approximated by EBITA) foregone) based on the two different scenarios. Maximum durations are given.

Financial loss	Product group	Time when the impact is expected to occur	Maximum Duration	Quantification***
Financial impacts for Scenario 1: Competitors can take over Roche's market share				
Loss based on the affected assays that cannot be sold	CC, DM, HIV	For 2 years after the sunset date until customers have switched	2 years	Sales / EBITA from affected assays; based on predicted figures for 2021 (without growth for the following 2 years; or predictions for mid-2022 till mid-2024 in case of a decline)*
Medium-term loss of customers for the entire affected portfolios if they switch to a competitor system	CC, DM, HIV****	From 3rd year after the sunset date after customers have switched to competitor system	3.5 years	Sales / EBITA from affected portfolios; based on predicted figures for 2021 (i.e. without growth from 2022 or predictions for mid-2024-2027 in case of a decline) INCLUDES sales of affected assays Possible loss of a part of the customers already during the first 2 years is not accounted for If substitutions are completed on time (i.e. within 2 years after the sunset date), no impacts are assumed
Short- to medium-term loss of customers for the entire system incl. components that cannot be sold	RTD	From the sunset date	5.5 years	Sales / EBITA from the systems that are not usable without the affected assay / component; based on predicted figures from 2021 (without growth)*
Loss of new customers for the entire affected portfolios or systems if competitors are able to deliver the market with complete systems	CC, DM, HIV RTD	Starting immediately after the sunset date	5.5 years	Growth predictions for sales /EBITA for mid-2022-2027**
Financial impacts for Scenario 2: Competitors cannot take over Roche's market share				
Loss based on the affected assays that cannot be sold	CC, DM, HIV	From the sunset date	5.5 years	Sales / EBITA from affected assays based on predicted figures for 2021 (without growth from 2022 or predictions for mid-2022-2027 in case of a decline)*
Medium-term loss of customers for the	CC, DM, HIV	No losses of customers expected		

Financial loss	Product group	Time when the impact is expected to occur	Maximum Duration	Quantification***
entire affected portfolios		as no alternative systems available		
Short- to medium-term loss of customers for the entire system incl. components that cannot be sold	RTD	From the sunset date	5.5 years	Sales / EBITA from the systems that need the affected assay / component based on predicted figures for 2021 (without growth from 2022)
Loss of new customers for the entire affected portfolios	CC, DM, HIV	No losses of new customers expected as no complete systems assumed to be available on the market		
Loss of new customers for the entire affected systems as they are not usable	RTD	Starting immediately after the sunset date	5.5 years	Growth predictions for sales /EBITA for mid-2022-2027**

* For minimum duration (i.e. if substitutions are completed on time): Sales / EBITA from affected assays or systems are not considered in the calculation from the planned completion date of substitution.
** For minimum duration (i.e. if substitutions are completed on time): Growth from complete systems that are planned to be replaced before the sunset date are not included in the calculation.
*** Range of years such as mid-2022-2027 mean from the middle of the first until the end of the last year.
**** For HIV customers could be lost for the entire portfolio. However, as a conservative approach only the cost of the affected assays was accounted for.

Additional cost is expected for Roche's **customers due to the assays not supplied and the switch to competitor systems**. The approach to estimate this for the two scenarios is summarised in Table 19.

Table 19. Expected cost for customers.

Financial loss / cost	Product group	Time when the impact is expected to occur	Maximum Duration	Quantification
Financial impacts for Scenario 1: Competitors can take over Roche's market share				
Cost of customers for affected operations and business lost or possibly increased testing efforts if samples can be sent to laboratories with competitors' systems	CC, DM, HIV, RTD	From the sunset date until customers have switched	2 years	Cost based on affected assays that cannot be performed for patients or possibly cost for sending out samples Approximated by assay cost*
Costs connected to the switch from Roche's system to a competitor system	CC, DM, HIV RTD	Customers are expected to switch mainly during the first two years after the sunset date	One-time cost for new system	Approximated by cost of new instruments (cost of instruments multiplied with installed base)**

Financial loss / cost	Product group	Time when the impact is expected to occur	Maximum Duration	Quantification
				Cost not accounted for: e.g. rebuilding of infrastructure etc.
Financial impacts for Scenario 2: Competitors cannot take over Roche's market share				
Cost of customers for affected operations and business lost or possibly increased testing efforts if samples can be sent to laboratories with competitors' systems	CC, DM, HIV, RTD	From the sunset date	5.5 years	Cost based on affected assays that cannot be performed for patients or possibly cost for sending out samples Approximated by assay cost*
Costs connected to the switch from Roche's system to a competitor system	CC, DM, HIV, RTD	Not applicable as no competitor systems available under this scenario		

* For minimum duration (i.e. if substitutions are completed on time): cost from affected assays or systems are not considered in the calculation from the planned completion date of substitution.
** For minimum duration (i.e. if substitutions are completed on time): Cost to change complete systems that are planned to be replaced before the sunset date are not included in the calculation.

3.3.2 Financial Losses

- ⇨ Under **Scenario 1** (competitors can take over Roche's market share), the **aggregated EBITA foregone** (without expected growth from 2021 onwards) **over the review period** is estimated at [redacted] mio £ (discounted to NPV) depending on whether substitutions are completed on time or not.
- ⇨ If **growth** occurred as predicted, an **additional EBITA** of [redacted] mio £ (discounted to NPV) is expected to be lost over the course of the review period due to new customers that could not be gained.
- ⇨ Under **Scenario 2** (competitors cannot take over Roche's market share), the **aggregated EBITA foregone** (without expected growth from 2021 onwards) **over the review period** is estimated at [redacted] mio £ (discounted to NPV) depending on whether substitutions are completed on time or not.
- ⇨ If **growth** occurred as predicted, an **additional EBITA** of [redacted] mio £ (discounted to NPV) is expected to be lost over the course of the review period due to new customers that could not be gained.

Financial losses were calculated for each scenario based on the approach described in Section 3.3.1.

For Scenario 1 (competitors can take over Roche's market share):

Detailed calculations of **sales foregone** including minimum and maximum values per product group are provided in the Supporting Document 2 to the SEA (File: SD2_SEA_Sales_RDL_Use3_CONFIDENTIAL). Sales is used instead of EBITA to provide details

on the level of the product group due to internal requirements for confidentiality. The maximum number of years over which a type of loss (sales from affected products, the entire portfolio at existing customers or growth) is assumed to occur for a product group is corresponds to the maximum duration for each impact given in Table 18. Summed ranges of **sales foregone** is given in Table 20**.** The aggregated ranges of **EBITA** (as an approximation of value added) foregone in Table 20 is based on the same assumptions as given for sales[1]. In addition, if growth occurred as currently predicted, an aggregated range of EBITA as given in Table 20 is **expected to be lost** over the course of the review period due to new customers that could not be gained.

The **given maximum values** are based on the assumption that competitors can take over Roche's market share and that substitutions are delayed until the end of the review period. However, they do not take into account potential losses of further portfolios not directly affected by non-authorisation. Therefore, in reality, maximum losses could be even larger.

The **minimum financial impact in case of Scenario 1**, i.e. if substitutions are completed on time (but competitors are able to take over part of Roche's market share) will differ between the different product groups. For some assays that concern separate systems, substitution in production would be completed before the sunset date if substitution was completed as planned (RTD). However, for some CC and DM assays, substitution in production is expected to be completed only after the sunset date. Therefore, for CC/DM impacts are expected to occur at the portfolio level, i.e. customers are expected to switch to a different supplier for the entire portfolio if possible. These impacts are expected to occur even if OPnEO / NPnEO is already substituted in some assays. Only if Roche could guarantee re-supply of all assays within the time needed to switch to a competitor system (24 months), which is unlikely, customers may not switch system. Otherwise, impacts are expected to be permanent, i.e. customers are not expected to switch back to Roche when a complete portfolio is available again. As in the best case, substitutions (apart from HIV, see below) may be completed within 24 months after the sunset date, for minimum impacts no portfolio losses are assumed. Maximum impacts are calculated considering the loss of the entire portfolio until the end of the review period for CC/DM. For the calculation of loss from affected assays for DM and CC during the first two years, planned substitution dates are considered (see footnotes to Table 18). For HIV, new instruments with a new NPnEO-free HIV assay are available on the UK market, but replacement with these instruments will not be possible before the sunset date. Since it cannot be predicted to what extent customers could be switched to the new Roche analzyers and to what extend they may switch to a competitor system in the course of the review period, only the loss from the affected HIV combiPT assays are calculated as a conservative approach. RTD, in which OPnEO / NPnEO is assumed to be substituted before the sunset date is not considered for minimum financial impacts.

[1] EBITA data are only given in an aggregated form due to internal requirements on confidentiality

Table 20. Scenario 1: Estimated range for economic losses in UK over the review period from 30th of June 2022 until the end of 2027, discounted to Net Present Value (NPV) at 4%. Competitors are assumed to be able to take over Roche's market share. Values do not include expected growth from 2021 onwards.

Economical loss	**Range over the review period (mio £)***
Sales foregone**	[redacted]
EBITA**	[redacted]
Sales foregone due to growth after 30th of June 2022	[redacted]
EBITA foregone over the review period due to growth after 30th of June 2022	[redacted]

* Minimum values: Substitutions are assumed to be implemented as planned. No economic losses for systems / assays or their growth that are planned to be substituted before the sunset date.
Maximum values: Substitutions are assumed to be delayed so that impacts continue until the end of the review period.
** Values do not include expected growth from 2022 onwards.

For Scenario 2 (competitors cannot take over Roche's market share):

Financial losses (i.e. sales / EBITA foregone) may be **smaller if competitors cannot take over Roche's market share** at all. However, this would **substantially increase health impacts**, especially if substitutions are delayed (see Figure 22). Financial losses for this scenario are calculated based on sales of the affected assays or systems. For **minimum losses**, planned substitution dates as given in the AoA are accounted for. **Maximum losses** are expected to occur until the end of the review period, i.e. are expected to occur over 5.5 years. **Minimum and maximum values are therefore the same as in Scenario 1** for those product groups where the entire system is affected (RTD) and for HIV where only the loss from the assays is accounted for. Sales / EBITA foregone are much **lower in comparison to Scenario 1** for those product groups for which the entire portfolio is affected after a switch of customers in Scenario 1 (CC, DM) (see Table 21). Detailed calculations and values per product group are provided in the Supporting Document 2 to the SEA (File: SD2_SEA_Sales_RDL_Use3_CONFIDENTIAL). In Scenario 2, Roche's IVD business on the portfolio level is expected to grow as currently predicted and no losses due to new customers not gained are estimated for entire portfolios (CC/DM). This is based on the assumption in this scenario that competitors are not able to offer more complete portfolios / solutions than Roche. However, losses of sales and EBITA based on growth from systems that are affected in their entirety (RTD) and losses based on growth of affected assays that are not available is still expected to occur.

Table 21. Scenario 2: Estimated range for economic losses in UK over the review period from 30th of June 2022 until the end of 2027, discounted to NPV at 4%. Competitors are assumed not to be able to take over Roche's market share. Values do not include expected growth from 2022 onwards.

Economical loss	**Range over the review period (mio £)***
Sales foregone**	[redacted]
EBITA**	[redacted]
Sales foregone due to growth after 30th of June 2022	[redacted]
EBITA foregone over the review period due to growth after 30th of June 2022	[redacted]

* Minimum values: Substitutions are assumed to be implemented as planned. No economic losses for systems / assays or their growth that are planned to be substituted before the sunset date.
Maximum values: Substitutions are assumed to be delayed so that impacts continue until the end of the review period.
** Values do not include expected growth from 2022 onwards.

3.3.3 Cost for Customers

- ⇨ Only a rough indication can be given for additional cost for **customers.**
- ⇨ Under Scenario 1 and 2, **business losses of customers are expected due to not supplied assays**. As a minimum, these costs are estimated based on the sales price of the assays for 'substitution on time' (min) or 'all substitutions delayed' (max):
  - Scenario 1: [redacted] mio £.
  - Scenario 2: [redacted] mio £.
- ⇨ In Scenario 1, the cost for Roche instruments (similar in prices and quality) is given as an indication of the **minimum cost of a switch to a different supplier**. Switching all customers would lead to an estimated cost of up to [redacted] mio £ for the instruments alone **not including the far more important cost** for the tender process, installation, training etc.
- ⇨ Any occurring cost that would have to be covered by the customers, i.e. laboratories and hospitals would ultimately be covered by the **healthcare system**. In some cases, cost may have to be compensated by Roche and would then represent an additional economic loss to RDL.

Customers of Roche i.e. laboratories and hospitals in the UK will face additional costs due to Roche's inability to deliver the affected assays. As government action may be considered as force majeure in contracts, it is expected that most customers will not be able to claim compensation or be indemnified for these costs by RDL. However, this will depend on the terms of each individual contract or framework agreement. In case of compensation by Roche, the cost for mitigation measures would represent an additional economic loss to RDL. Only a very rough estimate can be given for such cost which will in the following be considered as a cost to RDL's customers as the most likely scenario.

Customers will be faced with the fact that they cannot deliver results from certain assays to patients. To alleviate this situation they may send out samples for analysis to other laboratories. However, sending out samples would only be possible to a limited extent. If possible, this option is estimated to entail cost for the laboratory that are twice as high as the cost of running the assay in-house and ca. 3-8 times as high as the cost of the assay[2].

