SOCIO-ECONOMIC ANALYSIS

Legal name of applicant(s): Roche Diagnostics GmbH

Submitted by: Roche Diagnostics GmbH

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

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

Use 4: Use of Octyl- and Nonylphenolethoxylates in the production of proteins and the conjugation of latex beads, both being used as components or for the production of components of *in vitro* diagnostic (IVD) assays, research or quality control products and other, e.g. analytical applications (processes specified in Appendix 1 to the AoA)

Use number: 2, 3, 4

TABLE OF CONTENTS

TABLES

FIGURES

GLOSSARY

Term	Explanation
AA-EQS	Annual average environmental quality standard
ACS	American Chemical Society
AfA	Application for Authorisation
AIDS	Acquired Immunodeficiency Syndrome
AoA	Analysis of Alternatives
APAC	Asia-Pacific region
AT	Accutrend® Accutrend® is a flexible point-of-care handheld device for the determination of three important cardiometabolic parameters and the lactate level in blood
BGE	Blood gas and electrolyte BGE is part of the Point of Care Roche business unit and the affected product in this portfolio is the Hb Calibrator for the determination of haemoglobins and bilirubin. BGE analysis is used in critical care settings such as Intensive care units (ICU), Emergency department (ED) and Neonatology. The measured parameters comprise pO_2, pCO_2, pH, Hematocrit, Na^+, K^+, Cl^-, Ca^{2+}, Glucose, Lactate, Urea/BUN total haemoglobin, Oxygen saturation SO_2, O_2Hb, COHb, MetHb, HHb, bilirubin. These critical parameters indicate for example whether oxygen is adequately delivered to tissues (e.g. pO_2, pCO_2 and Hematocrit in arterial blood) or help detecting jaundice in new-borns which occurs when total bilirubin values are above a certain threshold.
BILT3	Bilirubin Total Gen 3
CAGR	Compound Annual Growth Rate - the mean annual growth rate of an investment over a specified period of time longer than one year.
CB	Custom Biotech is a segment of Centralised & Point of Care (CPS), which supplies raw materials, reagents, instruments and services within the Diagnostic division. Custom Biotech customises its offering to the quality and regulatory needs of other biopharmaceutical and diagnostic manufacturers.
CC	Clinical chemistry is a diagnostic method which tests for various components of blood and urine and enables healthcare professionals to overview significance of abnormal values. CC portfolio are part of the Serum Work Area.

Term	Explanation
CE mark	CE marking proves that your product has been assessed and meets EU safety, health and environmental protection requirements
CEC	Corporate Executive Committee
CEN	Cytokeratin 8/19
CER	Coupon Equivalent Rate
CESIO	Comité Européen des Agents de Surface et de leurs Intermédiaires Organiques - European Committee of organic surfactants and their organic intermediates
CFDA	China Food and Drug Administration
CH	Switzerland
CHF	Swiss francs
CLIA Waver	CLIA waiver means that this product is waived from Clinical Laboratory Improvement Amendments (CLIA) regulations that regulates laboratory testing and therefore do not require clinical laboratories certification by a state as well as the 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.
CMC	Critical micelle concentration
cobas®	Trade name of Roche diagnostic instrument
CPS	Centralised & Point of Care (CPS) is the largest business area of Roche Diagnostics. It is a leading supplier of solutions, instruments, tests, software and services for small- to mid-size and large-size commercial and hospital labs and laboratory networks.
CRP	C-reactive protein is an annular (ring-shaped), pentameric protein found in blood plasma, whose levels rise in response to inflammation.
CSF	CerebroSpinal Fluid is a clear, colourless body fluid found in the brain and spinal cord.
CSR	Chemical Safety Report
CVD	CardioVascular Disease
CYFRA	Name of a Roche IVD

Term	Explanation
DAGS	Double-antigen Sandwich
DIG	Digoxigenin
DJSI	Dow Jones Sustainability Indices. Indices evaluating the sustainability performance of thousands of companies trading publicly and a strategic partner. This is based on an analysis of economic, social and environmental performance of the company. The DJSI family of indices serves as a benchmark for investors who integrate sustainability considerations into their portfolios
DM	Drug Monitoring, that is included in clinical chemistry, specializes in the measurements of levels of therapeutic drugs or narcotic drugs.
DNA	Deoxyribonucleic acid (contains the genetic code of organisms)
DNP	Dinitrophenyl
EBITA	Earnings Before Interest, Taxes, Depreciation, and Amortization It is an accounting measure calculated using a company's net earnings, before interest expenses, taxes, depreciation, and amortization are subtracted, as a proxy for a company's current operating profitability (i.e., how much profit it makes with its present assets and its operations on the products it produces and sells, as well as providing a proxy for cash flow).
ECHA	European Chemicals Agency
ECLIA	Electrochemiluminescence immunoassay
ECS	Environmental Contributing Scenario
ED	Emergency department or Endocrine disrupting
EEA	European Economic Area is the area in which the Agreement on the EEA provides for the free movement of persons, goods, services and capital within the European Single Market.
Enzyme	A substance produced by a living organism which acts as a catalyst to bring about a specific biochemical reaction. Most enzymes are proteins with large complex molecules whose action depends on their particular molecular shape. Some enzymes control reactions within cells and some, such as the enzymes involved in digestion, outside them

Term	Explanation
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
EUSES	European Union System for the Evaluation of Substances, version 2.0. National Institute of Public Health and the Environment (RIVM), the Netherlands
FDA	US Food and Drug Administration
FTE	Full-Time Equivalents is a unit that indicates the workload of an employed person in a way that makes workloads or class loads comparable across various contexts.
GJ	Gigajoule, unit of energy
Hb	Haemoglobin
HDL	High Density Lipoproteins, commonly referred to as "good cholesterol"
HIV	HIV Assay or Human Immunodeficiency Virus
HIV Duo	Newer generation HIV assay which is OPnEO / NPnEO-free
HIVcPT	HIV combi PT assay
HPLC	High Performance Liquid Chromatography
ICU	Intensive care units
Ig	Immunoglobulin
IPC	In-Process Control
ISH	*In situ* hybridization which is a technique for identifying specific DNA or RNA sequence or portion within individual cells in tissue sections, providing insights into physiological processes and disease pathogenesis
IT	Information technology

Term	Explanation
IVD	*In vitro* diagnostic medical devices. IVD products are regulated and defined by European Regulation 2017/746/EU. IVD are defined as any medical device which is a reagent, reagent product, calibrator, control material, kit, instrument, apparatus, equipment, or system, whether used alone or in combination, intended by the manufacturer to be used in-vitro for the examination of specimens, including blood and tissue donations derived from the human body, solely or principally for the purpose of providing information: ▪ concerning a physiological or pathological process or state, or ▪ concerning congenital physical or mental impairments, or ▪ concerning the predisposition to a medical condition or a disease, or ▪ to determine the safety and compatibility with potential recipients, or ▪ to predict treatment response or reactions, or ▪ to define or monitoring measures.
IVDR	IVD regulation
IW	Industrial worker
LATAM	Latin America
LDLC	Low density lipoprotein cholesterol, commonly referred to as “bad cholesterol”
log Koc	Organic Carbon-Water Partitioning Coefficient
log Kow	Octanol-water partition coefficient
LSD	Lysergic acid Diethylamide
MAC-EQS	Maximum allowable concentration environmental quality standard
MD	Molecular Diagnostic
MDROs	Multidrug-resistant organisms
MDx	Molecular Diagnostics - MDx Enzymes production processes
MDx Enzyme	Enzyme used in molecular diagnostics

Term	Explanation
MES	2-(N-Morpholino) ethanesulfonic acid
MNQ	Low water discharge
mRNA	Messenger of the ribonucleic acid (RNA)
MRSA	Methicillin-resistant *Staphylococcus aureus*
NAD	Nicotinamide Adenine Dinucleotide
NADH	Nicotinamide Adenine Dinucleotide (NAD) + Hydrogen (H)
NHS	National Health Service
NICE	National Institute of Health and Care Excellence
NOEC	No Observed Effect Concentration
Non-EEA	All countries outside the European Economic Area (EEA).
NP	4-nonylphenol, branched and linear
NP1EC	4-nonylphenoxyacetic acid
NP1EO	Nonylphenolmonoethoxylate
NP2EC	4-nonylphenoxyethoxyacetic acid
NP2EO	Nonylphenoldiethoxylate
$NP_{equiv.}$	4-nonylphenol Equivalent
NPnEO	4-nonylphenol, branched and linear, ethoxylated (substances with a linear and / or branched alkyl chain with a carbon number of 9 covalently bound in position 4 to phenol, ethoxylated covering UVCB- and well-defined substances, polymers and homologues, which include any of the individual isomers and / or combinations thereof), 4-NPnEO [Corresponding to entry 43 of Annex XIV of the REACH regulation as defined in regulation 2017/999/EU]
NPV	Net Present Value It is a measurement of profit calculated by subtracting the present values (PV) of cash outflows (including initial cost) from the present values of cash inflows over a period of time. Incoming and outgoing cash flows can also be described as benefit and cost cash flows, respectively.
OC	Operational conditions

Term	Explanation
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]
OSH	Occupational safety and health
PBT	Persistent, Bioaccumulative and Toxic
PC	Article categories
PCR	Polymerase Chain Reaction It is a technique used in molecular biology to amplify a single copy or a few copies of a segment of DNA across several orders of magnitude, generating thousands to millions of copies of a particular DNA sequence.
PEC	Predicted environmental concentration
PMA	Pre-Market Approval
PNEC	Predicted no-effect concentrations
PoC	Point of Care is a segment of Centralised & Point of Care (CPS), which provides the market with instrument systems, tests, software and services that deliver quick, accurate and reliable results for critical- and primary-care clinicians and for patient self-monitoring in areas such as oncology and virology, as well as in cases of cardiovascular, inflammatory and infectious diseases. These instruments are smaller (Portable or bed-side), faster and less complex that the modular solutions of the SWA.
PP	Protein production processes
PPE	Professional protective equipment
PRO	Test-strips containing one field
PROC	Process category

Term	Explanation
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).
REACH	Regulation on Registration Evaluation, Authorisation and Restriction of Chemicals European Regulation (EC) No 1907/2006
RMD	Roche Molecular Diagnostics
RMMs	Risk Management measures
RNA	Ribonucleic acid (contains the genetic code of some viruses, for example HIV)
Roche	F. Hoffmann-La Roche Ltd. and its affiliates are collectively referred to as 'Roche'
RSV	Respiratory Syncytial Virus
RTD	Roche Tissue Diagnostics is a business area of Roche Diagnostics. It is the world's leading supplier of tissue-based cancer diagnostics. Its instruments and reagent systems are used in histology, cytology and drug discovery laboratories worldwide.
RT-PCR	Reverse transcription polymerase chain reaction is a variant of polymerase chain reaction (PCR), is a technique commonly used in molecular biology to detect RNA expression
SDG	Sustainable Development Goals
SDS	Safety data sheet

Term	Explanation
SEA	Socio-Economic Analysis
SEAC	Socio-economic Analysis Committee
SIN list	The SIN (Substitute It Now!) List is a comprehensive database of chemicals likely to be restricted or banned in the EU.
SOP	Standard operating procedure
spERC	Specific Environmental Release Category
STP	Sewage treatment plant
SVHC	Substances of Very High Concern A SVHC is a chemical substance (or part of a group of chemical substances) which meets the criteria of art.57 REACH In fact, listing of a substance as an SVHC by the European Chemicals Agency (ECHA) is the first step in the procedure for limiting the use of a chemical (either with an authorisation or a restriction)
SWA	Serum work area is a segment of Centralized & Point of Care (CPS), which is characterised by modular instruments. This includes immunoassays, clinical chemistry, and drug monitoring.
TM	Tumor Marker
TMPA	Total Mycophenolic Acid
TPA	Tripropylamine
UA	Urinalysis Or Uric Acid
UN	United Nations
UVCB	Substance of Unknown or Variable composition, Complex reaction products or Biological materials
US	United States
VLDL	very low-density lipoproteins
VOLY	Value of a Life Year Lost
vPvB	very Persistent very Bioaccumulative
VSCC	Value of a Statistical Case of Cancer
VSL	Value of a Statistical Life

Term	Explanation
WCS	Worker Contributing Scenario
WHO	World Health Organisation

DECLARATION

We, Roche Diagnostics GmbH, request that the information blanked out in the 'public version' of the Socio-Economic Analysis is not disclosed. We hereby declare that, to the best of our knowledge as of today (28th of May 2019) the information is not publicly available, and in accordance with the due measures of protection that we have implemented, a member of the public should not be able to obtain access to this information without our consent or that of the third party whose commercial interests are at stake.