In addition, customers may need to switch to a competitor system if possible i.e. to install the equipment from a competitor. Considerations for switching to a competitor system in Scenario 1 are discussed below. Since it is impossible to quantify losses that the customers would face, only an **indication of possible customer losses** can be given for the two scenarios.

[2] Roche internal information. Cost for running the assay would include cost for administration, personnel, running the laboratory infrastructure etc. For sending out samples, additional cost would be caused by the logistics of identifying and sending the samples as well as administrative integration of results and payment.

For Scenario 1 (competitors can take over Roche's market):

Costs for customers associated with business lost are expected when **assays cannot be supplied** and where customers cannot switch to a different system quickly due to them being used in centralised laboratories which is the case for all assays covered in this AfA, i.e. (CC, DM, HIV, RTD). In this case, assays cannot be performed for patients for the estimated two years until a switch to a competitor system can be completed for all customers. Additional costs may also arise for the limited cases where mitigation measures for the lack of assays are possible. For example, for cost of samples that have to be sent to other laboratories.

Based on the considerations listed above, the value of goods delivered i.e. sales of the affected assays (see the Supporting Document 2 to the SEA; File: SD2_SEA_Sales_RDL_Use3_CONFIDENTIAL) is used as a very conservative estimate for the minimum cost to customers. The sales of the affected assays were considered for the first two years after the sunset date. The **minimum estimate is calculated based on the assumption that substitutions are completed on time**. Therefore, for some assays there will not be an interruption in supply, or it will be shorter than two years. The **maximum is based on the assumption that all substitution projects are delayed** so that all assays are lacking during the first two years after the sunset date. This cost is estimated to be [redacted] mio £ based on the value of assays.

Within two years after the sunset date, the customers are expected to switch to a different supplier under Scenario 1 if Roche cannot guarantee re-supply of all affected assays within that timeframe. In this case they need to re-install laboratory equipment from another provider at significant time and financial costs to the health sector. The customers would most likely need to cover the **cost for the new instruments.** Moreover, **additional costs** would be required due to the organisation of a new tender, the installation cost including possible reconstruction of laboratories, training of personnel etc. associated with a switch. **These costs will be far more significant** than the instrument costs.

For the **cost of a switch** to a different supplier the **cost for the new instruments can be used as an indicator for minimum cost** (based on Roche's instrument cost which can be assumed to be similar to prices of competitor instruments of a similar quality (see details on cost per instrument in the Supporting Document SD1_SEA_Nr_Instruments_RDL_Use3_CONFIDENTIAL). Multiplying this cost with the number of instruments installed (see Supporting Document 1) leads to a potential total instrument cost of up to [redacted] mio £ (assuming all substitutions are delayed). If all substitutions are on time and Roche can guarantee re-supply of all assays within 24 months, only the cost for the switch to the new HIV instruments would need to be covered which is estimated at [redacted] mio £. It has to be noted that these values do not cover **additional costs** due to organisation of a new tender, installation cost including possible reconstruction of laboratories, training of personnel etc. associated with a switch. **These costs will be far more significant** than the instrument costs so that maximum cost is expected to be much larger than [redacted] mio £. Cost due to switching to a different supplier are mainly expected to occur within the first two years after a non-authorisation decision as customers are expected to switch during that period.

For Scenario 2 (competitors cannot take over Roche's market share)

In case of Scenario 2, Roche's competitors are assumed not to be able to offer complete systems either so that customers are assumed not to switch to competitors.

In such a case the customers would lose part of their business for as long as assays are not available. Such losses may vary from minimal, in case most of the substitutions are completed on time, to

maximal losses in case all the substitution projects are delayed so that all assays are lacking until the end of the review period.

The **minimum estimate is calculated based on the assumption that substitutions are completed on time**, so that for some assays there won't be an interruption in supply, or it will be shorter than the review period. The **maximum is based on the assumption that all substitution projects are delayed** so that all assays are lacking until the end of the review period.

Estimated minimum and maximum costs due to assays that are not available (based on the value of assays) are [redacted] mio £.

Additional losses for both scenarios could arise due to assays already delivered to the customers that cannot be used anymore after the sunset date. However, these cost are not quantified.

All the mentioned costs would need to covered by the customers themselves - and thus ultimately **insurance schemes and the healthcare system** except for some cases where customers may be able to claim compensation or be indemnified for these costs by RDL.

3.4. Social Impacts

⇨ Social impacts include cost of unemployment and increased healthcare and related costs.

- The **social impacts of a non-authorisation** would be situated **on two levels: Social cost of unemployment due to damage to reputation, loss of revenue and loss of opportunity for Roche** (and related unemployment).

- **Increased healthcare costs and related costs due to (temporary) unavailability of affected IVD assays** on the market in general or at least at the level of Roche's customers. A temporary unavailability on the market in general would occur when similar assays of other suppliers are affected as well (Scenario 2). A temporary unavailability at the level of Roche's customers would occur in case only the assays of Roche are affected by non-authorisation and customers need to switch to another supplier. Such a switch is anticipated to take a substantial amount of time in most cases, therefore resulting in a temporary unavailability of the affected assays at these customers (Scenario 1). It would additionally incur high cost to the healthcare system for the switch to a competitor system since it is expected that such cost cannot be claimed from Roche in most cases based on contracts (see Section 3.3.3.)

3.4.1 Social Cost of Unemployment

- ⇨ **Job losses** are expected as a result of damage to Roche's reputation, loss of revenue and loss of opportunity. However, these losses can currently not be quantified.
- ⇨ The **social cost of unemployment** as a result of non-authorisation **may contribute significantly** to the total impacts at the socio-economic side of the quotation in the socio-economic analysis depending on the scenario.

In case of non-authorisation, there will be **damage to Roche's reputation, loss of revenue and loss of opportunity which will lead to financial damage.** As a consequence of these effects loss of jobs is expected. However, this loss can currently not be quantified. Job losses may occur at RDL itself or at companies connected to RDL. Job losses may be most pronounced in case of Scenario 1, i.e. if Roche's competitors can take over Roche's market share.

The possibility cannot be excluded that the social cost of unemployment would also significantly contribute to the total impacts at the socio-economic side of the equation in case of RDL. However, this cannot be quantified based on the available information.

3.4.2 Social Impacts Due to Temporary Unavailability of *in vitro* Diagnostic Assays

- ⇨ The authors of published IVD cost analyses have concluded that the overall healthcare spending to IVDs is only roughly a few % of total healthcare expenditure while IVDs guide roughly **60-70% of clinical decisions**.
- ⇨ In general, IVDs help provide the appropriate healthcare services to patients thereby reducing **recovery times**, **the risk of serious complications** and the overall **cost of therapy.**
- ⇨ The efficiency of investments in healthcare interventions can be evaluated using cost-utility analysis, where the gain in QALYs (quality-adjusted life year) is weighed against the cost of the intervention. **Overall**, the **utility-cost ratio** for currently used IVDs appears to be **high**.
- ⇨ IVDs make an **important contribution** towards making **healthcare systems more efficient at a minimal cost**.

In vitro diagnostic assays are playing a major role in providing insights into the links between individuals, their illnesses and their treatment. Informed medical decision-making is better for patients and the healthcare system. Getting the right treatment for the right patient improves outcomes and **reduces recovery times**, ensuring that patients are back on their feet as quickly as possible. Early diagnosis and care can prevent illness from developing and slow down disease progression and even heal. Monitoring of people with ongoing disease can **reduce the risk of serious complications**. This information-powered approach makes healthcare systems more efficient by allowing early-stage interventions in patients, which are typically more cost-effective compared to advanced-stage therapy which is generally associated with worse prognosis and a higher use of healthcare resources [18][7]. Furthermore, new developments such as personalised Healthcare – a concept which is based on identifying patients with a high likelihood of response to a specific drug – have the potential to enable the selection of the correct drug dose at the appropriate time of a patient's treatment course, thereby further **reducing overall therapy cost**.

While life expectancy is increasing, healthcare systems need to find ways to become more efficient. IVD can make an important contribution towards addressing this problem, at a minimal cost. According to MedTech Europe (the IVD sector organisation), there are more than 40'000 IVD products available, providing information to physicians and patients on a huge range of conditions, yet IVDs cost remarkably little, with the total expenditure being ca. 21 Euro EUR per person per year [12]. By comparison, healthcare expenditure on pharmaceuticals is more than 450 EUR per head of population per year [13].

A report by the Lewin Group [17] mentions that **IVDs account for 60 – 70% of clinical decisions**. A value of 70% was reported by BIVDA, the British in Vitro Diagnostics Association [3]. Recent studies have reported similar values, such as the study by Rohr et al. [21] on the overall cost and utility of IVDs in the field of oncology and cardiology, where IVD testing was found to guide approx. 66% of clinical decisions. These studies also confirm that the **relative spending of healthcare costs on IVDs are low**. In the report of the Lewin Group [17] it was mentioned that IVDs comprise less than 5% of hospital costs and approx. 1.6% of all Medicare costs. In the report of the BIVDA on the value of IVDs [3], it was mentioned that the NHS (National Health Service) spends less than 1% of the total NHS budget on IVD products. The review of Rohr et al. [21] revealed that approx. 2.3% of all healthcare spending in the US was to IVDs (defined as payments to clinical laboratories for testing services), whereas in Germany, 1.4% of public healthcare expenditure was used for IVDs. Although different sources of data are used for these estimations, it is clear from all these reports that the total spending on IVDs is only responsible for roughly a few % of total healthcare expenditure.

The relative efficiency of investments in healthcare interventions can be evaluated using **cost-utility analysis**, a form of cost-effectiveness analysis, where the aim is to **maximise the gains in QALYs** (quality-adjusted life year) **per unit of healthcare expenditure**. The review of Fang et al. [14], in which 141 publications dealing with cost-utility analysis regarding diagnostic laboratory testing were reviewed, reported that over 55% of the incremental cost-effectiveness ratios (i.e. additional healthcare spending per gained QALY) reported in the reviewed publications were either dominant (i.e. more gained QALYs for less cost) or below 50'000 USD per QALY (2008 value), demonstrating that diagnostic laboratory testing in general represents good value of money. Together with the findings mentioned above, the findings of this literature review confirm that currently used **IVDs overall have a high utility-cost ratio** and can therefore be assumed to result in a **high overall reduction of healthcare spending.**

Although various examples of cost-utility analysis are available in the field of IVDs, such analyses are not available for all individual types of assays on the market, rendering it impossible to calculate a reliable value for the total amount of gained QALYs related to the use of the affected IVDs discussed in this dossier. Moreover, there is no generally agreed societal value of a QALY, which would allow (at least a rough) monetisation of the benefits to patients related to the use of the IVDs under evaluation in this dossier. Therefore, there is currently no straightforward approach to calculate an accurate and realistic range of social benefits of the affected IVDs in monetary terms. Consequently, in the sections below, first a qualitative description of social impacts per group of affected IVDs is given, followed by a few illustrative calculations added with the intention of getting a sense of the order of magnitude of the social impacts in case of temporary unavailability of IVDs.

More detailed information on the publications mentioned above can be found in Appendix 1.

Social impacts resulting from temporary unavailability of IVDs expected when no authorisation is received

The IVD assays that may be affected (see Section 2.7 for detailed descriptions) in case an authorisation would not be granted, belong to Roche's portfolios of Clinical Chemistry, Drug Monitoring, HIV, and tissue diagnostics. A brief qualitative description of the general impacts expected on patients is given below and is summarised in Table 8:

- Concerning the **Clinical Chemistry** portfolio, two assays would be affected (see Figure 8). The CC portfolio represents a wide array of tests that could give an initial indication on the general health status of a patient. The results of the tests could immediately lead to diagnosis and start-up of treatment. However, very often the results represent signals of potentially worrying health conditions which trigger further investigation (potentially including further IVD testing as well) which may in its turn result in diagnosis. The CC portfolio not only provides parameters for screening and **early markers** of disease onset, but also includes many markers that are used in **emergency settings** (like BILT3) that are required for **quick diagnosis** as a basis for treatment decisions in acute life-threatening conditions. Further, the assays in the CC portfolio may also be important for **monitoring** the **efficacy of a given therapy**, allowing adjustment of the therapeutic intervention. Several parameters are also used as **predictive markers for chronic diseases** (e.g. diabetes, cardiovascular diseases, atherosclerosis, etc.), providing important information for patients to adjust their lifestyle. Therefore, the CC portfolio is extremely important for timely detection and follow-up of worrying health conditions. In case various parameters could not be determined anymore, this early signalling function as well as diagnosis in emergency settings would be disturbed. This could result in delay of diagnosis or misdiagnosis and therefore a potential loss of QALYs in patients (and consequently, an increased healthcare expenditure).

- The area of **Drug Monitoring** comprises both testing for drugs of abuse and therapeutic Drug Monitoring. In the case of testing for drugs of abuse (depressants, stimulants, hallucinogens), the unavailability of certain assays could lead to issues with **confirming patients in the emergency department with suspected drug abuse or overdose**. This may delay timely diagnosis or cause complications during treatment for other health conditions. It could also lead to incapability **of screening for drug abuse in a working place or legal context**, or incapability of following up adherence to replacement drugs. All of these could result in indirect impacts on society. Concerning therapeutic Drug Monitoring, it would not be possible to **fine-tune therapeutic drug use** in patients, which could lead to non-optimal treatments. This could affect treatment duration as well as outcome, and therefore may result in a loss of QALYs (and consequently, an increased healthcare expenditure).

- Concerning **HIV**, reliable screening and diagnosis represents a crucial aspect of the global strategy for reducing the human and financial burden of HIV transmission. In the case of blood transfusion, for instance, the screening of blood donors / blood units in blood bank facilities before the blood units are transfused is essential to **prevent transfusion-transmissible infections**. Temporary unavailability of HIV assays could result in **delayed diagnosis and increased spreading of HIV** through the population, thereby substantially increasing healthcare expenditure related to HIV suppression and AIDS treatment as well as a substantial loss of QALYs.

- The affected **RTD** portfolio contains various ISH (in situ hybridisation) assays that are used to aid in the diagnosis of different types of cancer, such as cervical cancer. Further, some of the assays provide key information to help establish a personalised treatment, meeting the exact need

of the patient. The unavailability of these assays would result in the potential for **delayed diagnosis in cancer patients** and therefore delay in treatment or **failure to start up personalised treatment**, and consequently a potential loss of QALYs and increased healthcare expenditure.

Getting a sense of the magnitude of the social impacts in case of temporary unavailability of IVDs

- ⇨ Overall, **ca. [redacted] (10-50) mio (directly affected) tests** provided by Roche are carried out in the UK per year.
- ⇨ Assuming on average 10 tests per patient annually, this would result in **ca. [redacted] (1-5) mio patients per year** that benefit from these tests in the UK.
- ⇨ The overall number of **gained QALYs** resulting from the use of the affected IVDs cannot be calculated in a sufficiently reliable way but can reasonably be assumed to be **very high**.
- ⇨ Indicative calculations are used to demonstrate that the social impacts of non-authorisation can reasonably be expected to be much higher than the maximum economic impacts to Roche / RDL in terms of EBITA foregone.

As mentioned above, no overall amount of gained QALYs can be calculated for the use of the assays of which the availability may be interrupted by a non-authorisation. Nevertheless, the total amount of gained QALYs can reasonably be assumed to be very high. The number of tests performed yearly (directly affected assays only) per product group is presented in Table 7. The overall **number of (directly affected) tests** provided by Roche performed **in the UK** is [redacted] **(10 – 50) mio/year**, the majority (ca. 85%) being Clinical Chemistry tests. The number of patients that benefit from these tests is more difficult to estimate as some patients require multiple tests per year for a closer follow-up of health condition or treatment. If we would assume on average 10 tests per year, this would mean [redacted] (1 – 5) **mio patients/year**.

Because a forward calculation of the social impacts of non-authorisation due to temporary unavailability of IVDs would require too many accumulated assumptions, thereby resulting in huge uncertainty around the calculated values, it was decided to do several backward calculations to **check what the minimal efficiency of the affected IVDs would have to be in the scenario with the lowest expected health impacts in order for a non-authorisation to result in a social impact equalling the maximum economic impact to Roche / RDL in terms of EBITA foregone.** The lowest health impacts are expected in the scenario in which competitors can take over Roche's market share (Scenario 1) and in which substitutions are completed as planned, which implies that substitutions for RTD, and some of the affected CC and DM assays are completed before the sunset date. In this scenario, it was assumed that the **unavailability** of the remaining affected assays (number of assays ca. [redacted] mio tests per year in the UK) for which substitutions are not yet completed at the sunset date would only be temporary for a period of **12-24 months** (i.e. the period needed for customers to switch to systems of other suppliers in case the decision of non-authorisation would only be received after the sunset date or for Roche to complete the substitutions). For the calculations below, 12 months of temporary unavailability was assumed as a worst-case. The **economic impacts to Roche / RDL in terms of EBITA foregone** (see Section 3.3.2) have been calculated to range roughly **between [redacted] mio £** over the different scenarios not taking into account growth (see Table 20 and Table 21 for further details). The scenario with the highest economic impact to Roche / RDL in terms of EBITA foregone is the scenario in which competitors can take over Roche's market share (Scenario 1) and in which all substitutions are delayed. The idea behind this calculation is to demonstrate that the social impacts in terms of increased healthcare costs and related costs – although

at the same side of the equation as the economic impacts – can reasonably be assumed to be much higher than the economic impacts to Roche / RDL in terms of EBITA foregone. It will therefore be a dominant component in determining the weight of the socio-economic impacts in each of the scenarios presented in this document. How the outcome of this exercise is dealt with will be further explained at the end of this section and in further detail, in the combined impacts assessment section.

Both the ECHA Guidance Document on Socio-Economic Analysis in Authorisation [7] and the ECHA summary of the study on the valuation of selected health impacts of chemicals [8] report information on the Value of a Statistical Life (VSL) monetary concept, which represents the willingness to pay to avoid a health condition leading to death, and the Value of a Life Year Lost (VOLY) (which can be derived from the VSL). These VSL and VOLY estimates are increasingly being used for the assignation of monetary values to QALYs.

Key mean values for the VSL and the VOLY obtained in an EU-wide research programme [20] referred to in both documents are 1'211'189 and 64'244 £, respectively (recalculated to 2022 value). The VOLY value can be interpreted as the willingness to pay for avoiding a total loss of 1 QALY, not considering the type of health condition ran into[3]. Using this general **VOLY** value, one could roughly calculate that only [redacted] QALYs would have to be lost as a result of the assumed 1 year of temporary unavailability of affected assays to equal the maximum economic impacts to Roche / RDL in terms of EBITA foregone estimated to result from non-authorisation (i.e. [redacted] (10 – 50) mio £). Taking into account the fact that roughly [redacted] mio tests per year are currently performed in UK (affected assays only, not taking into account number of tests for assays for which substitution is planned to be completed before the sunset date), this would mean that **only 1 on ca. 17'000 tests would have to result in the gain of 1 QALY**. Based on the qualitative description of the importance of the affected tests / portfolios, it can reasonably be expected that the QALY gain of this number of tests is several orders of magnitude higher and consequently that the social impacts of temporary unavailability of affected assays would also be several orders of magnitude higher than the economic impacts to Roche / RDL in terms of EBITA foregone.

When considering the mean **VSL** mentioned above, a similar calculation would learn that roughly only about [redacted] fatal health conditions should be prevented per year under normal conditions of availability of the tests (not considering the type of health condition potentially leading to fatality) to equal the economic impacts to Roche / RDL in terms of EBITA fodregone resulting from non-authorisation (i.e. [redacted] mio £). Considering the fact that the affected assays (not taking into account number of tests for assays for which substitution is planned to be completed before the sunset date) are currently performed at roughly [redacted] mio tests per year, this would mean that **only 1 on ca. 321'000 tests would have to** be able to **prevent a fatal health condition**. Here too, it can be reasonably assumed that this is several orders of magnitudes higher, especially since various of the affected assays are used (either alone or together with other assays) to screen for signals indicating the potential existence of life-threatening health conditions (see above).

Based on the above considerations, it can be safely assumed that the social impacts of temporary unavailability of the affected assays in terms of **increased healthcare costs** and related costs, are **several orders of magnitudes higher than the economic impacts of non-authorisation to Roche / RDL in terms of EBITA foregone**. This conclusion is reached for the scenario with the lowest estimated health impacts (i.e. the scenario in which competitors can take over Roche's market share

[24] The mean value of VOLY (Value of Life Year Lost) calculated in the NewExt study (2003) was 55800 EUR, i.e. approx. 71000 EUR in 2018. This VOLY value can be interpreted as the willingness to pay for avoiding a total loss of 1 QALY, without taking into account the type of health condition.

and substitutions are completed as planned) and using the maximum economic impacts to Roche / RDL in terms of EBITA foregone (i.e. calculated for the scenario in which competitors can take over Roche's market share and all substitutions are delayed). This represents a worst-case calculation, as the [redacted] mio of tests used in the calculations above is equal to or lower than the total number of tests during the full period of temporary unavailability of the affected assays in each scenario. Therefore, the same conclusion holds for all scenarios presented in the economic impacts section (Scenario 1 and 2, each with two sub-scenarios depending on the timeline for substitution).

Overall, the calculations performed above are meant to get a sense of the magnitude of the social impacts related to temporary unavailability of the affected IVDs and the relative importance of these social impacts compared to the other social and / or economic impacts. This will be discussed in further detail in the section on combined assessment of impacts in view of drawing conclusions for the different scenarios.

Further background information on the monetisation of human health impacts can be found in Appendix 1.

Finally, a mini-case was performed for the affected HIV assay (combiPT) to further illustrate the expected magnitude of the social impacts due to temporary availability of IVDs.

Mini-case on HIV

As explained above, it is not possible to calculate the absolute social impacts in terms of increased healthcare costs and related costs related to the temporary unavailability of all affected assays, since important types of information are missing in all cases and therefore such a calculation would be associated with a huge and unacceptable uncertainty. However, for a single (group of) affected assay(s), such calculation may be more feasible. Therefore, in the text below, a **mini-case** was developed **for the affected HIV assays** of Roche.

According to information made available by the UK Health Security Agency[4], the **number of newly diagnosed HIV infections in 2020** was 2'766 in the UK.

Considering the **market share of RDL in HIV IVDs**, one could then by approximation calculate for how many diagnoses of new HIV infections per year RDL's HIV assays are responsible. The current market share of RDL in HIV IVDs in the UK is [redacted]%. Considering this market share, **RDL's HIV IVDs** can be assumed to be **responsible for the diagnosis of [redacted] new HIV infections per year** in the UK.

However, it should be noted that the only affected HIV IVD of Roche is the **HIV combiPT assay**, but this assay is **progressively being replaced** by a solution that is not subject to an authorisation duty (HIV DUO). This replacement will be completed at the end of the review period asked for in this AfA. The **relative contribution** of the combiPT assay **to the total market share** for Roche HIV solutions **is estimated to reduce** to [redacted] in 2022 and then progressively to [redacted] and [redacted] in 2023, 2024, 2025, 2026 and 2027, respectively. Further, the **temporary unavailability of the combiPT assay** is different **in the different scenarios** presented in the economic impacts section:

- Scenario 1 – Competitors can take over Roche's market share – i.e. unavailability until the switch to competitor systems is complete → 2 years.

4 Gov.UK website, 'HIV: annual data tables', 2021: https://www.gov.uk/government/statistics/hiv-annual-data-tables

- Scenario 2 – Competitors cannot take over Roche's market share – i.e. unavailability until substitutions by Roche are completed → until the end of 2027.

Consequently, the **HIV combiPT assay** can be calculated to be **responsible for the following number of newly diagnosed HIV infections** in the UK:

- Scenario 1: [redacted]
- Scenario 2: [redacted]

The **missing link** in the calculation is the **difference in quality-adjusted life expectancy between diagnosed HIV carriers and undiagnosed HIV carriers**. How much QALYs are gained through detection of new HIV infections depends on the screening program (e.g., one time, every five years, annually, voluntary or not, only high-risk groups or not, etc.) as well as on the prevalence of unidentified HIV infections, which drastically differs between different regions. Available publications usually present the results of a comparison of different screening programs and not between screening and no screening at all. Several publications also elaborate on the cost efficiency of different screening programs (i.e. cost per additional QALY gained) (e.g. [24][25][26][27][28][29]).

From the comparison of screening programs, it seems that even an increase of quality-adjusted life expectancy of the newly identified HIV-infected people by ca. 1 year or even more could be achieved by changing the screening approach. For instance, Walensky et al. [28] found that in South Africa (high prevalence of HIV and high prevalence of unidentified HIV), HIV screening one-time, every five years, and annually, would increase HIV-infected quality-adjusted life expectancy (mean age 33 years) from 180.6 months (current practice) to 184.9, 187.6 and 197.2 months, respectively.

Although HIV can be suppressed very well, it is clear that when undetected, a progression to a further stage or AIDS development can be expected to occur, which would be associated with an increased healthcare cost and a loss of QALYs. Moreover, transmission could occur as well and remain undetected. It seems that even in Western Europe, a substantial amount of people are living with undetected HIV (e.g., in France, roughly 40'000 out of an estimated 106'000-134'000 HIV-infected people remained unaware of their infection according to Yazdanpanah et al. [29] at the time of their analysis).

Let us now **assume that only 1 QALY would be gained per detected infection**. This is very likely a **large underestimation** because when timely detected, HIV-infected people could live up to an age of 70, whereas if undetected, it is likely to be detected only at a later stage or when AIDS is starting to develop. Further, let us assume 26'079-49'387 £ as value for a QALY, based on the values set by the NICE (i.e. the UK National Institute of Health and Care Excellence) as threshold for cost-effectiveness and those set by Fang et al. [14] (see Appendix 1). The following **social cost** could then roughly be calculated for the different scenarios:

- **Scenario 1:** [redacted] mio £
- **Scenario 2:** [redacted] mio £.

These estimates should be considered as **substantial underestimations** of the social impacts in terms of increased healthcare spending and related costs as a result of temporary unavailability of the affected HIV assay. The reasons for this are mainly the highly conservative **assumption of only 1 gained QALY per newly detected HIV infection**. In addition, the **indirect gain in QALYs resulting from the prevention of further spreading** of HIV through sexual transmission or blood

transfusions **was not taken into account** (due to too much further assumptions to be taken). This is an obvious and important underestimation. In addition, the HIV portfolio only contains one affected assay whereas other assays in different IVD product portfolios are affected as well. Therefore, the outcome of the exercise discussed above strongly supports the conclusion that the social impacts in terms of increased healthcare spending and related costs can be assumed to be a dominant factor at the socio-economic side of the equation.