Signature: Date, Place:

ppa. PENZBERG, MAY 29, 2019

Dr. Kai Simon, Head of Legal Penzberg

ppa. P2, MAY 29, 2019

Signature: Date, Place:

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

1. SUMMARY OF SOCIO-ECONOMIC ANALYSIS (SEA)

The applicant of this authorisation application is Roche Diagnostics GmbH (RDG), the leading company in the *in vitro* diagnostic (IVD) market in Europe (EEA) and worldwide. The current SEA was developed to support RDG's application for authorisation to continue the use of two groups of substances octylphenolethoxylates (OPnEO) / nonylphenolethoxylates (NPnEO) after the sunset date until complete substitution. OPnEO and NPnEO were included in Annex XIV (entries 42 and 43) of the regulation on Registration on Evaluation, Authorisation and Restriction of Chemicals (REACH) by the European Chemical Agency (ECHA) because of the endocrine disrupting properties for the environment of the degradation products with a sunset date of 4th January 2021.

RDG, as part of the Roche Group is publicly committed to substituting any Substances of Very High Concern (SVHC) from their processes and products if technically possible. RDG is applying for an authorisation to use OPnEO and NPnEO to support the current production in Penzberg and Mannheim to maintain its current business and potential growth in the European Economic Area (EEA) and worldwide and to be able to continue delivering healthcare services to patients via their customers in a reliable way.

This socio-economic analysis (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. For this authorisation, RDG currently engages OPnEO and NPnEO in four uses, three of which concern RDG's Diagnostics business:

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

In the 'non-use' scenario, RDG will not be able to continue the formulation and filling of the affected IVD assays (i.e. the products containing OPnEO / NPnEO; Use 2) as well as to produce and supply proteins (including MDx Enzymes which are specific types of proteins) and to conjugate latex beads. The proteins and latex beads are needed to formulate certain IVD assays at RDG and at other IVD manufacturers that are RDG's customers (Use 4). In addition, laboratories and hospitals will not be able to use certain IVD assays (Use 3) and will thus **not be able to provide complete healthcare services to patients**. RDG's formulation of IVD assays as well as the production processes will need to be interrupted until the necessary steps to switch to an alternative surfactant or, in some cases, alternative products are completed, including - where required - 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.**

Expected impacts based on the described 'non-use' scenario will occur throughout the entire EEA as RDG's IVD assays (Use 2&3 and downstream applications affected by processes of Use 4) are being used in the entire EEA. In addition, worldwide impacts are also considered as RDG produces in Penzberg and Mannheim for the global market and RDG's products are sold worldwide.

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] (700-7'000) mio EUR** in total for all uses. Several hundred million of patients worldwide are expected to face a temporary lack of healthcare services over at least 1 year up to 7 years after the sunset date.

For Roche, claims from its customers (i.e. laboratories and hospitals as well as other IVD manufacturers) based on breach of contracts could amount as a minimum to [redacted] (100-10'000) mio EUR. Maximum **claims** cannot be quantified but **pose a potentially business-critical financial risk to Roche**. 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 RDG over the course of the review period is estimated to range between [redacted] and [redacted] (100-7'000) mio EUR.

As shown in the Chemical Safety Reports (CSR) for the three uses, usage of OPnEO / NPnEO is substantially reduced before the sunset date based on substitutions already completed. Furthermore, additional risk management measures at the production sites and additional instructions for disposal for laboratories and hospitals **have reduced or will reduce emissions to wastewater** until the sunset date **by overall 29% OPnEO and 13% NPnEO compared to 2016-2017 for the uses covered by this application (Uses 2, 3 and 4).** Emissions will be further 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. 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 108-620 kg $OP_{equiv.}$ and 5.8-19 kg $NP_{equiv.}$ for surface water and 90-515 kg $OP_{equiv.}$ and 16-55 kg $NP_{equiv.}$ as a maximum for soil over the 7 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 risk management measures are not technically and practically feasible. Releases at the production sites are already reduced to low levels. Effectiveness of RMMs implemented by the submission date will be verified by a monitoring campaign for OPnEO in Mannheim and Penzberg. The required reconstructions to additional collect rinsing waters would be associated with high cost and a major part of the substitutions will likely be finalised before such reconstructions would be completed. At laboratories and hospitals additional risk management measures are not feasible within

a reasonable time frame to effectively reduce emissions. The majority of emissions is likely to be already eliminated within 1 to 3 years after the sunset date.

Based on the combined impacts assessment, **the ratio of minimal societal cost** (in terms of increased healthcare costs) per kg OP or NP_{equiv}. emitted are expected to be **much larger than 2-44 mio EUR / kg for Use 2&3 and much larger than 900-9000 mio EUR / kg for Use 4**.

Consequently, it can be concluded with high certainty that the socio-economic benefits of continued use of OPnEO / NPnEO associated with Use 2, 3, and 4 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 **7-year review period** will allow RDG to complete the evaluation of alternatives, validate and assure performance of the affected products, and if necessary, submit change notifications as a regulatory requirement for *in vitro* diagnostic assays. Millions of patients worldwide depend on the accurate, reproducible and reliable results of these assays. RDG is committed to **substitute OPnEO / NPnEO as fast as possible for each individual product and process**. However, RDG has concluded **that any review period shorter than 7 years** would not be sufficiently long for completing the substitution of OPnEO and NPnEO in all processes and products.

In summary, RDG is applying for an authorisation to continue the use of OPnEO and NPnEO in accordance with article 60(2) of REACH for the following reasons:

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

2) RDG IVD assays depending on the use of OPnEO / NPnEO in the assays (Use 2&3) or in the production of proteins and latex beads (Use 4) have an **unquestionable social value** and

3) **7 years** are needed for replacement of OPnEO / NPnEO in all products and processes 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.
- ⇨ It is subdivided in two main divisions: **Pharmaceuticals** and **Diagnostics**.
- ⇨ 40% of the 93'734 employees are based in Europe.
- ⇨ **Roche Diagnostics GmbH** (RDG) is an affiliate of Roche and one of Roche's legal entities in **Germany** with two sites: **Mannheim** and **Penzberg**.
- ⇨ Roche offers the industry's broadest range of *in vitro* diagnostic solutions.

Founded in 1896, F. Hoffmann-La Roche Ltd. is a Swiss multinational health care company that, together with its affiliates, works worldwide under two different main divisions: **Pharmaceuticals** and **Diagnostics**. Roche Diagnostics GmbH (RDG), is an affiliate of F. Hoffmann-La Roche Ltd[1]. 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 two uses covered in this Socio-economic analysis (SEA) concern the Diagnostics Division, which is therefore described in more detail below. The Roche group headquarters is located in Basel, Switzerland. In 2017, the Roche group employed 93'734 people[2] worldwide (i.e. number of employees expressed in **full-time equivalents (FTEs)**), invested 8.7 billion Euro (EUR)[3] in research and development (R&D), and posted sales of 44.4 billion EUR[2].

The presence of Roche is worldwide (Figure 1), with most of its sites and approx. 40% of its worldwide FTEs being located in Europe. In the European Economic area (EEA), 22 affiliates are responsible for more than 24 EEA countries. In the non-EEA, Roche sells its products through 35 affiliates worldwide.

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 health care[4]. 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, doctors can treat patients more precisely.

[1] For clarity: RDG does not sell its products directly to legal entities (customers) outside of Roche, but has its products sold by its affiliates dedicated to the sale of RDG's products. Hence, for facilitation reasons, the term 'Roche' is used in this document to describe the respective selling affiliates and the relationships to customers as well as market shares.
[2] 'Roche in Brief' brochure, 2017: https://www.roche.com/dam/jcr:5e7bf87e-616f-448f-be00-a3144b62fedf/en/rib17e.pdf
[3] The given financial data are either directly taken from the source in EUR or calculated in EUR with the exchange rate of 1.00 EUR=1.20 CHF
[4]Roche website, 'Personalised Healthcare': https://www.roche.com/about/priorities/personalised_healthcare.htm

Roche is the world leader in IVD and tissue-based cancer diagnostics and offers the industry's broadest range of *in vitro* diagnostic solutions. Moreover, Roche is one of the most well-known companies working on diabetes management. Roche's health care 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. Twenty-four medicines developed by Roche are included in the World Health Organisation Model Lists of Essential Medicines[5], among them life-saving antibiotics and chemotherapy.

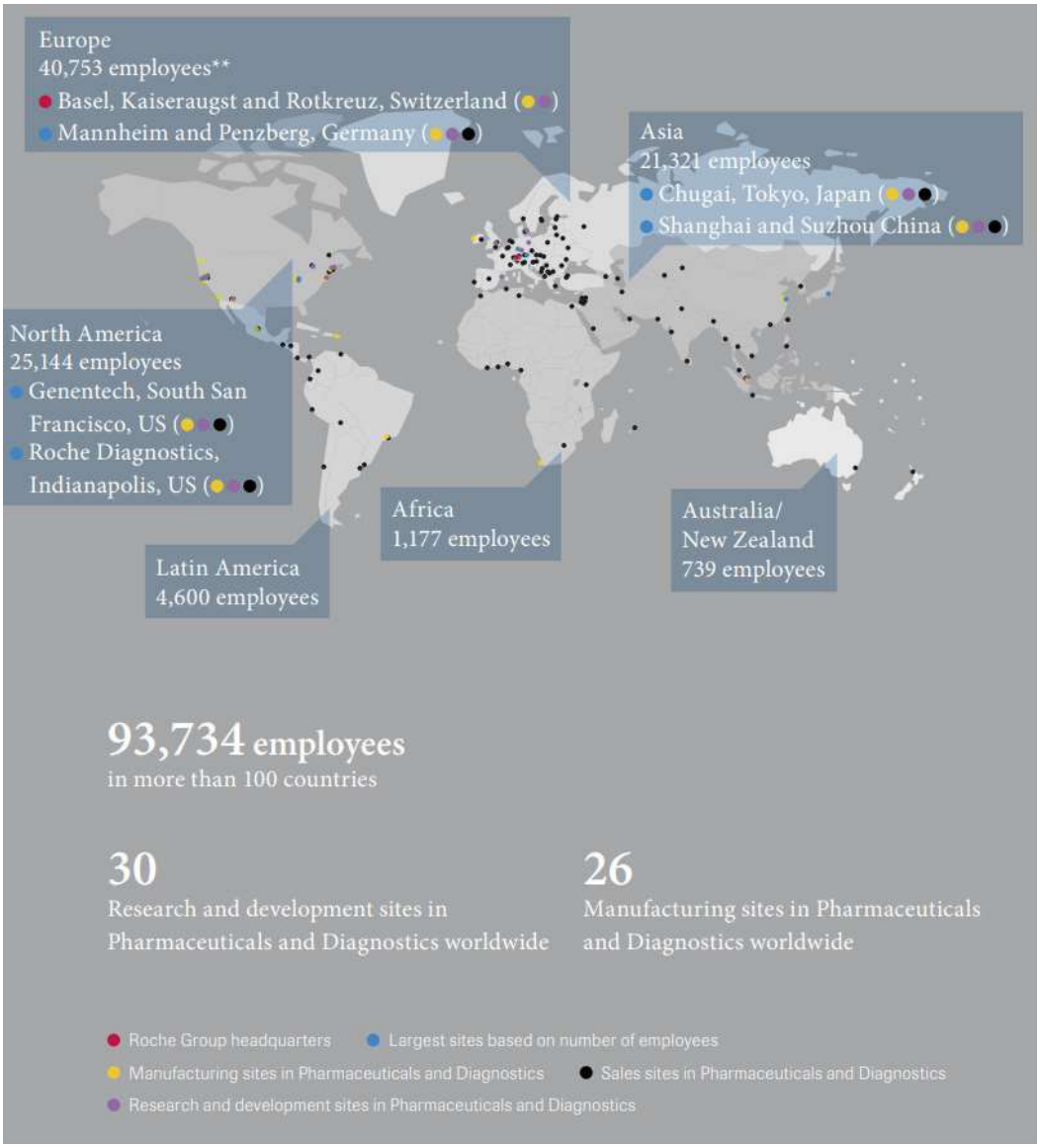


Figure 1. Roche's global presence (data from 2017)[6].

[5] WHO Website, 'WHO Model Lists of Essential Medicines', 2017: http://www.who.int/medicines/publications/essentialmedicines/en/

[6] 'Roche in Brief' brochure, 2017: https://www.roche.com/dam/jcr:5e7bf87e-616f-448f-be00-a3144b62fedf/en/rib17e.pdf

2.2. Roche Diagnostics 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, monitoring, etc.**
- ⇨ 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**. The Diagnostics Division reached EUR 10.1 billion sales in 2017 and worldwide growth with highest growth rates of +15% and 10% in Asia-Pacific and Latin America, respectively (see Figure 2).