Theoretical explanatory note on what type of costs can be considered covered by the indicative calculations

The abovementioned indicative calculations were performed using VOLY, VSL or QALY values. The costs that are covered by these values depend on the methodology followed to determine these values. It is therefore difficult to present a breakdown of what these values actually cover in monetary terms. It can be assumed that WTP studies concerning this subject – such as those performed to set the VOLY and VSL used in this section – cover not only labour income, but also non-labour income, value of nonmarket activities such as leisure, and any premium individuals attach to the avoidance of pain and suffering. In the above section, it is mentioned several times that increased healthcare costs are to be expected when certain IVD products would (temporarily) not be available anymore. Actually, these increased healthcare costs may even be considered social impacts on top of the impacts covered by e.g. the applied VOLY or VSL values. Therefore, in this SEA in several places 'social impacts of temporary unavailability of affected assays in terms of increased healthcare costs and related costs' is mentioned. **In the indicative calculations above, increased healthcare costs as such were not taken into account, but if they could have been taken into account, this would only further fortify the conclusion that the social impacts due to temporary unavailability of affected assays are dominant in the socio-economic part of the equation.**

3.5. Wider Economic Impacts

⇨ Impacts on the wider economy are covered in other sections of this SEA.

Impacts on the wider economy are **included in the description of economic impact**s (Section 3.2), the **quantification of economic impacts** (Section 3.3) and in particular in the **overview of distributional impacts** (Section 4.2).

4. COMBINED ASSESMENT OF IMPACTS

4.1. Comparison of Impacts

- ⇨ The ratio of minimal societal cost per kg OP or NP_{equiv}. emitted is estimated to be >> **0.3 – 1.3 mio £ / kg**
- ⇨ Based on the comparison of impacts, it can be concluded with high certainty that the **socio-economic benefits** of continued use of OPnEO / NPnEO associated with Use 3 **outweigh the remaining risks to the environment**.
- ⇨ The **environmental risks cannot be monetised**, but emissions of OPnEO / NPnEO are minimised as far as technically and practically feasible.

An overview of impacts on different stakeholders is given combined for Use 3 (Table 22) to compare impacts between the applied for use scenario (continued use of OPnEO / NPnEO until substitutions are completed) and the non-use scenario (interruption of supply until substitutions are completed). Socio-economic impacts are given based on the two following scenarios as discussed in the previous sections (see Figure 21 and Figure 22):

- **Scenario 1: Competitors can take over Roche's market share**
- **Scenario 2: Competitors cannot take over Roche's market share**

Table 22. Use 3: Overview of the impacts over the 5.5 years of the review period in the non-use scenario in comparison with the applied for use scenario. Economic impacts are given for Scenario 1 (competitors can take over Roche's market share) and Scenario 2 (competitors cannot take over Roche's market share)

Type of impact	**Stakeholders impacted**	**Applied for use scenario***	**Non-use scenario***
Environ-ment	Environment / surface water and soil	Total over the review period: <u>Release to surface water:</u> $OP_{equiv.}$: 20.41 – 44.79 kg $NP_{equiv.}$: 0.0385 – 0.0568 kg <u>Release to soil:</u> $OP_{equiv.}$: 17.0 – 37.3 kg $NP_{equiv.}$: 0.117 – 0.173 kg PEC < EQS / PNEC values	No releases of OP or $NP_{equiv.}$ from customers activities based on RDL's assays covered in Use 3

Type of impact	Stakeholders impacted	Applied for use scenario*	Non-use scenario*
Economic impacts	RDL / Roche	Roche / RDL will be able to continue their current IVD assay business with existing customers in the UK	Estimated loss of EBITA due to the interruption of IVD sales (existing assays and existing customers) **Scenario 1:** [redacted] mio £ **Scenario 2:** [redacted] mio £
	RDL / Roche	Roche / RDL is expected to be able to grow their IVD assay business in the UK by winning new customers	Loss of EBITA from growth of the IVD business due to the inability to provide a complete portfolio or from growth of systems or assays that cannot be provided **Scenario 1:** [redacted] mio £ **Scenario 2:** [redacted] mio £
	RDL	RDL will be able to keep their contractual obligations RDL will be able to keep or expand their position on the IVD market in the UK	Loss of trust in Roche as IVD supplier Loss in reputation Compensation claims may be brought by customers where force majeure provisions and other terms allow in individual contracts. RDL may also be required to indemnify customers where samples are outsourced for analysis. However, these costs are considered as costs to RDL's customers as the most likely scenario (see entry below).
	Customers (laboratories, hospitals)	RDL's customers will be able to continue their business providing laboratory services to the healthcare system	Due to non-supply by RDL, customers (laboratories / hospitals) will not be able to provide complete services to patients and therefore are expected to lose business. They will need to, where possible, employ mitigation measures. Customers will switch as soon as possible to a competitor if possible (Scenario 1). **Scenario 1:** Cost of assays not supplied (as a minimum indicator for loss of services not supplied): [redacted] mio £ Cost of switching to a competitor system (based on instrument cost only): [redacted] mio £ **Total Scenario 1:** [redacted] mio £ **Scenario 2:**

Type of impact	Stakeholders impacted	Applied for use scenario*	Non-use scenario*
			Cost of assays not supplied (as a minimum indicator for loss of services not supplied): [redacted] mio £
	Customers (laboratories, hospitals)	RDL's customers will be able to keep or expand their position on the IVD market	Loss of trust in laboratories, risk of loss of accreditation for reimbursement by health insurances
Social impacts	Patients	Thousands of patients will continue to benefit from health services based on Roche's IVD assays including diagnosis, monitoring etc.	**Patients will face a lack of healthcare services** over a minimum of 1 – 2 years (Scenario 1) to a maximum of 5.5 years (Scenario 2): Estimated cost to society in terms of increased healthcare costs and related costs: >> [redacted] (10 – 50) mio £**
	Workers	RDL will continue to be an important employer in the UK	Impact on employment: a loss of jobs at RDL and connected companies is expected but can currently not be quantified.

* All values are total values over the entire review period.
All minimum values: calculated based on a best-case with all substitutions on time according to the timelines given in the AoA.
All maximum values: calculated based on a worst-case with all substitutions delayed until the end of the review period (i.e. beyond the expected risk given in the timelines in the AoA).
** In the social impact assessment, it was estimated that increased healthcare costs and related costs will be higher than the maximum total estimate for EBITA foregone for Use 3.

Discussion of the likely impacts based on the given ranges

As discussed previously, **Scenario 1** with all substitutions delayed until the end of the review period and **Scenario 2** with all substitutions completed as planned are **extremes** and the likely impacts are expected to lie somewhere in between. Ranges based on the extremes are given as the **likely impacts cannot be quantified more precisely** due to associated uncertainties (see Section 3.2.1 for a qualitative discussion of the likely impacts and Section 4.3 for further considerations on uncertainty).

The **minimum and maximum** of the given ranges for monetised impacts **for each of the two scenarios as well as for the emissions of OP / $NP_{equiv.}$** are **calculated based on minimum and maximum timelines for the substitution projects**. As shown in the AoA, it was estimated that risks that are expected to occur with a certain likelihood would only in 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 is not very likely. Therefore, **the risk that the full review period will be needed for substitution of all the assays is very low**. However, for certain assays, such as the affected HIV assay, the full review period is needed for substitution with new generation instruments and assays. Therefore, with respect to substitutions, likely **completion will be in between the two extremes of 'all completed as planned' and 'all delayed until the end of the review period'** which were used for the minimum and maximum calculations.

Comparison of the most relevant impacts

As discussed in the social impacts analysis (see Section 3.4.2), the **social impacts related to the temporary unavailability of IVD assays** (resulting in a temporary lack of healthcare services for patients and an associated increase in healthcare and related costs) **are likely to be a dominant factor in determining the outcome of the SEA**. Increased healthcare and related costs due to temporary unavailability of the affected assays would inevitably put stress on the UK economy. A temporary unavailability of IVD assays is expected in all scenarios as discussed in Section 3.4.2. In the estimation of the social impacts, it was demonstrated that the social impacts in terms of increased healthcare and related costs in the minimum scenario are expected to be several orders of magnitude higher than the maximum economic impact to Roche / RDL in terms of EBITA foregone. Consequently, social impacts in terms of increased healthcare and related costs are expected to be higher than maximum EBITA foregone independent of the scenario. In addition, cost for RDL's customers (laboratories, hospitals) and therefore for the healthcare system are expected to be important especially under Scenario 1 if laboratories can switch to a competitor system and Roche can not provide certainty that substitution of all assays will be completed before such a switch could be executed (see further discussion below).

For comparison with emissions, the minimum value calculated for the social impacts (in terms of increased healthcare and related costs) was based on the estimated maximum EBITA foregone. This minimum value for social impacts ([redacted] (10 – 50) mio £) is used to **calculate the cost of non-use per kg of OP or $NP_{equiv.}$ emitted**. The latter is based on minimum emissions if substitutions are completed as planned (see Table 23). As discussed in the social impact analysis, the minimum social impacts in terms of increased healthcare and related costs related to the temporary unavailability of IVDs likely represents a **substantial underestimation of the social impacts in all scenarios**. Therefore, the **ratios presented below are expected to be several orders of magnitude larger as well**.

Table 23. Minimal societal cost of non-use (in terms of increased healthcare and related costs) per kg of OP or $NP_{equiv.}$ emitted for the scenario with minimum emissions.

	Calculation of ratio of minimal societal cost per kg OP or $NP_{equiv.}$ emitted
Total cost (mio £ per year)	[redacted] >>10 – 50
Total releases (kg OP / $NP_{equiv.}$ if substitutions are completed as planned)*	37.57**
Ratio (mio £/kg)	[redacted] >> 0.3 – 1.3

*****Releases are based on minimum (total releases in case substitutions completed as planned) as estimates for social impacts are also based on the minimum scenario.

**The value represents the sum of the releases to surface water and soil assuming that 100% of sludge from Use 3 is applied to agricultural soil.

Further impacts

Depending on the scenario, Roche will face **loss of EBITA** from [redacted] (1 – 50) mio £ over the course of the review period. The loss will be distributed between RDL and the mother company (RDG as well as Roche entities in the US as the producers of the affected products) and the actual loss for RDL has not been quantitied. Depending on the scenario, these impacts may additionally be distributional outside of Roche (see Section 4.2). As furhermore the social impacts based on temporary unavailability of the IVD assays are expected to be far more important, these losses are not included in the above calculation of cost of non-use per kg of OP / $NP_{equiv.}$ emitted.

In addition to financial losses, **loss of trust from customers** is expected to have an **important impact** on Roche's business **which cannot be quantified**.

Further impacts, such as **impacts on employment** can currently not be quantified. They could be substantial in case Roche should lose entire portfolios. However, in such a case the impacts would be distributional as Roche's competitor's would gain.

Finally, **impacts on laboratories and hospitals** will be important as they will not be able to provide complete services to patients. Short-term mitigation measures will only be possible to a very limited degree. Therefore, laboratories and hospitals will switch as soon as possible to competitor products and / or systems if possible but may lose their accreditation for reimbursement by health insurances. The **unavailability of assays will be disruptive for the operations of the laboratories and hospitals**. In addition, it is expected to **have financial implications** which would have to mainly be borne by customers themselves and thus ultimately by the healthcare system and / or patients. As government action may be considered as force majeure in contracts, it is expected that most customers will not be able to claim compensation or be indemnified for these costs by RDL. However, this will depend on the terms of each individual contract or framework agreement. In case of compensation by Roche, the cost for mitigation measures would represent an additional economic loss to RDL.

Expected cost for customers based on assays not provided, business lost and associated mitigation measures such as switching to a competitor system can only be estimated in an indicative way per scenario. This was based on the value of assays not delivered and the cost of new instruments for laboratories / hospitals as an indication of a minimum. Estimated costs are in total in the range of [redacted] (1 – 200) mio £. However, the total cost to customers could be much higher than this as e.g. the instrument cost is only part of the cost of switching to a competitor system. As reliable values cannot be estimated and impacts will highly depend on the scenario, it was not possible to include these impacts in the above calculation of cost of non-use per kg of OP / $NP_{equiv.}$ emitted.

Furthermore, additional financial pressure and disruption of the laboratories' operations could have an impact on the quality of healthcare services beyond the unavailability of the affected assays.

Based on the above analysis, it can be concluded with high certainty that the socio-economic benefits of continued use of OPnEO / NPnEO associated with Use 3 outweigh the remaining risks to the environment.

The environmental risks cannot be monetised, but emissions of OPnEO / NPnEO are minimised as far as technically and practically feasible.

4.2. Distributional Impacts

- ⇨ The **economic impact to Roche in terms of EBITA foregone** is **distributional in Scenario 1** (when competitors take over Roche's market share) because the financial losses to Roche would result in financial gains to the competitor(s) taking over. In addition, the EBITA foregone is partially a loss for RDL and partially for the mother company.
- ⇨ The **social impacts related to unemployment are distributional**.
- ⇨ The **social impacts in terms of increased healthcare and related costs** related to the temporary unavailability of Roche's affected products are **not distributional** and will put additional stress on the UK economy.
- ⇨ The **economic impact to Roche's customers in terms of cost for mitigation measures** would put additional pressure on the healthcare system even though Roche's competitors may gain from these measures.
- ⇨ **Environmental impacts may shift within the UK** in case of non-authorisation, depending on which competitors take over Roche's market share and whether these competitors are using NPnEO / OPnEO in their assays (based on a UK authorisation). Consequently, a non-authorisation for Roche does not necessarily result in an equivalent reduction of releases of NPnEO / OPnEO to the environment.