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**, **monitoring**, etc. 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 health care, they can only be placed on the market with a regulatory approval / market authorisation by the respective health authorities.
According to Regulation 2017/746/EU[7], *in vitro diagnostic medical devices* (or as referred to herein: *in vitro* Diagnostics are defined 'to be used *in-vitro* **for the examination of specimens**, including blood and tissue donations derived from the human body, solely or principally for the purpose of providing information:

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

[7] Regulation 2017/746/EU: https://eur-lex.europa.eu/legal-content/de/ALL/?uri=CELEX:32017R0746

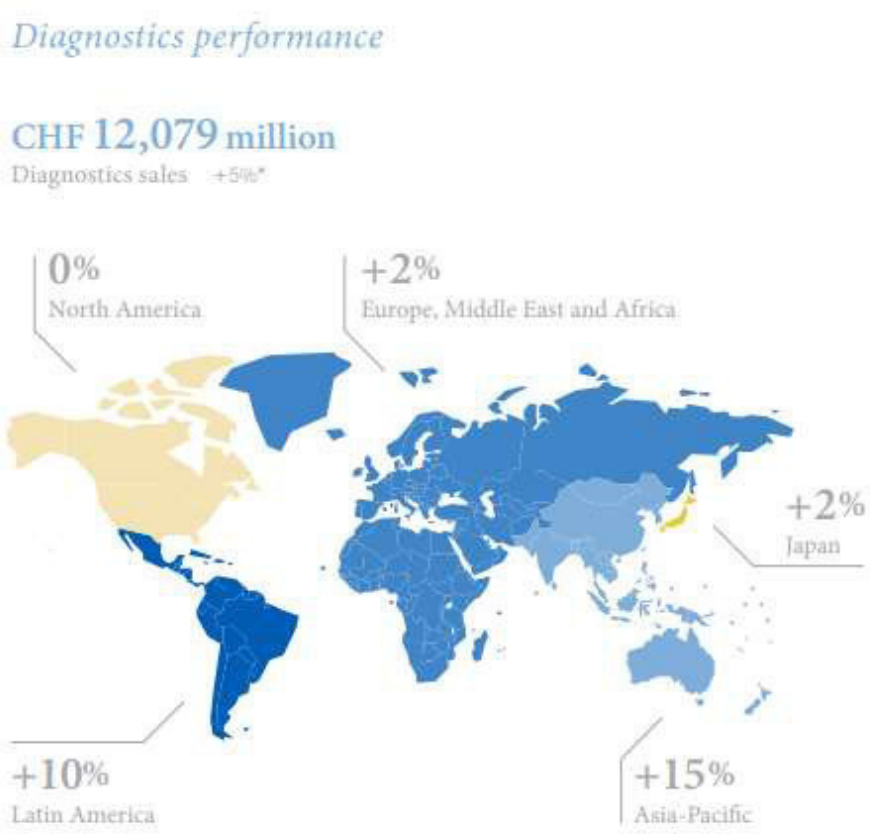


Figure 2. Roche Diagnostic Division performance in 2017[8]. Please note that the diagnostics performance is given in swiss franc (CHF), which corresponds to 10'066 mio EUR (exchange rate CHF / EUR 1.2).

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 3). 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.

[8] Roche in Brief' brochure, 2017: https://www.roche.com/dam/jcr:5e7bf87e-616f-448f-be00-a3144b62fedf/en/rib17e.pdf

Figure 3. 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. IVDs influence over 60% of clinical decision-making, while accounting for only about 1% of total healthcare spending (see Figure 4).

IVDs play an important role for global health care. 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, RDG 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. RDG is a leader in this segment and is trying to make health care spending smarter and more sustainable, through providing diagnostics that drive efficiencies, enable physicians to act earlier and eliminate unnecessary treatments and procedures.

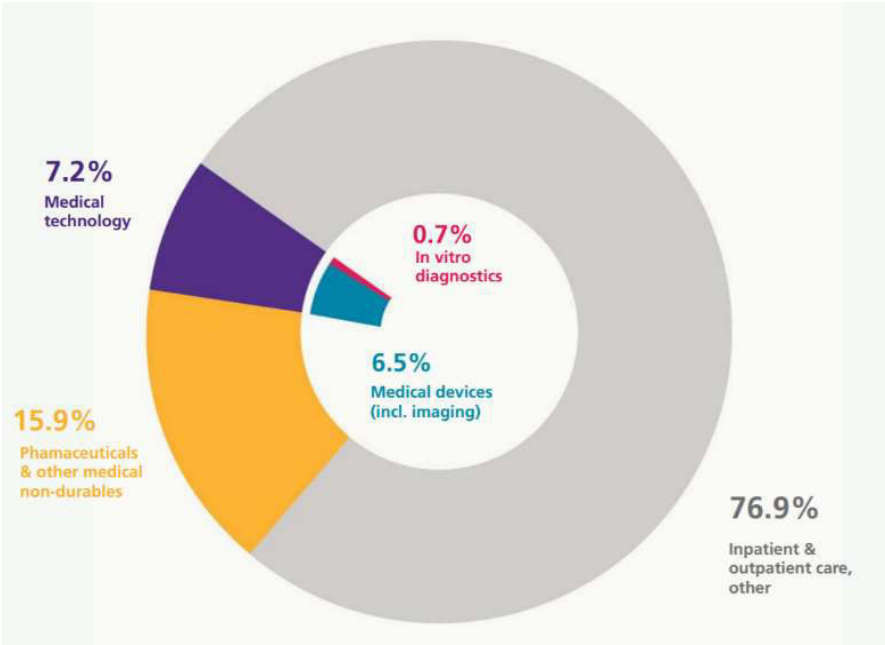


Figure 4. Breakdown of total health care expenditure in Europe[9].

[9] BMI Research, 'WHO, Eurostat, EFPIA, EDMA, MedTech Europe calculations. Europe refers to EU + Norway, Switzerland', 2018: https://www.medtecheurope.org/wp-content/uploads/2018/06/MedTech-Europe_FactsFigures2018_FINAL_1.pdf

2.3. RDG Sites

- ⇨ Roche sites in Mannheim and Penzberg employ 8'000 and 5'800 people, respectively.
- ⇨ **Roche in Mannheim** is the **third-largest** Roche site and headquarter of Roche Diagnostics GmbH.

The Roche sites in Mannheim and Penzberg employ **8'000**[10] and **5'800**[11] **people,** respectively. In Penzberg, **63% of the employees** are working for the Diagnostics division.

Figure 5. Roche Diagnostics site in Penzberg, Germany[11].

Large investments have been made at the RDG sites. For example, between 2015 and 2016 Roche has invested around 600 mio EUR in expanding the Penzberg biotechnology site (Figure 5). Roche has its third largest location worldwide in Mannheim which is the headquarters of Roche Diagnostics GmbH. In 2015, Roche opened a new production building for immunodiagnostics in Mannheim with an investment of around 1 billion EUR[12] (Figure 6).

[10] Roche Mannheim Website, ‚Mannheim': https://www.roche.com/research_and_development/who_we_are_how_we_work/rnd_locations/research_location.htm?id=965a8b01-aa54-4107-91da-f3e545b78d59
[11] Roche Penzberg Website, ‚Penzberg': https://www.roche.de/about/standorte/penzberg/index.html
[12] Roche Website, ‚Arbeiten in der Innovationsstadt': https://www.roche.com/de/careers/country/germany/de_service/blogs/arbeiten_in_der_inno.htm

Figure 6. Roche Diagnostics site in Mannheim, Germany[13].

[13] Roche Mannheim Website, ‚Mannheim‘:
https://www.roche.com/de/careers/country/germany/de_service/blogs/arbeiten_in_der_inno.htm

2.4. Roche - a Group Leader in Sustainability

- ⇨ Roche's public commitment: **to substitute any Substances of Very High Concern (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 Sustainable Development Goals.
- ⇨ Roche ranked the **most sustainable healthcare company** in the Dow Jones Sustainability Indices for the **tenth year running**.
- ⇨ Roche's **five sustainability pillars** are: innovating for patients, providing a great work place, being a trustworthy partner, protecting the environment, delivering continued growth.

Since 2015, RDG, 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 Substances of Very High Concern** (SVHC) used in its medicinal 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 medicinal products and processes. Roche engages to avoid regrettable substitutes by close collaboration of medicinal 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 AoAs of an additional AfA submitted by RDG. An authorisation is however required to allow for sufficient time to switch to the alternatives taking into account uncertainties in the timelines.

Roche is also an **active member of the 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 SDGs (**Sustainable Development Goals**) in line with the business strategy; in particular SDG3, which aims at ensuring healthy lives and promoting wellbeing for all[14].

In 2018, for the tenth consecutive year, **Roche has been recognised as Group Leader in sustainability within the Pharmaceuticals**[15], Biotechnology & Life Sciences Industry index of the Dow Jones Sustainability Indices (DJSI). This is based on an analysis of economic, social and

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

environmental performance of the company. The DJSI family of indices serves as a benchmark for investors who integrate sustainability considerations into their portfolios [16].

The Roche **five sustainability pillars** (Figure 7) are the following:

1) **Innovating for patients**: Meet the patients' needs for high-quality products and services. Investment in R&D (8.7 billion EUR in 2017) 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**: 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.

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 7. Sustainability's pillars at Roche.

[16] Roche Website: 'Investor Update Report', 07 September 2017: https://www.roche.com/investors/updates/inv-update-2017-09-07.htm

Roche is committed to improve global health care 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 or inadequate. In 2017, more than 23 types of cancer insurance policies were available in different countries and millions of people can have access to this service.

'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 Roche's application for an authorisation to **continue the use of OPnEO / NPnEO after the sunset date** until complete substitution.
- ⇨ Because of the uncertainties associated with endocrine disrupting properties, the applicant decided to assume that **no threshold applies** for this endpoint as the safest option.
- ⇨ **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 **three uses** covered in this dossier are:
  - Use in the formulation and filling of IVD assays (Use 2: Formulation).
  - Use in IVD assays (Use 3: Products).
  - Use in the production of proteins and the conjugation of latex beads, both being used as components or for the production of components of IVD assays, research or quality control products and other, e.g. analytical applications (Use 4: Processes).
- ⇨ The geographical scope of this SEA is the entire EEA. In addition, worldwide impacts are also considered.
- ⇨ This SEA examines impacts of the non-use scenario starting from the **sunset date on 4th of January 2021** until the end of the applied for review period (4th of January 2028).

The current SEA was developed to support Roche Diagnostics GmbH's application for authorisation (AfA) to **continue the use** of two groups of substances **OPnEO / NPnEO after the sunset date** until complete substitution. OPnEO and NPnEO were included in Annex XIV (entries 42 and 43) of the Registration on Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) by the European Chemical Agency (ECHA) because of the endocrine disrupting properties for the environment of their degradation products with a sunset date of 4th January 2021.

In its note from December 2017[17], the Committee for Risk Assessment (RAC) leaves 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 Socio-economic analysis committee (SEAC) note on 'SEA-related considerations in AfAs for **endocrine disrupting substances for the environment**, specifically OPnEO and NPnEO'[18]. Because of the uncertainties associated with these specific properties, the applicant decided to assume that **no threshold applies** for this endpoint as the safest option. Therefore, the applicant (RDG) will demonstrate in this SEA that the **benefits of continued use outweigh the risks to the environment.**

The two groups of substances **OPnEO and NPnEO are addressed in the same dossier** since the Guidance on the preparation of an application for authorisation, Annex I [2], concludes that if the

[17] 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

[18] 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

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.

OPnEO and NPnEO are used in a wide array of IVD kits and production processes of RDG. In accordance with the provisions of the 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 this AfA, RDG currently engages OPnEO and NPnEO in four uses, three of which concern RDG's Diagnostics business:

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 (NeoRecormon® and MIRCERA®)
2	Diagnostics	RDG	Formulation	Use of Octyl- and Nonylphenolethoxylates in the formulation and filling of *in vitro* diagnostic (IVD) assays specified in Appendix 1 to the AoA
3	Diagnostics	Downstream Users (e.g. laboratories)	Products	Use of Octyl- and Nonylphenolethoxylates in *in vitro* diagnostic (IVD) assays specified in Appendix 1 to the AoA
4	Diagnostics	RDG	Processes	Use of Octyl- and Nonylphenolethoxylates in the production of proteins and the conjugation of latex beads, both being used as components or for the production of components of *in vitro* diagnostic (IVD) assays, research or quality control products and other, e.g. analytical applications (processes specified in Appendix 1 to the AoA)

Several IVD assays depend on both Use 2&3 and Use 4 of OPnEO and / or NPnEO. Therefore, socio-economic impacts are the same or overlap to a large degree. To be able to illustrate this interconnection and jointly discuss common benefits, **this SEA covers both Use 2&3 and Use 4**.

Despite of Use 1 taking place at the legal entity of RDG, the products belong to the Pharmaceutical Division and a separate SEA document has been prepared for this use which is submitted in a separate application.

RDG is applying for an authorisation to use OPnEO and NPnEO to **support the current production in Penzberg and Mannheim to maintain its current business** and **potential growth** in the EU and worldwide. Concurrently, RDG is applying for an authorisation for the formulation of IVD assays (Use 2) containing OPnEO and NPnEO and the use of the assays (Use 3) by its customers, i.e. mainly laboratories and hospitals, that are distributed throughout the entire EEA. In addition, IVD assays based on Use 2 and use of downstream products based on processes covered in Use 4 are sold and used worldwide.

The expected impacts based on the described 'non-use' scenario will occur throughout the entire EEA, not just in Germany, and the geographical scope of this SEA is consequently the entire EEA. In addition, worldwide impacts are also considered as RDG produces in Penzberg and Mannheim for the global market and RDG's products are sold worldwide.

As outlined in the AoA for Use 2&3 and Use 4, RDG is applying for an authorisation for a **review period of 7 years** due to quality and regulatory requirements for the replacement of OPnEO and NPnEO in all products and processes. Therefore, this SEA examines impacts of the non-use scenario starting from the sunset data on 4th January 2021 until the end of the applied for review period, i.e. 4th of January 2028.

2.6. Roche Diagnostics Products and Business Model

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

- **Centralised & Point of Care (CPS):** 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 following **business segments**:
  - **Serum work area (SWA)**: 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.
  - **Point of Care (PoC)**: Providing the market with instrument systems, tests, software and services for critical- and primary-care clinicians and for patient self-monitoring.
  - **Specialty testing**: Which includes products range from single-use test strips to semi- and fully-automatic systems.
  - **Custom Biotech (CB)**: Suppling raw materials, reagents, instruments and services to other Diagnostic and Pharmaceutical Companies.

- **Molecular Solutions:**
  - **Roche Molecular Diagnostics (RMD)**: Developing and providing a wide array of innovative medical diagnostic products, tests, platforms and technologies. RMD has a broad portfolio of oncology, virology, microbiology and blood screening tests.
  - **Roche Tissue Diagnostics (RTD)**: Is the world's leading supplier of tissue-based cancer diagnostics.

As described before, Roche Diagnostics is the diagnostic division of F. Hoffmann-La Roche Ltd., 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 8 these units are graphically displayed.

Figure 8. 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 9):

1) **Centralised & Point of Care Solutions** is the largest business area. 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. CPS is complementing its solution offerings by constantly strengthening its portfolio in point-of-care testing. 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 physician' offices, emergency rooms and other primary and specialty care settings. The CPS headquarters is in Rotkreuz (Switzerland). In the portfolio, there are approximately 115 clinical chemistry assays, 111 immunoassays and more than 450 instrument configurations. CPS includes a variety of business segments and among them the affected business segments by this AfA are the following:

   a) **Serum work area:** The SWA segment is characterised by modular instruments. These instruments (**cobas**® 4000, 6000, or 8000; Figure 9) 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**.

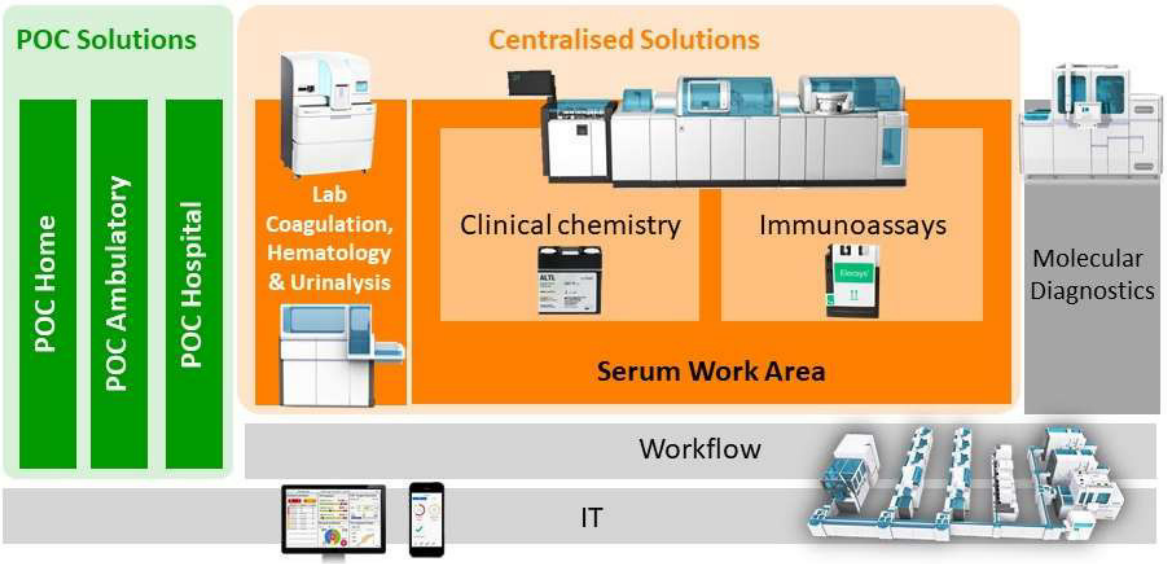


Figure 9. Overview of the Units within the Roche Business Area CPS, together with the Business Unit SIS (Workflow, IT) and the Roche Molecular Diagnostics (RMD) and their mutual relationship.

b) **Point of Care**: provides the market with instrument systems, tests, software and services that deliver quick, accurate and reliable results for critical- and primary-care clinicians and for patient self-monitoring in areas such as oncology and virology, as well as in cases of cardiovascular, inflammatory and infectious diseases. These instruments are smaller (portable or bed-side), faster and less complex than the modular solutions of the SWA shown on Figure 10.

c) **Speciality testing**: It includes **urinalysis, coagulation, and haematology**. Urinalysis products range from single-use test strips to semi- and fully automatic systems.

d) **Custom Biotech**: Supplies raw materials, reagents, instruments and services. CB customises its offering to the quality and regulatory needs of other biopharmaceutical and diagnostic manufacturers. The CB customers have supply contracts with Roche with a duration of up to **20 years**. The headquarters of CB is in Penzberg (Germany) where many raw materials and biotechnology products sold by CB are produced and processed.

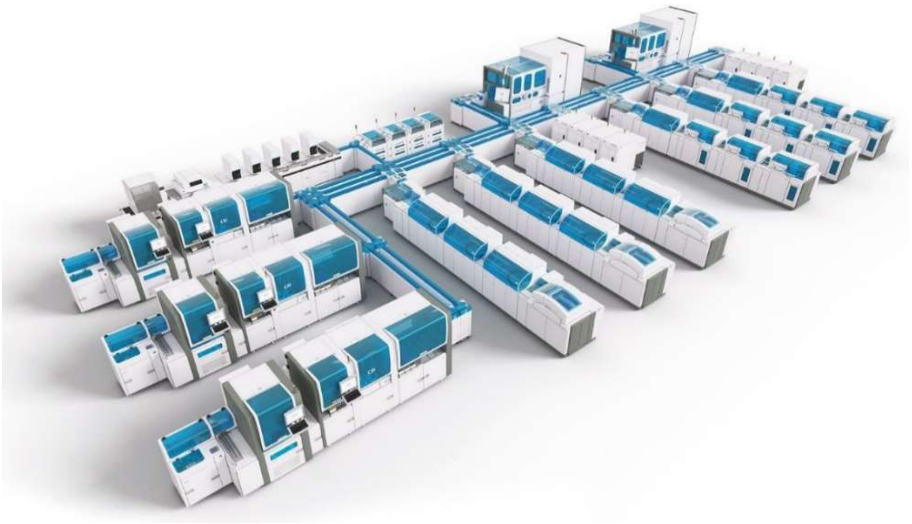


Figure 10. Example of a **cobas**®: the modular instrument of Roche[19].

2) Molecular Solutions:

a) **Roche Molecular Diagnostics** develops, manufactures and supplies a wide array of innovative medical diagnostic products, tests, platforms and technologies. With its broad portfolio of oncology, virology, microbiology and blood screening tests, RMD's clients include researchers, physicians, patients, hospitals, laboratories and blood banks around the world[20].

b) **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.

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' RDG 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.

[19] Roche Service Website 'cobas connection modules': http://products-solutions.roche-service.com/app/webroot/book/en/cobas-connection-modules-ccm.html
[20] Roche Website, 'RMD': https://diagnostics.roche.com/global/en/about/roche-molecular-diagnostics.html

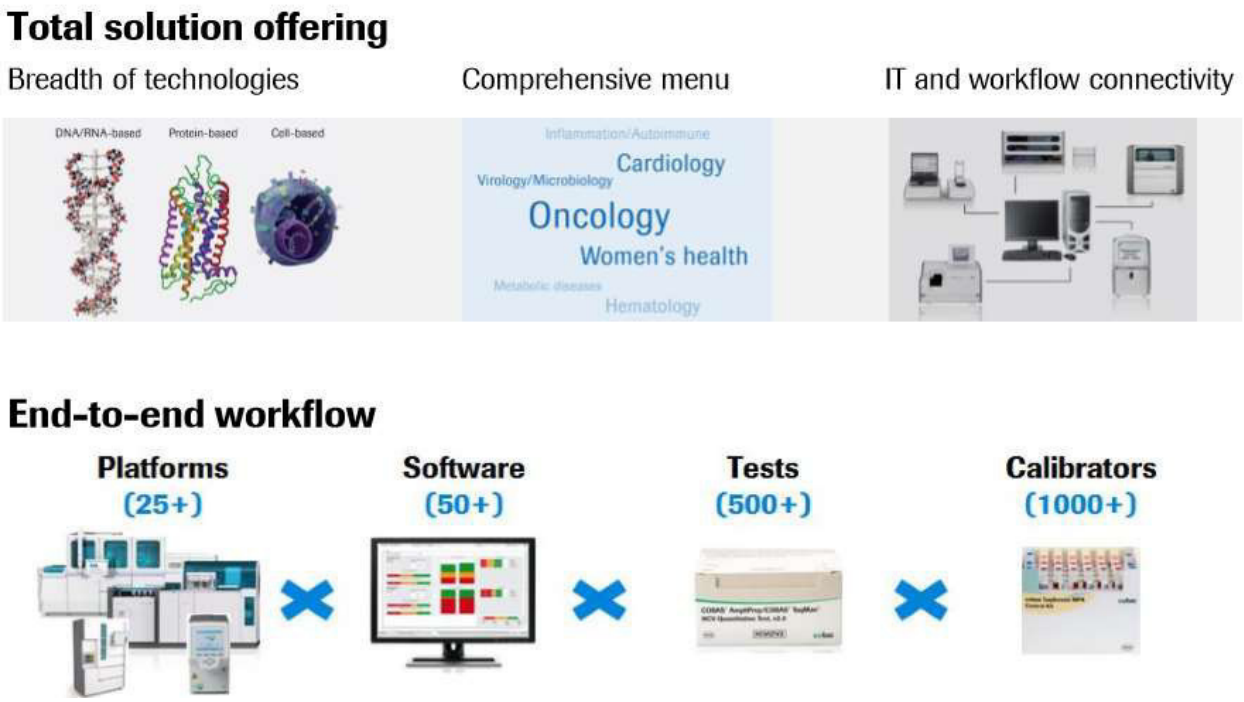


Figure 11. Roche total solution offer.

Roche's automated pre- and post-analytical solutions are integral to providing complete flexibility and process optimisation (see Figure 11). 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 11).

2.7. Overview Products and Processes and their Downstream Applications

⇨ **OPnEO and NPnEO** are **used** in **wide array of IVD assays and production processes** of RDG.

⇨ Nine different RDG product groups and the Custom Biotech business are affected.

OPnEO and NPnEO are **used in wide array of IVD assays and production processes** of RDG. **Three distinct uses were identified** within RDG and are listed in Table 1.

For each use, different product groups are depending on the use of OPnEO / NPnEO. In Table 2 an **overview** of **affected products and processes**[21] **with downstream applications** per each use is provided. Nine different RDG product groups and the Custom Biotech business are affected. The business areas, which have been described in the previous section (2.6), is also indicated per product group in order to understand **the relationships** between these groups. In Table 2, reference is made to product groups as a basis for the analysis. The business area is only given here for information. Moreover, in this SEA, focus for Use 4 is on the description of the affected downstream applications, in particular related to IVD assays and the CB business. This is due to the fact that these downstream applications determine the socio-economic impacts.

Table 2. Overview of uses and affected product groups (Incl. Custom Biotech Business).