Some of the impacts described quantitatively or qualitatively in the previous sections can be considered distributional. **Distributional impacts** may relate to **shifts of impacts between economic operators** (applicant, competitors, customers, general public), potentially including **shifts of impacts** within the applicant's business itself. An overview is given in Table 24.

Table 24. Distributional impacts overview.

Affected group	Economic impact	Health and environmental impact
Economic operator		
Applicant	The quantified economic impact to Roche in terms of EBITA foregone could be a distributional impact – while a loss for Roche, it could be a gain of the same magnitude for (a) competitor(s) if (a) competitor(s) can take over Roche's market share (Scenario 1).	

Affected group	**Economic impact**	**Health and environmental impact**
Roche (RDG in Germany) as producer and supplier of the affected assays; Roche in the US as producer of the RTD assay	In case of a non-authorisation, part of the economic loss described in the economic impacts section will have to be borne by Roche as the producer and supplier of the affected assays and the affected portfolios (mainly RDG in Germany, but also Roche in the US as producer of the RTD assay). If the affected assays are not allowed to be used in the UK, RDG will not be able to sell them to RDL. If customers switch to competitor systems (Scenario 1), the assays of the entire portfolios cannot be sold. Also further opportunities for growth in the UK will be lost. These impacts will be distributional as Roche's competitors will gain. As the impact on healthcare is considered the dominant impact, the distribution of loss between RDL and RDG was not quantified. Note that this UK-specific impact for RDG would only occur if the EU authorisation was granted to RDG. If this was not the case, RDG would not even be in the position to produce and deliver the affected assays to RDL.	
Competitors in the UK	In case competitors can take over Roche's market share (i.e. Scenario 1), the economic benefit to these competitors can be expected to be of a similar magnitude as the economic impact to Roche in terms of	

Affected group	**Economic impact**	**Health and environmental impact**
	EBITA foregone. Note that multiple competitors may be involved. Also note that competitors are expected to at least have a distributor in the UK, like Roche. Therefore, the shift is expected to take place within the UK. In case a competitor was producing IVD assays in the UK, additional economic benefit may shift from Germany (location of RDG) to the UK.	In case a competitor was producing IVD assays in the UK using OPnEO / NPnEO based on a UK authorisation, additional emissions of these substances may be shifted to the UK if emissions occurred during production.
Downstream users of IVD assays	The downstream users of IVD assays (laboratories / hospitals, blood banks, etc.) will be faced with a temporary unavailability of IVD assays from Roche. In many cases, this will lead to a temporary inability to provide complete services to patients as immediate mitigation measures are expected to be possible only to a limited extent. Within 1-2 years laboratories / hospitals are expected to switch to a competitor system if possible. The cost related to assays that could not be performed and / or mitigation measures would in a first instance need to be borne by the downstream users. Such costs may however be distributional as well and may eventually shift to patients and insurance companies. Also, in those cases where RDL's customers may be able to claim compensation or be	As there is a lot of financial pressure on the healthcare system, hospitals running into additional costs may experience increased financial pressure, which eventually could lead to a reduction of the quality of provided services, which may indirectly affect human health of the general public. This is a distributional impact that cannot be quantified and further adds to the health impacts described below. The magnitude of environmental impacts may change at the downstream user sites

Affected group	Economic impact	Health and environmental impact
	indemnified for these costs by RDL, the cost may shift to RDL and represent an additional economic loss to RDL. This is not expected in many cases as government action may be considered as force majeure in contracts. However, it will depend on the terms of each individual contract or framework agreement.	in case of non-authorisation, depending on which competitors take over Roche's market share and whether these competitors are using NPnEO / OPnEO in their assays (based on a UK authorisation) or not. Consequently, a non-authorisation for Roche does not necessarily result in an equivalent reduction of releases of NPnEO / OPnEO to the environment.
Patients in the UK	As Roche represents a substantial market share in the UK for most of its affected products, a temporary unavailability of its products (as expected in all possible scenarios) would affect patients (resulting in a decrease of quality adjusted life years (QALYs)) and consequently increased healthcare and related costs. These increased costs are expected to represent a net loss to the UK economy.	Reduced patient outcome (e.g. expressed as an overall reduction of QALYs) is to be expected in the UK due to a temporary unavailability of Roche's affected IVD assays, i.e. lack of healthcare services.
Geographical scope*		
Germany and the US	See impacts described above for Roche (RDG in Germany) as producer and supplier of the affected assays; Roche in the US as producer of the RTD assay.	
UK		For a possible shift of OPnEO / NPnEO

Affected group	Economic impact	Health and environmental impact
		emissions to the UK see impacts described above for 'competitors in the UK'.
Applicant's business		
Employees	Unemployment is expected as a result of damage to RDL's reputation, loss of revenue and loss of opportunity and therefore economic loss. The social cost of unemployment is considered both temporary and distributional as in Scenario 1 new jobs are expected to be created at competing companies taking over Roche's market share. These jobs may – at least partially – be created in the same region as the jobs lost at RDL. In Scenario 2, some employees may flow back to Roche during re-hiring after finalisation of substitution projects. However, the more delay the substitution projects would run into, relatively more new employees (with similar qualifications as the previous employees) would have to be hired.	
Owners	Owners will be affected by the financial losses of Roche described above. An expected loss of trust in Roche by customers may trigger shareholders to sell their shares and shift their capital to other companies.	
Socio-economic group		

Affected group	Economic impact	Health and environmental impact
Socio-economic groups based on skills (A (highly skilled) / B (skilled / semi-skilled) / C (manual / non-skilled)[5]	Job losses are expected predominantly in group B (skilled, semi-skilled) due to job losses in administrative/supporting/sales functions that would become redundant due to interruption of supply of assays. The lost jobs in group B may be generated elsewhere in the UK when (a) competitor(s) can take over Roche's market share but depending on the location of the competitor(s) taking over, these jobs would have to be filled by other employees than those that lost a job at Roche. A small loss could be expected in group A (highly skilled). Also, in this group potentially additional people would need to be hired to be able to head the crisis in the company (e.g. in case relevant, employees that deal with requests from customers to find solutions, lawyers supporting the company, etc.). This impact is nevertheless considered to be limited compared to all other socio-economic impacts described in this dossier.	

* Geographical scopes of economic impacts are described in the respective sections on the impacts at the level of the different economic operators.

The **overall conclusions** drawn from the evaluation whether or not the impacts described in this SEA are distributional can be summarised as follows:

- The **economic impact** to Roche / RDL in terms of **EBITA foregone** are distributional in Scenario 1 (when competitors take over Roche's market share) because the financial losses to Roche would result in financial gains to the competitor(s) taking over. In case a competitor was

[5] ECHA Guidance on the preparation of socio-economic analysis as part of an application for authorisation: https://echa.europa.eu/documents/10162/23036412/sea_authorisation_en.pdf/aadf96ec-fbfa-4bc7-9740-a3f6ceb68e6e

producing IVD assays in the UK, additional economic benefit may shift from Germany (location of RDG) to the UK.

- The **economic impact** to the downstream users (i..e laboratories, hospitals etc.) in terms of **cost for mitigation measures** may be distributional and may eventually shift to patients and insurance companies. In some cases, the cost may shift to RDL and represent an additional economic loss to RDL. In any case the cost will put additional pressure on the healthcare system even though Roche's competitor's may gain from these measures.

- The **social impacts** related to **unemployment are** distributional i.e. jobs are expected to shift to competitors and may – at least partially – be created in the same region as the jobs lost at RDL.

- The **social impacts** in terms of **increased healthcare and related costs** related to the temporary unavailability of Roche's affected products are not distributional and will put additional stress on the UK economy.

- The magnitude of **environmental impacts** may change at downstream user sites in case of non-authorisation, depending on which competitors take over Roche's market share and whether these competitors are using NPnEO / OPnEO in their assays (based on a UK authorisation). Consequently, a non-authorisation for Roche does not necessarily result in an equivalent reduction of releases of NPnEO / OPnEO to the environment. In case a competitor was producing IVD assays in the UK using OPnEO / NPnEO based on a UK authorisation, additional emissions of these substances may be shifted to the UK if emissions occurred during production.

4.3. Uncertainty Analysis

- ⇨ The **uncertainty concerning** whether or not **competitors** can take over RDL's market share and whether or not **substitutions** will be completed as planned **has been covered quantitatively in the economic impact assessment**, resulting in a range between which the actual impact would be situated.
- ⇨ The **uncertainty concerning** whether or not substitutions will be completed as planned has also **been covered quantitatively in the environmental impacts assessment**, resulting in a range of releases to the environment between which the actual releases would be situated.
- ⇨ **Remaining factors of uncertainty were assessed qualitatively** in this section. The overall conclusion of the assessment is that **all impacts were quantified using conservative assumptions** and that therefore the **social and economic impacts are underestimated** whereas the **releases to the environment** as well as the PECs are **rather overestimated** than underestimated.

In this section, the **uncertainty associated with assumptions** made is discussed in order of relevance to the outcome of the socio-economic assessment. It should be noted that some of the uncertainty was already covered in a quantitative way in the impacts assessment by including several scenarios. Regarding the economic and social impacts of a non-authorisation, the **following scenarios** were **considered**:

- Scenario 1: **Competitors can take over RDL's market share**.
- Scenario 2: **Competitors cannot take over RDL's market share**.

For each scenario, two sub-scenarios were discussed:

- All substitutions are completed as planned.
- All substitutions are delayed until the end of the review period.

Regarding the environmental impacts in case of authorisation, separate calculations were made for the situations in which substitutions are completed as planned or delayed until the end of the review period.

Consequently, an important part of the uncertainty around the calculations has been covered quantitatively already in the impact assessment. In addition, in this section, assumptions for which the influence on the assessment could not be assessed quantitatively, are evaluated in a qualitative way. This is done with the goal to understand their potential importance with regard to the outcome of the assessment. A summary table of this qualitative assessment is provided in Table 25.

Uncertainty related to the assessment of social impacts in terms of increased healthcare and related costs related to temporary unavailability of IVDs

An **accurate quantification of the social impacts** under the different scenarios **in terms of increased healthcare and related costs** related to the temporary unavailability of IVD assays **is not possible** for several reasons. The main reasons are the following:

- The relationship between the use of each affected IVD assay and the benefits to society in terms of a reduction in healthcare and related costs is not available for the affected IVD assays.

- The relationship between the use of each affected IVD assay and its benefits to human health in terms of a qualitative, non-monetary value (such as gained QALYs) is not available either for most IVD assays. If such relationship would be available, a total number of QALYs lost could be calculated and monetised.

- In case a total number of lost QALYs (in case no authorisation would be granted) could be calculated, its monetisation would also be associated with an important uncertainty as there is no generally agreed monetary value for a QALY.

Because no accurate estimation would be possible for all affected assays together, **two separate exercises** were performed **to obtain an indication of how high the social impacts could be and how they would relate to the other impacts at the same side of the equation** (i.e. economic and other social impacts).

In a first series of indicative calculations, it was calculated what the minimal efficiency of the total number of affected assays would have to be in terms of gained QALYs / avoiding mortality resulting from potentially fatal health conditions to equal the economic impacts to Roche / RDL in terms of EBITA foregone. This calculation was done using the total number of missing tests under Scenario 1 (competitors can take over RDL's market share) with all substitutions completed as planned, which is the scenario with the lowest expected health impacts, and using the maximum calculated EBITA foregone under Scenario 1 (competitors can take over RDL's market share) with all substitutions delayed. In the combined impacts assessment section it is explained why exactly this comparison was made. The outcome was that the social impacts related to the temporary unavailability of the affected assays would equal/exceed the maximum economic impacts to Roche / RDL in terms of EBITA foregone already in case of an unrealistically low efficiency of the affected assays.

An overview of the factors of uncertainty associated with this calculation and their potential impact on the outcome of the assessment is given in Table 25.

Altogether, the indicative calculations, although associated with a lot of uncertainty, can be concluded to demonstrate that the **social impacts are several orders of magnitude higher than the economic impacts to Roche / RDL in terms of EBITA foregone**. Consequently, **using the maximum EBITA foregone calculated** (Scenario 1, all substitutions delayed) as a minimum estimate for the social impacts in all scenarios **represents a substantial underestimation of the social impacts – even in the scenario with the lowest expected health impacts**.

In a second indicative exercise, a **mini-case** was performed **for the affected HIV assay**, in which an attempt was made to quantify the expected increase in healthcare and related costs related to a temporary unavailability of the affected assay. Such an exercise was expected to be more straightforward than the overall case for all affected assays, because a very specific health impact is concerned and because various publications are available discussing the effectiveness (sometimes in

terms of gained QALYs) of different HIV screening programmes. Nevertheless, assumptions needed to be made on the amount of gained QALYs resulting from the use of the affected assay, as no publications were available comparing the gain in QALYs of different screening programmes compared to no screening at all. Therefore, based on the available publications, the assumption was made that, as a worst-case, on average only one QALY would be gained at the level of the patient per newly detected HIV carrier. The following factors bring along uncertainty around the outcome of the calculation (not included in Table 25 as the outcome of this exercise was not used quantitatively in the combined impacts assessment and only served as supporting evidence for the underestimation of the social impacts due to temporary unavailability of affected assays):

- The assumed reduction in market share of the affected HIV assay (combiPT) over time.
- The assumption of the direct positive relationship between market share and number of diagnoses.
- The assumption that the 2021 figures of new HIV infections detected would still be relevant at and after the sunset date, as newly detected cases are decreasing over the years in the UK, and in 2021 the decrease may have been higher than expected due to the measures taken in view of the Covid-19 pandemic, which were focused on reducing social contacts.
- The assumption of only one gained QALY per newly detected infection. This assumption brings along the largest uncertainty around the estimation. However, as changing between different screening programmes could already result in an increase of quality-adjusted-life expectancy by 1 year or even more, an assumed gain of one QALY per newly detected HIV infection (compared to no screening at all) is clearly a substantial underestimation of the social benefits of HIV IVDs.
- The monetary value of a QALY and its recalculated value for 2022 (with use of actual inflation figures and currency conversion using conversion rates reported for January 2022).
- The fact that the calculation does not take into account the indirect gain in QALYs resulting from the prevention of further spreading of HIV through sexual transmission or blood transfusions.