Use	Product Group	Abbreviation	Business area concerned*
Use 2: Formulation **Use 3:** Products **Use 4:** Processes	Clinical Chemistry	CC	SWA Core reagents
	Drug Monitoring	DM	
Use 2: Formulation **Use 3:** Products	HIV	HIV	SWA Infectious diseases and oncology
Use 3: Products	Blood gas and electrolyte	BGE	PoC
Use 2: Formulation **Use 3:** Products **Use 4:** Processes	**Accutrend®**	AT	PoC
Use 2: Formulation **Use 3:** Products	Urinalysis (Test strips)	UA	Specialty testing
Use 3: Products	RMD	RMD1	RMD
		RMD2	
Use 3: Products	Roche Tissue Diagnostics	RTD	RTD
Use 4: Processes	Tumor marker	TM	SWA Infectious diseases and oncology
Use 4: Processes	Custom Biotech	CB (proteins)	CB

[21] Throughout this document, products or processes depending on the usage of OPnEO or NPnEO and covered in this AfA will be referred to as 'affected' products or processes.

Use	Product Group	Abbreviation	Business area concerned*
Use 4: Processes		CB (MDx Enzymes)	

*SWA: Serum Work Area; PoC: Point of Care; RMD: Roche Molecular Diagostics; RTD: Roche Tissue Diagnostics; CB: Custom Biotech.

2.7.1 Use 2&3 (Formulation and Products)

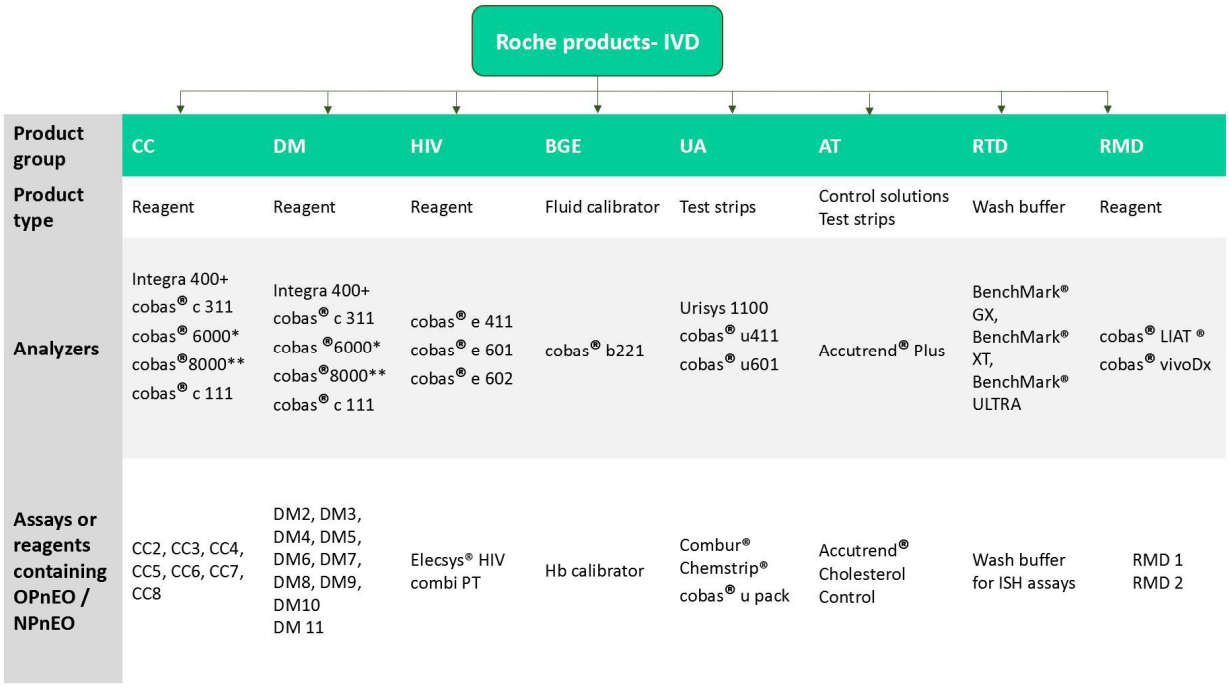
2.7.1.1 Overview of Products

- ⇨ 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.

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 for Use 2&3 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 and the relevance of these assays for health care 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.

Figure 12 presents an overview of the different product types containing OPnEO / NPnEO, including their associated analysers and assays.



Product group	CC	DM	HIV	BGE	UA	AT	RTD	RMD
Product type	Reagent	Reagent	Reagent	Fluid calibrator	Test strips	Control solutions Test strips	Wash buffer	Reagent
Analyzers	Integra 400+ cobas® c 311 cobas® 6000* cobas®8000** cobas® c 111	Integra 400+ cobas® c 311 cobas ®6000* cobas®8000** cobas® c 111	cobas® e 411 cobas® e 601 cobas® e 602	cobas® b221	Urisys 1100 cobas® u411 cobas® u601	Accutrend® Plus	BenchMark® GX, BenchMark® XT, BenchMark® ULTRA	cobas® LIAT ® cobas® vivoDx
Assays or reagents containing OPnEO / NPnEO	CC2, CC3, CC4, CC5, CC6, CC7, CC8	DM2, DM3, DM4, DM5, DM6, DM7, DM8, DM9, DM10 DM 11	Elecsys® HIV combi PT	Hb calibrator	Combur® Chemstrip® cobas® u pack	Accutrend® Cholesterol Control	Wash buffer for ISH assays	RMD 1 RMD 2

*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 12. Overview of the IVD products using OPnEO / NPnEO.

2.7.1.1.1 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 approximately **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 health care professionals **to check for abnormal values**. **Typical CC tests** may include, **e.g. blood glucose** (testing for the risk for diabetes or hypoglycemia), electrolytes (e.g. indication of certain metabolic and kidney disorders), enzymes (assessment of specific organ function or damage), hormones (gland function check), lipids (evaluation of heart and liver disease), other metabolic substances and proteins (e.g. assessment of metabolic or nutritional disorder)[22]. DM, that is included in CC, specialises in the measurements of **levels** of **therapeutic drugs** or **drugs of abuse**.

The OPnEO / NPnEO in the **reagents** lead to improvement of the **assays' performance** (specificity, linearity etc.), promote stabilisation, prevent aggregations, improve solubilisation and are used for cell lysis. The CC and DM portfolios include approximately **120 tests** and **220 applications** (the measurement of a specific analyte in a specific sample type).

Within the **CC portfolio** OPnEO and NPnEO are used for assays such as albumin, creatinine, cholesterol, and bilirubin, that are included in the basic metabolic panel physicians commonly order for each patient seen at a general physician or a hospital (including emergency room). These tests, among others, give information e.g. about **the liver** and **kidney functions** of the patient and can help in the prognosis of e.g. cardiovascular risk. Fructosamine can be used for diagnosis and monitoring of diabetes, while Uric Acid (UA) is used for **renal and metabolic disorders**, renal failure, leukemia, etc. The C-reactive protein (CRP), a protein that increases in the blood with **inflammation** and **infection** as well as following a **heart attack**, is measured. The high-sensitivity CRP tests can measure low levels of CRP in the blood to identify low levels of inflammation that are associated with risk of developing cardiovascular disease (CVDs).

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 (opioids, barbiturates, benzodiazepines, alcohol), stimulants (amphetamines, cocaine), hallucinogens (Lysergic acid diethylamide (LSD), mescaline, phencyclidine) and to check the adherence to substitution drug therapy in urine (buprenorphine, methadone). 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

[22] F. Hoffmann-LaRoche Ltd, Clinical chemistry, 2018 https://www.roche.com/research_and_development/what_we_are_working_on/research_technologies/diagnostic_technologies/clinical_chemistry.htm

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, for example, 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 2 and Section 2.7.1.1.2) 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 13). 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 **cobas**® 8000 for the high-throughput segment (combining e.g. 1x e801 and 2x **cobas**® c702). 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.

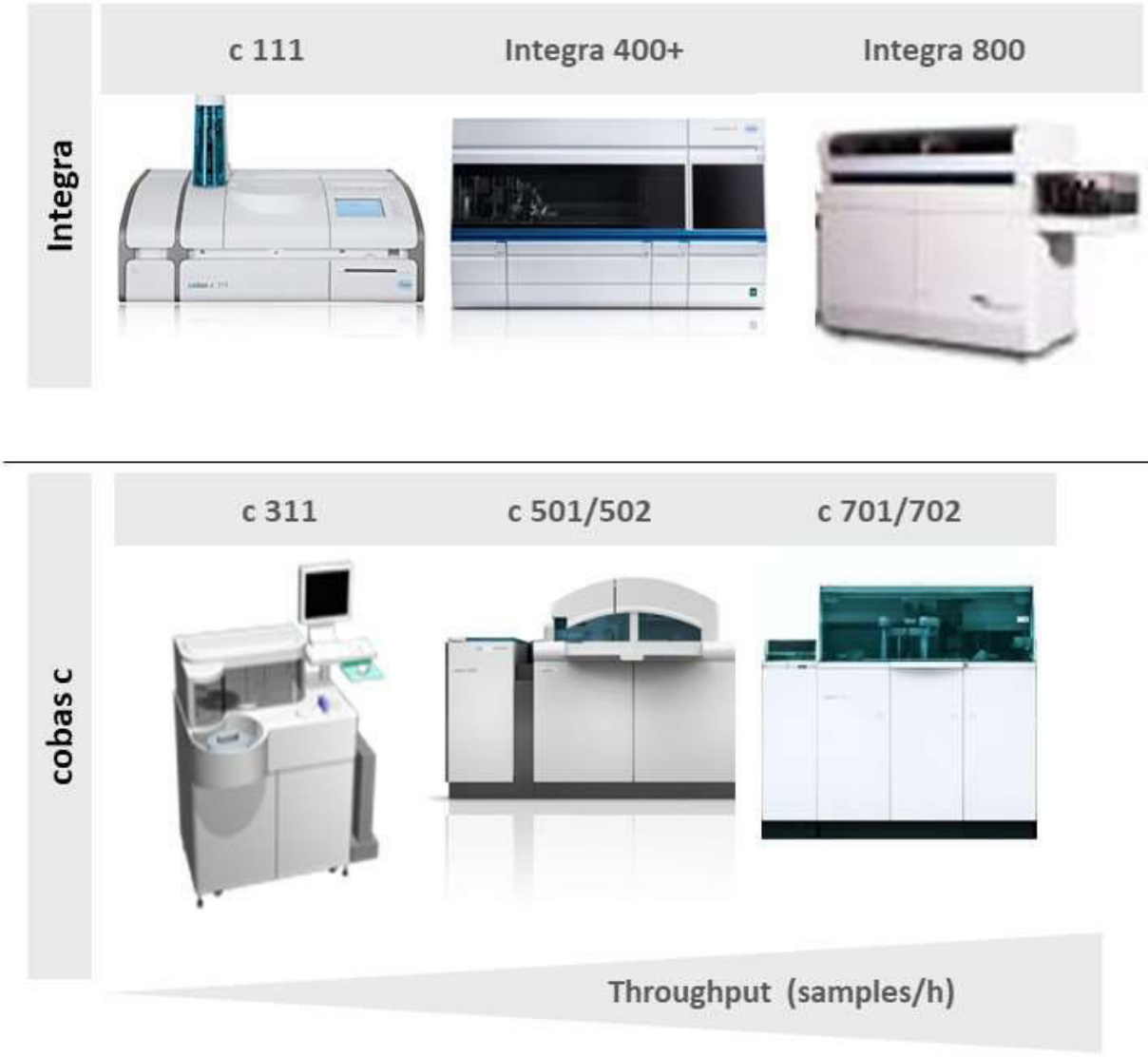


Figure 13. CC / DM analysers. Please note that Integra 800 was phased-out in 2018.

2.7.1.1.2 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.
- ⇨ Tests for **infectious diseases**, **fertility / hormones, thyroid function, oncology**, etc. (please write a sentence here).

The **HIV** portfolio is included in the Elecsys® immunoassay portfolio 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 **fertilityhormones, thyroid functionand oncology** tests among others. Figure 14 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 14. cobas® e411 instrument.

2.7.1.1.3 Point of Care

Roche PoC business line aims at delivering quick, accurate and reliable results for critical- and primary-care clinicians (e.g. in intensive care or emergency units) but also for patient self-monitoring. PoC includes the Blood Gas and Electrolyte (BGE) and **Accutrend**® (AT) portfolios.

2.7.1.1.4 Blood Gas and Electrolytes

- ⇨ Blood gas analysis (BGE) is considered the one of the **most important tools** for diagnosis in **critically ill patients**.
- ⇨ The affected product (containing OPnEO) is the **Hb Calibrator** used with the **cobas**® b 221 system and which is required for calibration of total haemoglobin, haemoglobin derivatives and bilirubin.
- ⇨ The BGE parameters that can be measured in critical care situations comprise pO2 (partial pressure of Oxygen), pCO_2 (partial pressure of carbon dioxide), pH, Hematocrit, Na^+, K^+, Cl^-, Ca^{2+}, Glucose, Lactate, Urea, total haemoglobin, etc.

The affected product in the BGE portfolio is the **Hb Calibrator for calibrating haemoglobin, haemoglobin derivatives, and bilirubin** measured by the **cobas**® **b** 221 instruments. Blood gas analysis is considered one of the **most important tools** for diagnosis in **critically ill patients**. Analysers should deliver rapid and reliable results, be easy to handle and require little maintenance. Roche **cobas**® b 221 (Figure 15) system offers these features and a flexible configuration. This system can in fact meet customer specific requirements for **critical care testing** in Intensive care units, Emergency departments, Operation rooms and Neonatology. A blood gas analysis system needs to offer a broad range of measured parameters. The BGE parameters required in critical care situations comprise but are not limited to: pO_2 (partial pressure of Oxygen), pCO_2 (partial pressure of carbon dioxide), pH, Hematocrit, Na^+, K^+, Cl^-, Ca^{2+}, Glucose, Lactate, Urea, total haemoglobin, SO_2 (Oxygen saturation), haemoglobin derivatives (oxyhemoglobin O_2Hb), Carboxyhemoglobin (COHb), methaemoglobin (MetHb), and bilirubin.

The Hb Calibrator is used with the **cobas**® b 221 system and is required for calibration of total haemoglobin, haemoglobin derivatives and bilirubin. The **Hb Calibrator contains OPnEO above 0.1%** w/w. **OPnEO and NPnEO** are also present **in solutions and electrochemical sensors** used in 9180 Electrolyte Analyzer, **cobas**® b 121 system, **cobas**® b 221 system and **cobas**® b 123 POC system. OPnEO and NPnEO are present in **concentrations below 0.1%** w/w in these products. These sensors and solutions are **produced in Switzerland** and are therefore **not in scope** of this AfA. However, their production will be subject to authorisation requirements in Switzerland as soon as OPnEO and NPnEO have been added to the respective list in Swiss legislation[23].

[23] Common notification authority for chemicals, Admin CH Website: https://www.anmeldestelle.admin.ch/chem/en/home/themen/pflicht-hersteller/stoffe/besonders-besorgniserregenden-stoffe-svhc.html

Figure 15. cobas® b 221 system[24] .

[24]cobas b 221 system, Instructions for Use, April 2017

2.7.1.1.5 Accutrend®

- ⇨ AT is a handheld device used in the **physician' practices** and **clinics** for the determination of important **metabolic disorders** and **cardiovascular** risk factors.
- ⇨ Control solution for the cholesterol test strips contains OPnEO (Use 2&3).
- ⇨ Enzymes / proteins produced and extracted using OPnEO are inserted into the test strip (Use 4).

Accutrend®[18] is a flexible point-of-care **handheld device** for the determination of three important **cardiometabolic parameters**, cholesterol, triglyceride and glucose, as well as lactate (see Figure 16) The system is intended for use in the **physician' practices** and **clinics** for the monitoring of **metabolic disorders** and **cardiovascular** risk factors in patients. Enzymes / proteins produced and extracted (using OPnEO in the process, Use 4) are used on the test strip for AT to measure the parameters cholesterol and triglycerides. The affected product (Use 2&3) in this portfolio is the control solution (Figure 17) for the cholesterol test strips.

The measurement requires only a **small amount** of **capillary blood**. In addition, this proven capillary blood test strip technology is fast. e.g cholesterol and triglycerides are measured in 180 and in 174 seconds, respectively[23].

Figure 16. **Accutrend**® Plus device[25].

[25] Accutrend® Plus System, Roche website: https://www.roche.de/diagnostics/systeme/point-of-care-diagnostik/accutrend_plus.html#Merkmale

Figure 17. **Accutrend®** Cholesterol Control solution packaging bottle.

Specialty testing

Roche Speciality Testing includes Urinalysis products ranging from single-use test strips to semi- and fully-automated systems.

2.7.1.1.6 Urinalysis

- ⇨ The affected products in the Urinalysis (UA) portfolio are the **test strips containing the PRO (protein)** test pad in which NPnEO is used as **wetting agent**.
- ⇨ The urine test strip is a key **screening tool** that yields quick and reliable information **on pathological changes in the urine**.
- ⇨ The Combur® and the Chemstrip® test strips are either used on (semi-) automated systems or as for visual reading.

The affected products in the UA portfolio are the **test strips of** Combur®, Chemstrip®, **cobas®** u pack portfolio containing the PRO (protein) test pad in which NPnEO is used as **wetting agent** Pathological changes in urine are key indicators of many diseases such as urinary tract infection, kidney disease and diabetes. The urine test strip is a major diagnostic tool that yields quick and reliable information on **pathological changes in the urine**[26]. The Combur 10 strip can simultaneously measure specific gravity (e.g. evaluating the concentrating ability of kidneys), Leucocytes (e.g. indication of bacterial infection), Glucose, Protein and Ketones levels (e.g. indicating signs of diabetes mellitus), Bilirubin (e.g. indication of obstructive jaundice), pH (e.g. indication of urinary tract infection), Urobilinogen (e.g. indication of viral hepatitis) and blood (e.g. indication of renal cysts). Figure 19 shows in detail the different clinical aspects for each parameter. The Combur® 10UX, 10M and **cobas®** upack are used in automated reading with the analysers Urisys 1100, **cobas®** u411 and **cobas®** u601 / **cobas®** 6500, respectively (Figure 18). While the **cobas®** u601/6500 are adapted to **hospitals** or **laboratories**, the Urisys 1100 is used in **physician's offices** or **wards**. The visual reading Combur (EU brand) / Chemstrip (US / Canada brand) tests trips are used for early and reliable detection of kidney diseases, diabetes and urinary tract infection in small scale settings.

[26] Roche Article, 'Roche launches fully automated urine testing analyzer', 2014: http://www.cobas.com/home/news-room/news/fully-automated-urine-testing-analyzer.html

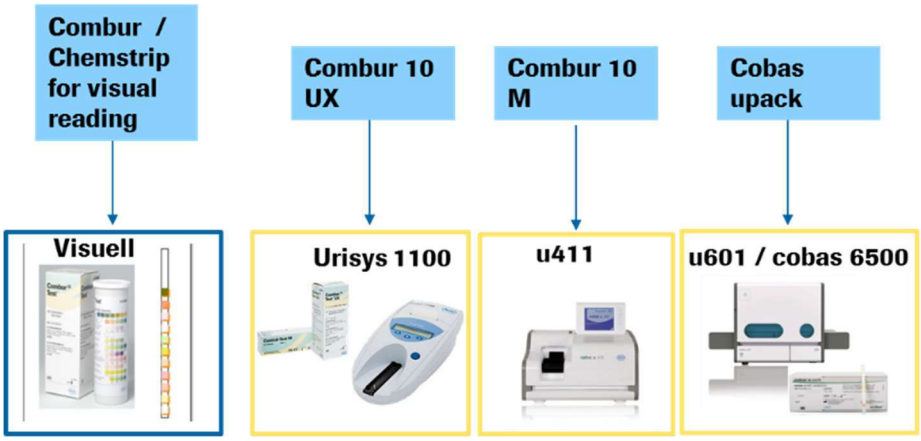


Figure 18. UA instruments with corresponding strip portfolio.

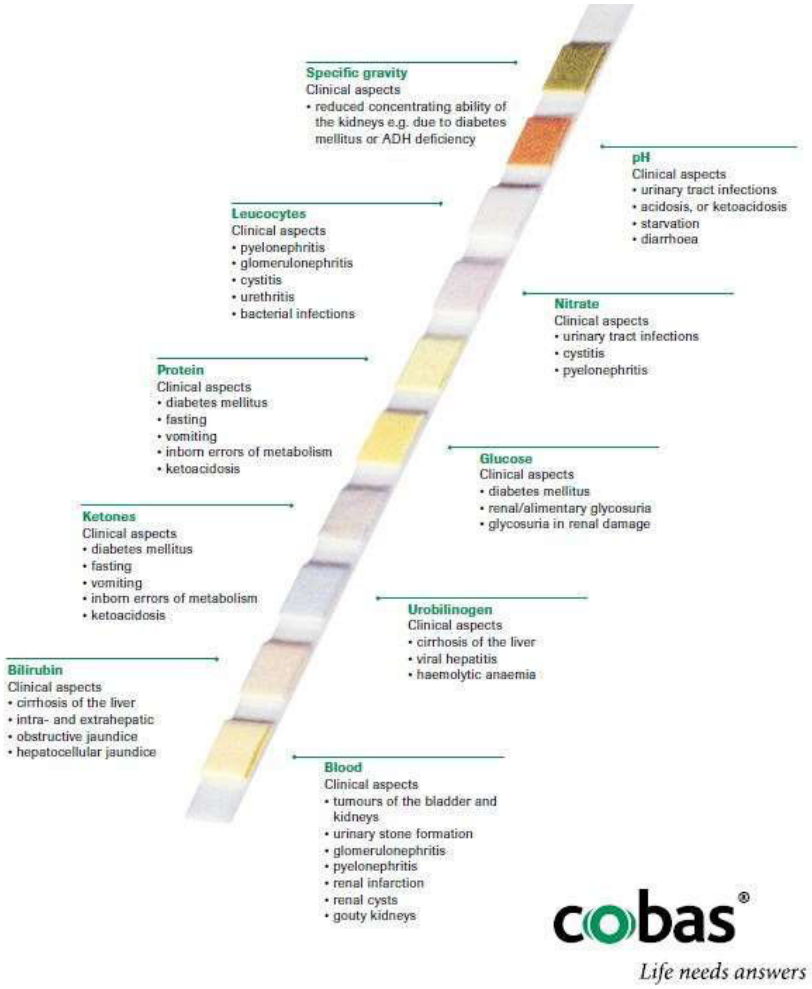


Figure 19. Combur10 test parameters.

2.7.1.1.7 Roche Molecular Diagnostics

⇨ **Roche Molecular Diagnostics** (RMD) develops and markets **advanced diagnostics, blood screening platforms, and tests based on Polymerase Chain Reaction** (PCR) technology.

⇨ Affected products:
- RMD1 nucleic acid test → OPnEO is used in the **lysis buffer** for sample preparation.
- RMD2 qualitative live cell molecular test →OPnEO is added for its surface-active properties / flow properties which are important for complete **mixing of substrate** (sample) and **reagents**.

RMD develops and markets advanced diagnostics, blood screening platforms and tests based on Roche's proprietary real-time Polymerase Chain Reaction (PCR) technology[27]. RMD's clients include researchers, physicians, hospitals, laboratories and blood banks around the world. Its broad menu of kits and assays allows for diagnosing and monitoring various diseases in **oncology**, **virology**, **microbiology** and **blood screening tests**.

The affected products in the RMD portfolio are the **cobas**® Influenza A / B nucleic acid test used on the **cobas**® **Liat**® System (RMD1, Figure 20) for the determination of Influenza A or Influenza B and the **cobas**® vivoDx MRSA, qualitative live cell molecular test use on the **cobas**® vivoDx System (RMD2, Figure 21).

- In the **RMD1 test assay**, **OPnEO** is used in the **lysis buffer**. The **cobas**® **Liat**® System is unique as a point of care system that delivers lab-quality PCR results in 20 minutes or less.

- In the **RMD2**, **OPnEO** is added for its **surfactant properties** that are important for solution homogeneity and flow rate of the dispensed solution that are important for complete **mixing of substrate** (sample) and **reagents**. The **cobas**® vivoDx MRSA was launched with an OPnEO containing surfactant in December 2018. This is the first IVD assay using Smarticle technology, an innovative class of live cell molecular diagnostics that quickly identifies multidrug-resistant organisms and **assesses antibiotic susceptibility** directly from clinical samples, without the need for traditional enrichment, culture or sample preparation processes.

[27] RMD Website: https://molecular.roche.com/innovation/pcr/

Figure 20: **cobas**® **Liat**® System (RMD1)

Figure 21. **cobas**® vivoDx System (RMD2)

2.7.1.1.8 Roche Tissue Diagnostics

- ⇨ **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 hybridization 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** (i.e. type of hybridization that uses a labelled complementary DNA, RNA or modified nucleic acids strand (i.e., probe) to localize a specific DNA or RNA sequence in a portion or section of tissue (in situ)) products which 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 22). In situ hybridization (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 for Use 2&3.