Altogether, it is clear that also **in this mini-case the social impacts are substantially underestimated**. This further supports the conclusion that the **social impacts related to temporary unavailability of IVDs can be assumed to be the most dominant factor in the socio-economic part of the equation**.

Uncertainty related to the economic impact assessment

As stated above, in order to **cover some of the uncertainty in the economic impact assessment in a quantitative way, two scenarios, each with two sub-scenarios**, were put forward:

- In Scenario 1, it is assumed that **competitors can take over** RDL's market share.
- In Scenario 2, it is assumed that **competitors cannot take over** RDL's market share.

For both Scenario 1 and 2, a **minimum and a maximum impact** was then calculated using two sub-scenarios, i.e. one sub-scenario in which all **substitutions** are assumed to be completed **as planned** (i.e. yielding the minimum financial impact), and another in which all substitutions are assumed to be **delayed** until the end of the 5.5-year review period (i.e. yielding the maximum financial impact).

These scenarios were put forward because of the following main uncertainties (not included in Table 25 as the impact of these uncertainties is already quantified in the impact assessment):

- Whether or not Roche's competitors also have authorisation duties for similar uses as those applied for by Roche, affecting similar IVD assays/portfolios.
- Whether or not the competitor(s) would be granted an authorisation (in case they also have authorisation duties for similar uses).
- Whether or not one or more competitors of Roche, which remain unaffected by authorisation or are granted an authorisation, are capable of taking over Roche's market share or not.
- Whether or not substitutions as scheduled by Roche will be completed on time.

By performing calculations for two sub-scenarios depending on whether substitutions are completed on time or delayed, a range of economic impacts is obtained for both Scenario 1 and 2. The **actual impacts** are expected to **lie between the minimum calculated for Scenario 2 and the maximum calculated for Scenario 1**. Considering the likelihood of the different scenarios, as described in the economic impact assessment section, Scenario 1 (competitors can take over) and Scenario 2 (competitors cannot take over) are both considered extremes that are not likely to occur. At the level of the sub-scenarios (substitutions completed on time or delayed until the end of the review period), it is considered unlikely that a majority of the substitutions would require until the end of the review period in order to be completed.

The estimates of the economic impacts to Roche / RDL in terms of EBITA foregone (calculating separate values for EBITA foregone as a result of expected growth) are considered to be the most accurate estimates of the total economic impacts assessment. Next to the quantitatively assessed uncertainties mentioned above (covered by the estimations for the different scenarios and sub-scenarios), there are some additional factors bringing along uncertainty around these estimates, which are assessed in a qualitative way in.Table 25.

Altogether, it can be concluded that **the estimated range for the economic impacts on Roche / RDL in terms of EBITA foregone nevertheless represents a conservative estimate**, i.e. the maximum impact could be (substantially) larger, especially because the estimation only includes the economic impact related to directly affected assays/portfolios/systems and does not include potential economic impact related to unaffected portfolios for which RDL may lose market share due to a general loss of customers' trust in the company.

Further, the uncertainty related to the assumptions made for the estimation of the economic impacts to RDL's customers in terms of **cost for mitigation measures** is also assessed qualitatively in Table 25.

Altogether, it can reasonably be concluded that the **estimates** provided **for this type of economic impact are very conservative and in each scenario likely represent underestimations of the actual impact** in case of non-authorisation. Even more, it can be concluded based on the uncertainty assessment presented in Table 25 (and discussed in the economic and combined impacts assessment sections) that maximum cost to customers cannot be quantified. Due to terms of each individual contract or framework agreement, it cannot be estimated how many customers may be able to claim compensation or be indemnified for these costs by RDL. As government action may be considered as force majeure in contracts, it is however expected that most customers will not be able to do so.

As the estimated cost represent a minimum, it is reasonable to assume that cost of such magnitude as a minimum would have to be borne by customers, but that actual cost will likely be higher. Finally, it should also be noted that the estimates of economic impacts to RDL's customers in terms of mitigation cost are the highest in Scenario 1, where competitors can take over RDL's market share and where the temporary unavailability of assays and consequently the social impacts in terms of increased healthcare and related costs are expected to be the lowest.

Uncertainty related to the social cost of unemployment

No quantitative estimates were made for the social cost of unemployment as no accurate estimates are available of the number of jobs that may be lost in the different scenarios.

Uncertainty related to the environmental impact assessment

As stated earlier, regarding the environmental impacts in case of authorisation, separate calculations were made for the situations in which substitutions are completed as planned or delayed until the end of the review period. This already covers a large part of the uncertainties regarding total release in a quantitative way.

The main uncertainties that were encountered during the assessment of the environmental impacts are summarised in Table 25. The assessment is based on releases of $OP_{equiv.}$ and $NP_{equiv.}$ to surface water and soil, which are considered as a proxy for the environmental impacts. Uncertainties having an influence on release to wastewater, release to surface water or soil and calculation of PEC in surface water or soil are discussed. Taking all uncertainties together, it can be safely concluded that the calculated releases represent reliable estimates. Comparisons of PECs with existing environmental quality standards and PNECs were used for illustrative purposes to support the environmental impacts assessment. As it was shown that modelling assumptions are very conservative, actual releases and actual PECs are rather over- than underestimated.

Table 25. Main uncertainties in the impact assessment: Overview of assumptions and influence on the outcome of the assessment.

Source of uncertainty	Description of assumption	Justification	Influence on the outcome of the assessment
Social impacts related to temporary unavailability of IVDs			
Number of tests of affected assays currently performed per year	[redacted] mio tests/year in general, (Scenario 1, all substitutions completed as planned)	Worst-case scenario – Under Scenario 1 with all completed as planned, the lowest health impacts are expected: lowest number of missing tests per year and lowest duration of temporary unavailability.	The number of missing tests per year is a reasonably accurate estimate. For CC/DM and RTD, the number was scaled to the UK from EU numbers based on the number of instruments as it can be assumed that on average the number of tests per instrument is the same. For HIV actual numbers were used since the situation for the switch to the new instruments is different in the UK than the average situation in the EU. Using this number in the calculations, together with the maximum estimated EBITA foregone (i.e. for Scenario 1 with all substitutions delayed) yields the minimum efficiency of the assays in order to equal the maximum estimated EBITA foregone. All other scenarios have either a higher number of missing tests and / or a lower estimated EBITA foregone and would therefore yield an even lower minimum efficiency. Since the minimum efficiency was extremely low in each calculation, it could be concluded with high certainty that the social impacts resulting from temporary unavailability of IVDs would easily be several orders of magnitude higher than the maximum estimated EBITA foregone and will therefore be a dominant factor at the socio-economic side of the equation.

Source of uncertainty	Description of assumption	Justification	Influence on the outcome of the assessment
Contribution of affected assays to the gain of QALYs / prevention of fatalities	It was assumed that all assays contribute to this	It is impossible to take the relative contribution of all different types of affected assays into account. Therefore, all are considered to contribute equally, which is considered justified based on the qualitative explanation of their social benefits in the social impacts section.	Although the calculated minimal efficiency of the affected assays* could not be compared to an actual efficiency figure, the outcome was such an obvious underestimation, that a more accurate estimate of the relative contribution of all different types of affected assays is not considered required to be able to conclude on the likely magnitude of the social impacts. **i.e. only 1 on 17'000 tests should result in the gain of 1 QALY, only 1 on 321'000 tests should prevent a fatal health condition*
Monetary values used for VOSL and VSL	VOSL: 55'800 EUR (2003) VSL: 1'052'000 EUR (2003)	Values used were taken from the ECHA guidance on socio-economic analysis under authorisation (VOSL, VSL) [10]	The magnitude of the values used is associated with a lot of uncertainty, but no better estimates are currently available in this context.
Extrapolation of VOSL, VSL to 2022 and currency conversion	From the date the value was derived for until 2022, actual inflation figures were applied For currency conversion (EUR to £), the conversion rates of beginning of January 2022 were used	The use of actual (historical) inflation figures provides the best estimation of the current value of a certain amount of money in the past. Currency conversion rates are not known in the future, consequently only the most recent conversion rates can be used as approximation.	Use of different historical inflation calculators yields only marginal differences between the obtained values. As the VOSL and VSL value were only recalculated to the value in 2022 and not for the consecutive years up to 2027, significant changes in future inflation figures and currency conversion rates may affect the calculation accordingly.
Type of social benefit of affected assays	The social benefits of the affected assays were narrowed (in view of the indicative	The social benefit of the affected assays/portfolios is much broader than what is considered in this	Not taking into account the wider social benefits of the affected assays/portfolios further adds to the underestimation of the

Source of uncertainty	Description of assumption	Justification	Influence on the outcome of the assessment
	calculations) to gain of QALYs / prevention of fatalities	series of indicative calculations, as they are indispensable in the general improvement of quality of life. Even more, some of the affected assays, such as those involved in screening for drugs of abuse, have even wider social benefits than the contribution to a reduction in healthcare and related costs (e.g. see Table 8).	social impacts resulting from a temporary unavailability of affected assays.
Economic impacts – EBITA foregone			
EBITA figures including predictions for the UK	EU figures are scaled to the UK based on percentage of number of instruments in the UK versus total number of instruments in EEA + UK For HIV, current figures were collected and assessed.	The figures were verified and represent a reasonable estimate since the business for the assays covered in this AfA has not substantially changed since the preparation of the EU dossier. Scaling based on number of instruments is a reasonable approximation since turnover is mainly generated by the sales of assays and the need for (and therefore purchase of) assays per instrument can be assumed to be on average the same. In addition, average EU prices are slightly below UK prices so that scaling average EU sales or EBITA figures to the UK without	Impact on the outcome of the assessment is considered to be limited.

Source of uncertainty	Description of assumption	Justification	Influence on the outcome of the assessment
		further adjustment represents a conservative approach. For HIV the situation on the UK market regarding the replacement of instruments with new generation instruments for HIV differed substantially from what was described for the EU market.	
Distribution of sales / EBITA foregone between RDG and RDL	Assays are delivered from RDG to the RDL for a certain transfer price. The transfer price is arranged that RDL can cover sales and administration costs and also gains some profit with taxation in UK. The distribution of sales / EBITA foregone was not assessed.	For this dossier the conclusion was drawn that the health impacts are far more important than the economic impacts. For this reason, further differentiation of losses between RDL and the mother company Roche was not performed.	As the actual figure for the economic impacts or the distribution between RDG and RDL is not considered decisive for the assessment, the impact on the outcome is limited.
Time frame during which financial losses would occur because affected assays cannot be sold anymore after the sunset date	See Table 18– Depending on the scenario, until switch to another supplier is completed or until substitution is completed	This assumption is depending on one other assumption: i.e. the time needed for a customer to switch to a competitor system.	Impact on the outcome of the assessment is considered to be limited. Reference can be made to the next assumption.
Time needed for a customer to switch to a system from a competitor (Scenario 1)	Ca. 24 months (CC, DM, HIV)	The assumption is considered acceptable considering the extended requirements for switching: quotation phase, overcome spatial difficulties,	A shorter time frame needed for switching would result in a smaller loss of EBITA due to the non-ability of selling affected assays but would increase the loss of EBITA due to the non-ability of selling the entire portfolios →

Source of uncertainty	Description of assumption	Justification	Influence on the outcome of the assessment
		installation phase, need for training, need for re-validation, etc. Moreover, a longer time frame may be needed when competitors face capacity issues due to increasing demand for installation of systems. Therefore, 24 months for all systems for CC, DM and HIV can be considered as a minimum.	would increase the estimate of EBITA foregone. The opposite is true when a longer time would be needed for switching. Only a marginal effect is expected on the overall outcome.
Time frame during which entire portfolios are affected and lost (Scenario 1)	Financial losses assumed to occur during the remaining 3.5 years of the review period after completed switch of customers to competitor systems (CC, DM)	This assumption is depending on the assumption concerning the time needed for a customer to switch to a system from a competitor.	Impact on the outcome of the assessment is considered to be limited. Reference can be made to the assumption on time needed to switch to a competitor system.
Time frame during which entire systems on which the assays are run would be affected	Financial losses assumed to occur immediately after the sunset date until the end of the review period or until substitution is completed (RTD)	This assumption is justified since the systems cannot be used anymore without the missing assays.	Impact on the outcome of the assessment is considered to be limited.
Loss of predicted growth	All predicted growth lost over the entire review period	The assumption is justified since it can reasonably be expected that no new customers would be gained anymore after the sunset date.	Predicted growth could be slightly over- or underestimated but in general, conservative predictions are made and therefore no substantial effect on the outcome of the assessment is expected.