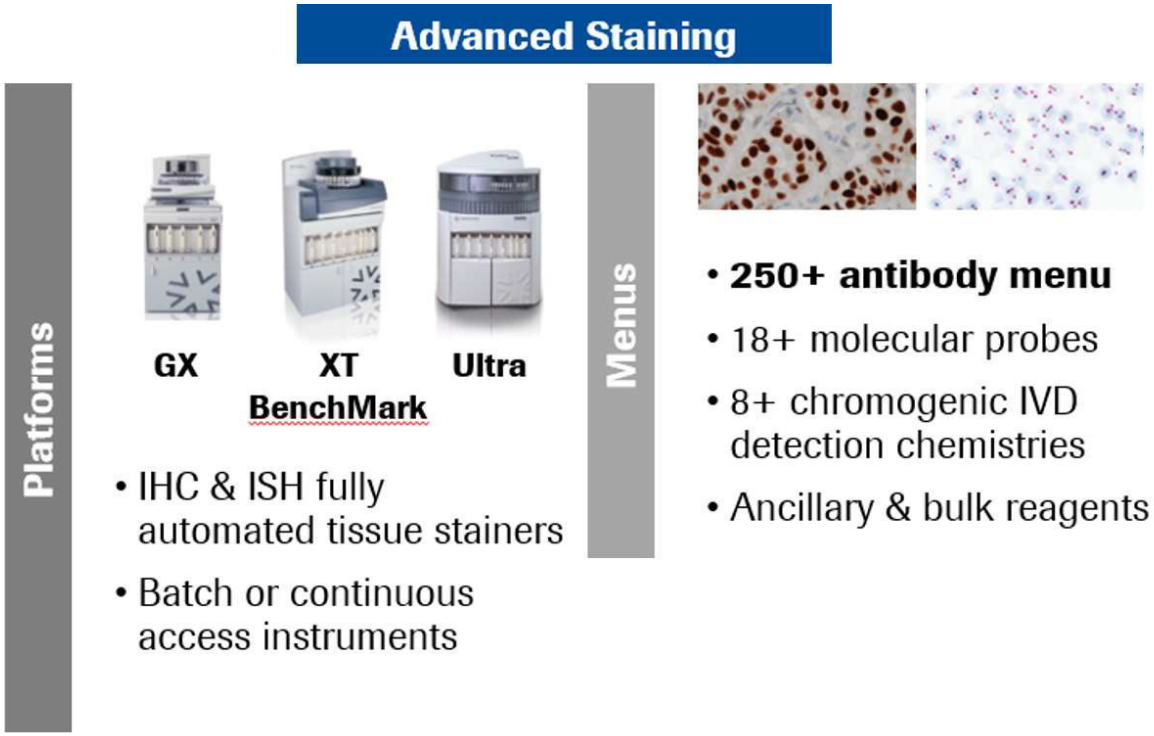


Figure 22. **VENTANA®** BenchMark GX, XT and ULTRA.

2.7.2 Use 4 (Processes)

- ⇨ OPnEO and NPnEO entered in the **production of proteins, MDx Enzymes and the conjugation of latex beads** to be used as components of or for the production of components of IVD assays, research products, quality control reagents and other products for analytical applications.

- ⇨ The processes can be divided into **three groups**:
  - **Process group 1**: Protein production processes and their downstream applications.
  - **Process group 2**: MDx Enzymes (which are specific types of proteins) production processes and their downstream applications.
  - **Process group 3**: Latex beads conjugation for drug monitoring assays.

Figure 23 shows the process groups with the type of processes (dark blue) and the kind of downstream products that are produced. More detailed information is provided in the following sub-chapters.

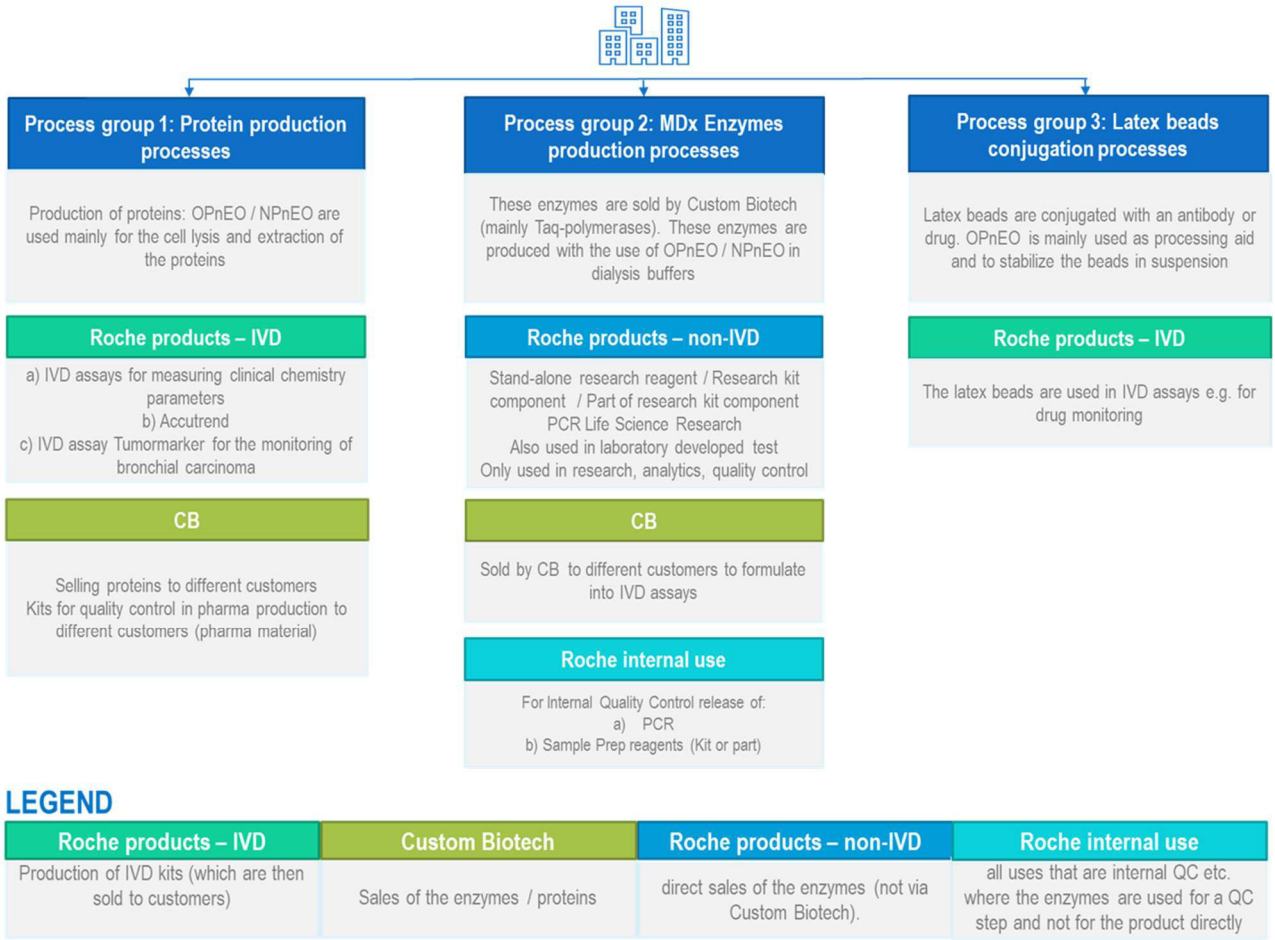


Figure 23. Overview of the processes affected including relevant downstream applications of the produced materials.

2.7.2.1 Description of the Enzyme and Protein Production Processes and their Downstream Applications - Process Group 1

- ⇨ Process group 1: OPnEO / NPnEO are used under Use 4 as **detergent**, to **lyse the cells** and **extract the produced proteins / enzymes.**
- ⇨ Process group 1 covers **5 processes** for the extraction of the target protein or enzyme.
- ⇨ **Enzymes** are known as **biological catalysts** due to their ability **to promote reactions quickly and efficiently**.

PROCESS GROUP 1

a) Processes and function of OPnEO / NPnEO

*Under Use 4 and process group 1, five processes use either NPnEO (1 process) or OPnEO (4 processes) for **cell lysis** and for the **extraction of the target protein or enzyme**.*

Enzymes are of the family of proteins and are known as biological catalysts due to their ability to promote reactions more quickly and more efficiently. The RDG production of proteins (e.g. cytokeratin) and enzymes affected by this AfA come from bacteria, yeast cells and pig kidney. The description of the enzyme and protein production processes, including recombinant protein and enzyme production using bacteria is in detail described in the Section 3.2 of the AoA. To extract and purify the target protein / enzyme from the cell cultures a lysis process (5 in total under the process group 1) is used.

Historically, physical lysis, such as the mechanical lysis or the sonification, was the method of choice for cell disruption and extraction of cellular contents (the target enzymes or proteins in this case). However, the physical lysis often requires expensive equipment and involves protocols that can be difficult to repeat due to variability in the apparatus. Detergent-based lysis methods have therefore become the norm for cell extraction [4]. OPnEO / NPnEO are used under Use 4 as **detergent**, to **lyse the cells** and **extract the produced proteins / enzymes.**

b) Downstream products

For clarity purposes, the following section is divided in two parts, which includes:

- A description of IVD applications based on the processes (‘**Roche IVD assays’**),
- A subsection regarding the Custom Biotech (CB) applications (‘**Custom Biotech’**).

An overview of the interrelation between IVD and CB applications is given in Figure 24.

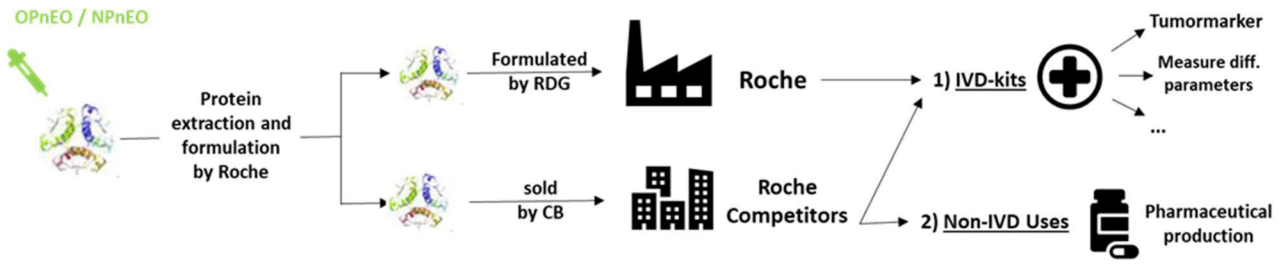


Figure 24. Overview of the interrelation between IVD and CB applications.

The enzymes / proteins extracted are either used directly at RDG in Roche IVD applications or sold by CB and then used at Roche's competitors. Not necessarily all IVD applications listed are used by both RDG and Roche's competitors (graph for illustrative purposes).

Roche - IVD assays

- ⇨ The **proteins, extracted in the processes with OPnEO / NPnEO**, are **used in IVD assays** within the Roche product groups Clinical Chemistry, Drug Monitoring, **Accutrend®** and Oncology (**Tumour marker**).
- ⇨ Details on the proteins produced are shown in Table 3.

Table 3. Roche downstream products used as IVD. For more details, please refer to the text below the table.

Protein name	Product group	IVD assay / feature
CE (Cholesterol Esterase)	AT	Used in Accutrend® TG IVD test strip to measure triglycerides.
Cytokeratin	TM	Used to measure the serum cytokeratin 19 fragment in human serum and plasma→marker for lung cancer
Gamma-GT (gamma-Glutamyltransferase)	CC	PRECINORM U plus, PRECIPATH U plus (2 products) used as quality control materials for several CC assays
IMPDH (Inosinmonophosphat-Dehydrogenase)	DM	Used for drug monitoring (2 products)
Uricase	CC	Used to measure two substrates: Uric acid, Fructosamine (8 products)

- **CC/ DM: IVD assay to measure different parameters:** A description of Clinical Chemistry (CC) and Drug Monitoring (DM), including the importance for healthcare and patients, is above discussed in Section 2.7.1.1. Besides being directly affected by the use of OPnEO and NPnEO in reagents (Use 2&3), enzymes, extracted with OPnEO / NPnEO, are used in a number of CC and DM assays. The affected extracted enzymes are shown in Table 3.

  As already described above 'Enzymes and substrates' CC assays are included in **the basic metabolic panel** physician commonly order for each patient seen at a general physician or a hospital (including emergency room). These tests, among others, give information about **the general health status of a patient** as well as information about the function and **pathological condition of specific organs** such as for example the liver or the kidneys. Fructosamine is used for diagnosis and monitoring of diabetes, while UA is used for **renal and metabolic disorders**, **renal failure**, **leukemia** etc. The total mycophenolic acid (TMPA) DM assay is an immunosuppressant drug used to **prevent rejection in organ transplantation**. A reason for therapeutic drug monitoring of TMPA during post-transplant period is to **determine the relationship** between TMPA pharmacokinetic parameters and clinical outcomes to adjust the dose.

  As mentioned above, CC and DM assays are run on modular instruments, which allow to measure a range of different parameters in one single sample (see for example Figure 13).

- **Accutrend**® (Figure 16) is a flexible **point-of-care handheld device** and it is already described under Use 2&3 Section 3.3.1.1. Under Use 4, the usage of enzymes / proteins produced and extracted with an OPnEO / NPnEO detergent, in the test strip for AT is necessary to **measure the parameters cholesterol and triglycerides**.