Source of uncertainty	Description of assumption	Justification	Influence on the outcome of the assessment
			In addition, EBITA foregone based on growth is assessed separately from EBITA foregone based on the existing customers.
Actual duration of current contracts	The actual duration of current contracts is not taken into account	This is a level of detail that is unfeasible to add in the assessment considering the multitude of contracts and therefore no account has been taken of this in the assessment.	As in the applied-for-use scenario it could be assumed that the amount of active contracts stays relatively stable (contracts are extended, or – in case lost to competitors – compensated by contracts with new customers), there is no need to take actual duration of contracts into account to calculate economic impact.
Scope of financial losses	Limited to financial losses related to directly affected assays/portfolios/systems	Worst-case assumption – Impact on other portfolios (although expected due to a general loss of trust of customers) is difficult to quantify and therefore not included in the assessment in a quantitative way.	This limitation leads to the conclusion that the estimated economic impacts in terms of EBITA foregone should be considered as very conservative. A general loss of trust among existing and potentially new clients may lead to non-inclusion of Roche in requests for proposal for unaffected portfolios as well, resulting in a further increase of the economic impact at the level of Roche.
Discounting rate	4%	Recommended in the ECHA guidance on socio-economic analysis under authorisation.	Limited impact. If actual inflation rate would appear to be lower, a directly proportional decrease of impact in terms of EBITA foregone would be calculated.
Economic impacts – customer's cost for mitigation measures			
Magnitude of customer's loss of business or cost for mitigation measures for assays not supplied	Assumed to be equal to the value of goods delivered (i.e. cost of affected assays)	The value of goods delivered was used as a very conservative estimate for the minimum cost or loss for customers due to the lack of the affected assays over a certain period of time (Scenario 1:	Only a rough indication of possible cost to customers can be given. Likely results in an underestimation of actual customer cost.

Source of uncertainty	Description of assumption	Justification	Influence on the outcome of the assessment
		until switch to competitor system completed; Scenario 2: until substitution completed). Concerning time needed to switch to a competitor system, the same assumptions as described above are taken.	
Cost for switching to competitor systems (Scenario 1)	Approximated by the cost of equivalent Roche systems	This is only considered as an indicator for minimum cost. The total cost would also include the more important costs for the tender process, installation, training, etc. However, as these additional costs are more difficult to estimate and would further add to the uncertainty around the estimation, it was preferred to omit them in view of a conservative estimation.	Leads to an important underestimation of the impacts. Maximum cost is expected to be much larger than the estimated minimum cost.
Discounting rate	4%	Recommended in the ECHA guidance on socio-economic analysis under authorisation.	Limited impact. If actual inflation rate would appear to be lower than a directly proportional decrease of impact in terms of EBITA foregone would be calculated.
Social cost of unemployment			
Estimation of number of affected jobs at RDL and calculation of social cost of unemployment	No quantification of social cost of unemployment was performed	No accurate estimates of number or % of jobs lost are available.	Social cost of unemployment (although distributional) may significantly contribute to the socio-economic side of the equation even though this was not quantified. This further leads to an underestimation of the socio-

Source of uncertainty	Description of assumption	Justification	Influence on the outcome of the assessment
			economic costs, and will therefore not affect the conclusion.
Estimation of number of jobs affected outside RDL (Roche production sites in Germany/USA, customers of RDL, etc.)	Not included in the assessment.	No accurate estimates could be made.	As mentioned above, the social cost of unemployment was not quantified, which therefore adds to the underestimation of the impacts at the socio-economic side of the equation. Nevertheless, the contribution of jobs lost outside RDL is expected to limited compared to those that may be lost at RDL itself.
Environmental impacts*			
Usage and release figures including predictions for the UK	EU figures for usage and release are scaled to the UK based on percentage of number of instruments in the UK versus total number of instruments in EEA + UK For HIV current figures were collected and assessed.	The figures were verified and represent a reasonable estimate since the business for the assays covered in this AfA has not substantially changed since the preparation of the EU dossier. Scaling based on number of instruments is a reasonable approximation since (liquid and solid) waste generation mainly depends on the use of assays and the use of assays per instrument can be assumed to be on average the same. For HIV the situation on the UK market regarding the replacement of instruments with new generation instruments for HIV	Impact on the outcome of the assessment is considered to be limited.

Source of uncertainty	Description of assumption	Justification	Influence on the outcome of the assessment
		differed substantially from what was described for the EU market.	
Estimates of release to wastewater for laboratories / hospitals (Use 3)	Amount released to wastewater is determined as 'sold amount' minus 'amount going to waste' (not accounting for possible treatment)	Sold amounts are estimated based on EU data (CC/DM, RTD) or directly assessed (HIV) (see uncertainties regarding sales in the UK) and fractions going to waste were estimated per assay and instrument.	Estimates of fractions going to waste – and therefore also the estimates of releases to wastewater – may be associated with some error but influence on the outcome of the assessment is expected to be small. If OPnEO / NPnEO were removed by treatment of liquid waste, releases to wastewater would be overestimated.
Continuation of releases from laboratories and hospitals after completion of substitution in production	As a worst-case it is assumed that from the completion of substitution at the production site until the end of the shelf life of the assay, the release of OPnEO or NPnEO from the assays remains constant	Stocks at customers are assumed to last as long as the shelf life of the products as a worst-case as accurate data on stocks are not available and will be highly variable between customers.	It is likely that stocks of 'old' product will be replaced by new products earlier than the end of the shelf life. Therefore, releases due to remaining stocks are likely overestimated.
Sum of releases used for comparison with social impacts as given in Table 23	Sum of releases from the sunset date until the end of the review period in case all substitutions are completed on time.	Both the indicative calculations of the social impacts resulting from temporary unavailability of IVDs and the calculation of releases were based the scenario in which all substitutions are completed on time.	Although the same scenario was used, for the social impacts only a minimum value could be determined. As a consequence, the ratios presented in Table 23 should be considered as minimum societal benefit per kg OP or $NP_{equiv.}$ released. If releases were higher (due to delayed substitutions), social impacts would also be higher.

Source of uncertainty	Description of assumption	Justification	Influence on the outcome of the assessment
Fraction of sewage sludge from STPs applied to agricultural soil (Use 3)	100% of sewage sludge is applied to agricultural soil	Application of sewage sludge to agricultural soil varies between countries. Detailed information linked to location of the laboratories is lacking.	In the UK, on average 80% of total sewage sludge are used in agriculture [5]. Therefore, releases to soil represent a maximum and are likely overestimated.
Release and resulting PEC from waste disposal (Use 3)	Disposal of all waste on municipal landfills was assumed and standard parameters for wide-dispersive use and standard release factors to wastewater are used for the waste scenario	Assumption of disposal of all waste as municipal waste in landfills is recommended in the ECHA guidance document on exposure assessment from waste.	Disposal of all waste as municipal waste on landfills is a worst-case. Due to small contribution of waste to the overall release and to PECs, the influence on the outcome of the assessment is expected to be marginal.
Distribution over time of release to wastewater from downstream uses (Use 3)	Number of operating days between 255 (assays rather used in centralised laboratories) and 360 (assays rather used in emergency settings) were assumed.	Laboratories and hospitals need to operate on a continuous basis. The number of operating days were based on data from laboratories.	Only a marginal effect is expected on the overall outcome.
Distribution of laboratories / hospitals throughout the UK (Use 3) for calculation of local release and thus local PEC	Fraction of total tonnage used in the region: 1 (whole UK is considered one region) Fraction of regional tonnage used at local scale: 0.004 (OPnEO) and 0.025 (NPnEO)	Estimated releases to wastewater from wide-dispersive use were compared with collected data for an average laboratory: predicted release from wide-dispersive use was ca. 5% lower for OPnEO and ca. 25% higher for NPnEO than actual release from an average laboratory. Maximum predicted releases and PECs were estimated based on actual data for large laboratories.	For OPnEO, both approaches, the (adapted) wide-dispersive use scenario and calculations based on an average laboratory, were in good agreement. As site specific information was available for the big laboratory, a local scenario for OPnEO was applied in this case. For NPnEO, releases from large laboratories provide an upper value for local releases and local PECs therefore accounting for any underestimation that may have been done for average local releases or local PECs.

Source of uncertainty	Description of assumption	Justification	Influence on the outcome of the assessment
Point in time used for calculation of PECs	PECs are calculated based on maximum releases over the review period in case all substitutions are delayed	Worst-case scenario: all substitution projects were assumed to be delayed until the end of the review period, although this is not likely.	Maximum PECs will be lower if at least some substitution projects are completed as planned.
Modelling parameters: physico-chemical parameters	Log Koc values based on measured values and derived values using the pp-LFERs** concept	The pp-LFER concept is a widely accepted approach for the prediction of the partitioning behaviour of chemical substances in the environment using the numerical contributions of individual functional groups to overall partitioning coefficients.	Under the assumption that the log Koc is not more than one log unit wrong, the STP effluent concentration of OP or $NP_{equiv.}$ is underestimated by a maximum of 50%. See also 'sum of modelling parameters'. Note that log Koc was determined to be the key parameter for the outcome of the model calculations.
Modelling parameters: degradation	For the exposure assessment the 'inherently' scenario was selected with a degradation rate of 0.1/h and no mineralisation (i.e. all compounds are assumed to be ultimately degraded to OP or NP in the environment)	The influence on the OP or $NP_{equiv.}$ concentration in the STP effluent is small when comparing scenarios using different degradation rates in the range of 0.0005/h to 0.3/h without mineralisation. Due to uncertainties regarding mineralisation, no mineralisation is assumed.	In case mineralisation occurred in the STP, releases and PECs would be overestimated. See also 'sum of modelling parameters'.
Sum of modelling parameters	See assumptions listed above	See assumptions listed above	Monitoring data after the STP in Penzberg confirm that the assumptions used in the model 'Multifate' were very conservative. Modelled OP concentrations for two monitoring campaigns were a factor of 30 to

Source of uncertainty	Description of assumption	Justification	Influence on the outcome of the assessment
			300 higher than maximum measured concentrations in STP effluents. Furthermore, modelled $OP_{equiv.}$ for the third and fourth monitoring campaign were a factor of 100 to 440 higher than measured $OP_{equiv.}$

* 'PEC' (Predicted environmental concentration) in this section refers to surface water PEC or PEC for agricultural soil

** pp-LFER: polyparameter linear free energy relationship

5. CONCLUSION

- ⇨ IVD assays covered under this AfA have an **unquestionable social value.**
- ⇨ **Unavailability of certain IVD assays** due to the ban of OPnEO / NPnEO usage would result in a **temporary lack of healthcare services for patients and an associated increase in healthcare costs of >> [redacted] (10 – 50) mio £.**
- ⇨ Not being able to supply the affected products will be associated with an important **loss of customer trust and reputation** for Roche.
- ⇨ Additionally, the **loss of EBITA** for Roche / RDL over the course of the review period is estimated to range between [redacted] and [redacted] (1 – 50) mio £.
- ⇨ Business **losses of customers** are expected due to assays not supplied. Cost for customers (i.e. laboratories and hospitals) based on Roche's inability to supply assays could amount as a minimum to [redacted] (1 – 200) mio **£**. Maximum cost cannot be quantified
- ⇨ Emissions of OPnEO / NPnEO are **minimised** as far as technically and practically feasible.
- ⇨ **Socio-economic benefits** of continued use of OPnEO / NPnEO associated with Use 3 **outweigh the remaining risks** to the environment.
- ⇨ Due to **quality and regulatory requirements** for IVD assays, any review period shorter than 5.5 years would not be sufficiently long for completing the substitution of OPnEO and NPnEO in all products.

This SEA aims to quantify the relevant environmental, economic and social impacts related to the continued use of two groups of substances octylphenolethoxylates (OPnEO) / nonylphenolethoxylates (NPnEO) after the sunset date.

The applicant of this AfA is RDL, a UK-based affiliate company of Roche which is the leading company in the *in vitro* diagnostic market in Europe and worldwide. The current SEA was developed to support RDL's AfA to continue the use of two groups of substances OPnEO / NPnEO after the sunset date until complete substitution.

UK REACH has been implemented based on the EU REACH regulation including the Annex XIV entries. The group of substances included in this SEA are therefore also listed in Annex 14 of UK REACH in entries 42 (OPnEO) and 43 (NPnEO). As an EU application for authorisation for the same use for these substances was submitted to ECHA before the latest application date (LAD) of the 4th of July 2019, Article 127GA of UK REACH extends the UK LAD/sunset date to the 30th of June 2022. Since the requirements for authorisation under UK REACH were adopted from the EU, the same approach as for the EU dossier is used in this application.

In the '**non-use' scenario**, **RDL will not be able to continue the supply of the affected IVD assays in the UK** (i.e. the products containing OPnEO / NPnEO). This will lead to laboratories and hospitals being not able to use certain IVD assays and will thus **not be able to provide complete healthcare services to patients**. RDL's supply of affected IVD assays will need to be interrupted until the necessary steps to switch to an alternative surfactant or, in some cases, alternative products are completed, including adapted or new registrations with health authorities for the different markets.

Therefore, an **interruption of the supply of the products is expected until substitution will be completed**.

The most important impacts for the UK will be the social impacts related to the temporary unavailability of IVD assays. This will result in a **temporary lack of healthcare services for patients** and an associated **increase in healthcare and related costs of >> [redacted] (10 – 50) mio £**. More than a million of patients in the UK are expected to face a temporary lack of healthcare services over at least 1 year up to the end of 2027.

Not being able to supply the affected products will be associated with an **important loss of customer trust and reputation.** Additionally, the **loss of EBITA** for Roche / RDL over the course of the review period is estimated to range between [redacted] and [redacted] (1 – 50) mio £.

Costs for customers (i.e. laboratories and hospitals) based on Roche's inability to supply assays could amount as a minimum to [redacted] (1 – 200) mio £. Maximum **cost** cannot be quantified. In some cases, RDL may be liable to indemnify customers for the financial losses, or customers may be able to claim for breach of contract from RDL. The cost for mitigation measures would then represent an additional economic loss to RDL.

As shown in the CSR, emissions will be reduced by **completion of substitution projects** over the course of the review period and will be fully eliminated by the end of the review period. It should be emphasized that in the past 6 years a large substitution effort has already been made and emissions of OPnEO / NPnEO have already been substantially reduced. For example, the number of assays containing OPnEO / NPnEO has already been reduced from 19 in 2019 (when the EU dossier was prepared) to 10 in the current dossier. Considering the implemented RMMs and depending on the completion of substitution (i.e. on time or delayed until the end of the review period), total releases will range from 20.4 – 44.8 kg $OP_{equiv.}$ and 0.04 – 0.06 kg $NP_{equiv.}$ for surface water and 17.0 – 37.3 kg $OP_{equiv.}$ and 0.12 – 0.17 kg $NP_{equiv.}$ as a maximum for soil over the 5.5 years of the review period for all three uses combined. As it is highly unlikely that all substitutions are delayed until the end of the review period, the risk that releases will reach the maximum is very low.

Any further RMMs are not technically and practically feasible. At laboratories and hospitals additional RMMs are not feasible within a reasonable time frame to effectively reduce emissions. The majority of emissions is likely to be already eliminated within 3 years after the UK sunset date.

Based on the combined impacts assessment, **the ratio of minimal societal cost** (in terms of increased healthcare and related costs) per kg OP or $NP_{equiv.}$ emitted are expected to be **much larger than 0.3 – 1.3 mio £ / kg Consequently, it can be concluded with high certainty that the socio-economic benefits of continued use of OPnEO / NPnEO associated with Use 3 outweigh the remaining risks to the environment.**

The environmental risks cannot be monetised, but emissions of OPnEO / NPnEO are minimised as far as technically and practically feasible.

The AoA explains the unique technical and regulatory challenges associated with validating alternatives. A **review period until the end of 2027** will allow Roche to complete the evaluation of alternatives, validate and assure performance of the affected products, and if necessary, submit change notifications as a regulatory requirement for *in vitro* diagnostic assays. More than a million patients in the UK depend on the accurate, reproducible and reliable results of these assays. Roche is committed to **substitute OPnEO / NPnEO as fast as possible for each individual product**.

However, Roche has concluded **that any review period shorter than 5.5 years** would not be sufficiently long for completing the substitution of OPnEO and NPnEO in all products.

In summary, RDL is applying for an authorisation to continue the use of OPnEO and NPnEO in accordance with Article 127GA of UK REACH for the following reasons:

1) The **releases of OPnEO and NPnEO are minimised as far as technically and practically feasible**,

2) RDL IVD assays depending on the use of OPnEO / NPnEO have an **unquestionable social value** and

3) **time until the end of 2027** is needed for replacement of OPnEO / NPnEO in all products due to high quality and regulatory requirements for IVD assays.

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APPENDIXES

- Appendix 1. Valuation estimates with respect to social impact analysis.

Appendix 1. Valuation estimates with respect to social impact analysis

Role of IVDs and relative spending of healthcare costs on IVDs

A literature review and research performed by Rohr et al. [21] confirms the relatively **low** contribution of **IVD-related spending** to total healthcare expenditure as well as the extremely high utility in terms of number of diagnoses depending on the results of *in vitro* diagnostics assays. In this study, healthcare expenditure related to the field of cardiology and oncology was investigated in two developed markets (the US and Germany). Additionally, the perceived value of IVDs on clinical decision making was investigated by means of interviews of oncologists and cardiologists.

In this study it was found that 74% of patients seen underwent IVD testing in the US and 76% in Germany. IVD testing was used in 88%, 77% and 72% of patients for initial diagnosis, treatment monitoring, and follow-up respectively. More oncology patients underwent IVD testing than cardiology patients (92% versus 60%) in both US and Germany. IVD testing guided approx. 66% of clinical decisions. A status report by Rohr et al. previously mentioned that overall, IVDs account for 60 – 70% of clinical decisions. The British In Vitro Diagnostics Association (BIVDA) estimated that 70% of clinical decisions are made using IVDs and states that they are a vital component of all NHS (National Health Service) front line services and an integral part of almost all patient pathways [3]. The findings from the study of Rohr et al. [21] – focused on oncology and cardiology services – are completely in line with these other estimated figures. Clearly, the contribution of IVDs to healthcare systems around the world should not be underestimated. Moreover, Roche pursues the concept of 'personalised healthcare', i.e. to develop more targeted therapies, and clinically differentiated products to meet the patients' needs[1]. IVDs play an important role in personalised healthcare to identify which medicines are expected to be effective for a specific patient.

At the same time, the relative spending of **healthcare costs on IVDs** appear to be **low**. In the report of the Lewin Group [17] it was mentioned that IVDs comprise less than 5% of hospital costs and approx. 1.6% of all Medicare costs. In the report of the BIVDA on the value of IVDs, it was mentioned that the NHS spends about 850 million £ annually on IVD products, which is less than 1% of the total NHS budget [3]. The review of Rohr et al. [21] revealed that approx. 2.3% of all healthcare spending in the US was to IVDs (defined as payments to clinical laboratories for testing services), whereas in Germany, 1.4% of public healthcare expenditure was used for IVDs. Although the source of the data used for the estimations may be responsible for slight incomparability of the results, it is clear from all these reports that the total spending on IVDs is only responsible for roughly a few percent of total healthcare expenditure. Although the actual benefits in monetary terms are not easy to calculate, it is highly likely that the utility-cost ratio of IVD products in general is very high.

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Cost-utility analysis and monetisation of health benefits / impacts

The relative efficiency of investments in healthcare interventions can be evaluated using cost-utility analysis, a form of cost-effectiveness analysis, where the aim is to maximise the gains in **QALYs** (quality-adjusted life year) per unit of healthcare expenditure. QALY is a measure that integrates quantity of life with quality of life, i.e. the arithmetic product of life expectancy combined with a measure of the quality of life in those years (between 0 and 1). For instance, a person living for 40 years at perfect health (quality of life = 1), followed by 10 years of life at a disabled state resulting in a quality of life of 0.5, and death at 50 years old, would be assigned 45 QALYs. In case the event resulting in the disabled state could be detected earlier, resulting in better prognosis and more efficient treatment, in its turn resulting in a longer life with less years at reduced quality of life, there would be a gain in QALYs. In case healthcare interventions are evaluated / compared in a cost-utility analysis, the gain in QALYs would be weighed against the cost of the intervention, where those interventions with the lowest additional healthcare spending per QALY gained are preferred over those with higher additional healthcare spending per gained QALY.

Although various examples of cost-utility analysis are available in the field of IVDs, such analyses are not available for all types of assays on the market. For those where studies are available, typically incremental cost-effectiveness ratios are reported, i.e. the additional healthcare spending per gained QALY. The review of Fang et al. [14] evaluated the available literature of cost-utility analyses regarding diagnostic laboratory testing. The authors reviewed all publications related to diagnostic laboratory testing in the Tufts Medical Center Cost-Effectiveness Analysis Registry (www.cearegistry.org) and identified 141 relevant publications, which contained 433 separated 'incremental cost-effectiveness ratios', i.e. additional healthcare spending per gained QALY. The diagnostic tests which were the subject of the cost-utility analyses belonged to diverse clinical areas, including hematology / oncology (29.8%), obstetrics / gynaecology (25.5%), gastroenterology (24.1%), endocrinology (14.2%) and cardiovascular disease (7.1%). In terms of the types of testing, the cost-utility analyses focused most frequently on virology tests (25.5%), general chemistry tests (21.3%) and genetic testing (17.7%). Over 55% of the reported incremental cost-effectiveness ratios were either dominant (i.e. more gained QALYs for less cost) or below 50'000 USD per QALY (2008 value). The authors concluded that the examined literature reveals many areas in which testing represents good value of money. The findings of this review, together with the findings mentioned above that the **overall healthcare spending to IVDs is only roughly a few % of total healthcare expenditure** as well as the fact that **roughly 60-70% of clinical decisions involve the results of IVD testing**, confirm that **IVDs overall have a high utility-cost ratio** and can therefore be assumed to result in a high overall reduction of healthcare spending.

The difficulty of placing monetary values on QALYs has been recently discussed in a study ordered by the ECHA, in which the quantification and valuation of the human health impacts of chemicals based on quality and disability-adjusted life years was investigated [22]. In this study, reference was made to several existing studies, e.g.:

- Within the UK, the National Institute of Health and Care Excellence (NICE) has set a threshold value of 20'000-30'000 £ per QALY [19], which is (somewhat) lower than the threshold used in the review of Fang et al. [14] (50'000 USD in 2008 is ca. 49'387 £ in 2022 - 20'000-30'000 £ in 2010 is ca. 26'079-39'119 £ in 2022).

- The Social Value of a QALY project, performed by Donaldson et al. [9], was reported to yield values of 10'000-70'000 £ per QALY (ca. 12'570-87'988 £ in 2022). Most methods of aggregating the data resulted in values of 18'000-40'000 £ per QALY (ca. 22'625-50'279 £ in 2022).

- In the study of Ryen and Svensson [23], the overall mean and median willingness to pay (WTP) per QALY were reported to be 118’839 and 24’226 EUR, respectively (in 2010, i.e. ca. 119’094 and 24’278 £ in 2022, respectively). Around 80% of all estimates were below 75’000 EUR (in 2010, i.e. < 75’161 £ in 2022). These authors concluded that a common societal value for one QALY may not be appropriate as the willingness to pay values vary widely and are dependent on several methodological factors.

Based on the abovementioned information it has become clear that the use of IVDs in healthcare interventions is ideally subject to cost-utility analysis and that overall for the currently used IVDs the utility-cost ratio appears to be high. However, there is **no easy way to calculate the total amount of gained QALYs related to the use of the affected IVDs** discussed in this dossier, neither is there a generally agreed societal value of a QALY, which would allow (at least a rough) monetisation of the benefits to patients related to the use of the IVDs under evaluation in this dossier. Therefore, there is currently no straightforward approach to calculate an accurate and realistic range of social benefits of the affected IVDs in monetary terms. A more general evaluation of the social benefits of IVDs in monetary terms is currently not available yet either. Therefore, some further information from ECHA publications is discussed below Both the ECHA Guidance Document on Socio-Economic Analysis in Authorisation [10] and the ECHA summary of the study on the valuation of selected health impacts of chemicals [11] report information on the VSL monetary concept, which represents the willingness to pay to avoid a health condition leading to death, and the VOLY (which can be derived from the VSL). Note that VSL and VOLY estimates are increasingly being used for the assignation of monetary values to QALYs. A central study referred to is the NewExt study [20]. Key mean values obtained in this EU-wide research programme for the VSL and the VOLY are 1’052’000 and 55’800 EUR, respectively (in 2003, i.e. ca. 1’211’189 and 64’244 £ in 2022). For sensitivity analysis, the median values of 2’258’000 and 125’200 EUR, respectively, should be considered (i.e. 2’599’681 and 144’145 £ in 2022).

- More recently (for a summary and critical review see [11]), ECHA commissioned a service contract to examine the economic benefits of avoiding selected adverse human health outcomes due to exposure to chemicals. Willingness to pay values were derived for about 20 health outcomes, including acute and chronic dermatitis, kidney injury, cancer risks, chance of conceiving a child, birth defects and very low birth weight, or respiratory sensitisation within both private as well as public good contexts. In contrast to this study, the aim in this SEA is to get a sense of the magnitude of the social impacts in case of non-authorisation and consequent temporary general or Roche client-limited unavailability of certain IVD assays. Even though the values in the above cited study were obtained in the context of exposure to chemicals (for comparison, those from the NewExt study [20] were obtained in view of the assessment of external costs from energy technologies), the obtained values to avoid certain health outcomes could be used as indicative values in our analysis as well. Monetary valuation of health impacts is typically undertaken using WTP values to assess the economic value of preventing specific health endpoints (intangible costs) and opportunity costing. These values are used to account for the resources spent on medical treatment and healthcare (treatment costs) as well as for productivity losses and other non-healthcare related costs associated with specific health endpoints. All these cost factors would be very similar regardless of the cause that led to the health condition under consideration. The most relevant values obtained are the willingness to pay to avoid premature death in the context of cancer (VSL, Value of Statistical Life, or Value of a Prevented Fatality) and the willingness to pay for reducing the chance of developing cancer (VSCC, Value of a Statistical Case of Cancer). The VSL was reported to be 5’000’000 EUR based

on the original results and 3’500’000 EUR after a robustness check (in 2012, i.e. 4’771’012 and 3’339’707 £ in 2022), and the VSCC was 396’000 EUR based on the original results and 350’000 EUR after a robustness check (i.e. 377’864 and 333’971 £ in 2022). Further, also a value to avoid disutility caused by cancer morbidity in addition to premature death was set (VCM, Value of Cancer Morbidity), which was 410’000 EUR (i.e. 391’223 £ in 2022).