- **Tumour marker assay (1):** TM assays determine the serum cytokeratin 19 fragment in human serum and plasma. High **CYFRA 21-1 serum levels** indicate an advanced **tumour stage** and a poor prognosis. This electrochemiluminescence immunoassay is intended for use on **Elecsys**® and **cobas**® immunoassay analysers centralised private or hospital laboratories. In fact, TM belongs to a wide range of different immunodiagnostic assays based on the **Elecsys**® technology for a wide range of different indication areas, among them assays to detect infections with the HIV virus (see Use 2&3) (Figure 14). Cytokeratins are a type of protein found on epithelial cells, which line the inside and outside surfaces of the body. Twenty different cytokeratin polypeptides have so far been identified. Due to their specific distribution patterns they are eminently suitable for use as **differentiation markers** in tumour pathology. Cytokeratins, especially fragment 19, show increased levels in patients with carcinomas. TM is the most important tumour marker for non-small cell lung cancer. But the marker is also a marker for breast cancer and other carcinomas. For the assay a cytokeratin 19 is needed, that is produced with a process using OPnEO / NPnEO.

  Roche **TM is used in lung cancer panel** (carcinoembryonic antigen and cytokeratin 19 fragments CYFRA 21-1), which is a series of different markers used to test the patient. Lung cancer is the leading cause of cancer deaths worldwide. Every year, lung cancer causes more than 1.6 million deaths worldwide; more than breast, colon and prostate cancers combined[28]. Globally, cigarette smoking by itself is responsible for over 80 percent of all lung cancer cases. Tumour markers are of particular interest in this respect[26].

[28] International association for the study of lung cancer, 2017: http://wclc2017.iaslc.org/wp-content/uploads/2017/09/2017-WCLC-Fact-Sheet-Lung-Cancer-Final.pdf

Custom Biotech

⇨ Custom Biotech supplies industrial customers in the life science, pharmaceutical and diagnostics sectors with **high-quality raw materials and reagents** worldwide.

Roche's Custom Biotech business unit **supplies** industrial customers in the life science, pharmaceutical and diagnostics sectors with **high-quality raw materials and reagents worldwide**[29]. To understand better the intercorrelation between RDG and CB (IVD and non-IVD) please consult the overview in Figure 24.

CB sells either enzymes and proteins, which are produced and extracted with OPnEO / NPnEO. These enzymes, proteins and further substances (in the following summarised as 'substances') are **used in several applications** depending on the substances sold by CB are shown below in Table 4.

Table 4. Overview CB affected downstream products.

Category	Description	Affected products	No. of total affected products sold by CB
IVD test raw material	CB sells enzymes and cofactors	• 2x Cholesterol Esterase, *Candida cylindracea* • Cholesterol Esterase Modified • Uricase from *Arthrobacter protophormiae* • g-Glutamyltransferase from Hog Kidney	5
Raw material for cell cultures in pharmaceutical manufacturing	CB sells cell culture ingredient	• Cytokeratin 8/19, CEN	1

In the following section, further details are provided on the CB downstream products listed in Table 4.

As mentioned before, CC is a field of IVD which tests for various components of blood and urine. CB sells enzymes and cofactors as **raw material for CC IVD applications**. A cofactor is a non-protein chemical compound or metallic ion that is required for an enzyme's activity.

Cytokeratin 8/19 is sold as **raw material for cell cultures in pharmaceutical manufacturing**. As mentioned above for the tumor marker, cytokeratins are a type of protein found on epithelial cells, which are suitable for use as differentiation markers in tumour pathology and are important for carcinoma diagnosis.

[29] Custom Biotech Catalog: http://www.custombiotech.roche.com/content/dam/internet/dia/custombiotech/custombiotech_com/en_GB/pdf/Custom Biotech_Catalog_Clinical_Chemistry_Immunology_2017.pdf

2.7.2.2 Description of the MDx Enzyme Production Processes and their Downstream Applications – Process group 2

⇨ MDx Enzymes are enzymes frequently used in Polymerase Chain Reaction (PCR)-based IVD assays.

⇨ MDx Enzymes in process group 2 have two downstream usages:
- The enzymes are sold by CB
- The enzymes are used by RDG and sold for Research and Development.

The MDx Enzymes covered in this AfA are enzymes **frequently used in Polymerase Chain Reaction (PCR)-based IVD assays**. Note that enzymes are a specific type of protein, therefore MDx Enzymes are covered when in this AfA general reference is made to proteins (e.g. in the use name). PCR is a method widely used to make many copies of a specific DNA or RNA segment. PCR-based IVD assays are, among others, used for **identification and quantification of pathogen-specific DNA or RNA** in human samples to identify the **bacteria** causing an infection and thus allowing for a targeted antibiotic treatment. Further, they are also used for the detection of **microbial or fungal contamination** in sterile formulations. In the AoA Use 4, an overview of the MDx Enzymes affected by this AfA is given. The production processes of the MDx Enzymes are grouped together in the process group 2. In the MDx production processes OPnEO / NPnEO are used (for more details see the AoA Use 4)

The MDx Enzymes in process group 2 have two **downstream usages**:

- **The enzymes are sold by CB** (see Table 5 for a list of CB downstream products): CB includes these MDx Enzymes in final products such as PCR-based reagents for IVD assays or sells them directly to IVD manufacturers.

- **The enzymes are used by RDG and sold for Research and Development.** The MDx Enzymes are used as generic reagents internally and at customers for PCR e.g. in research.

Table 5. Overview of CB downstream products manufactured using MDx Enzymes.

Process Group 2	Number of downstream products	Substance
MDx1	3	OPnEO
MDx2	13	NPnEO
MDx3	2	NPnEO
MDx4	1	NPnEO
MDx5	1	NPnEO
MDx6	1	NPnEO

2.7.2.3 Description of the Latex Beads Production for Drug Monitoring Assays – Process group 3

Eight of **the ten Drug Monitoring assays** described covered in Use 2&3 (see product descriptions for Use 2&3) require latex beads for the functioning of the assay. The latex beads are conjugated either with an antibody or the drug to be measured. The principle of the assays is based on the **measurement of an aggregation or disaggregation of the particles depending on the presence of drug in the sample**.

2.7.3 Interrelation Between Affected Products (Use 2&3) and Processes (Use 4)

- ⇨ Some of Roche's IVD product groups (CC, DM, and AT) are **affected by both Use 2&3 and Use 4**.
- ⇨ The Immunodiagnostic **Elecsys**® portfolio (Figure 25) includes the **HIV combi PT** which is affected by Use 2&3 and a TM assays which is affected by Use 4.
- ⇨ **CC and DM assays** are offered as part of complete test portfolio for central laboratories with binding contracts for several years. If individual assays are not available, the whole portfolio is affected.
- ⇨ The Accutrend® system includes a meter, test trips and control solutions. The control solutions are impacted by authorisation via Use 2&3 'products' whereas the test strips via Use 4 'processes'. If control solution or test strips are not available, the system cannot be used any more.

As described in the previous sections, some of Roche's **IVD product groups are affected both by the direct use of OPnEO / NPnEO in the assays** (Use 2&3) as well as use of proteins or latex beads produced with OPnEO / NPnEO as processing aid (Use 4). This section aims at describing how these assays are connected within their respective portfolio.

The Immunodiagnosic **Elecsys**® portfolio includes Infectious Disease, fertility / hormones, thyroid function, oncology, pregnancy, Anemia, Cardiac markers, and Rheumatoid Arthritis testing. The only directly affected product (Use 2&3) in this portfolio is the **HIV combi PT** (see Figure 25), that is used to simultaneously detect the HIV-1 p24 antigen and antibodies to the distinct types HIV-1 and HIV-2 in one single reaction. This assay belongs to the Infectious Disease portfolio which also includes e.g. Hepatitis assays, which are usually run on the same samples as the HIV assay. HIV combi PT assay is used in many **blood banks** to safeguard the supply with blood products.

The other assay, which is affected by a process use (Use 4) is the TM assay within the oncology indication area (see Figure 25).

Figure 26 represents a **'subway' map of the assays in the CC and DM portfolios showing some assays that are directly (Use 2&3) or indirectly impacted (Use 4) by this AfA**. In these portfolios there may be different sample types (blood or urine) for an analyte (subway stop), for example creatinine can be measured in serum or urine. Test that belong to the same indication area (e.g. oncology) or to the same type of analyte (e.g. enzymes) are grouped as a subway line.

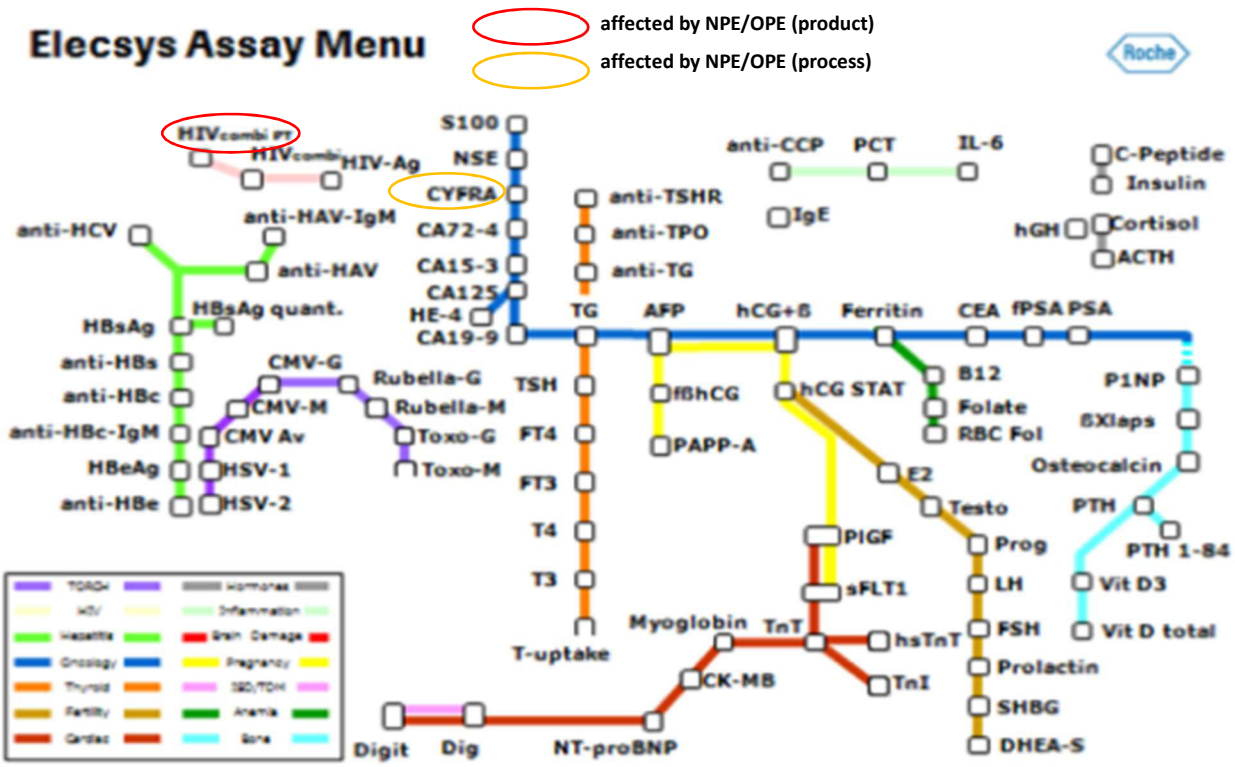


Figure 25. Assays from the **Elecsys**® portfolio that are directly or indirectly impacted.

The majority of diagnostic testing of patient samples (blood, serum, plasma, urine, etc.) takes place in the central laboratory. These specialised laboratories are either part of a (medium to large) hospital or are dedicated facilities (in most cases private commercial laboratories) where physicians and (small) hospitals send their patient samples together with the order to test a specific set of parameters as defined by the ordering physician.

Besides quality of results, reliability and turn-around time, cost efficiency is one of the major drivers of the central laboratory. As a result, **two major trends can be observed in the market**:

- **Increased automation** of all parts of the testing processes (including pre-analytics, the actual testing, sample handling, data management, etc.)
- Consolidation to **larger laboratories with a broad** (ideally complete) **portfolio of diagnostic parameters**.

As a consequence, **large automated solutions that provide the entire diagnostic portfolio are offered to the customers by IVD providers** such as RDG and competitors.

The offered solutions include automated sample handling (sorting, aliquoting, centrifuging, labelling, storage, disposal), automated testing on large analyser modules (such as **cobas**® 6000 and **cobas**® 8000), dedicated reagents optimised for the corresponding instruments (such as **cobas**® c501, **cobas**® c701, etc.), user software for test handling and data management of test results. These solutions are therefore **'closed systems'** in which single components (e.g. disposables, reagents, software, instruments) **cannot be exchanged or replaced** with third-party components.

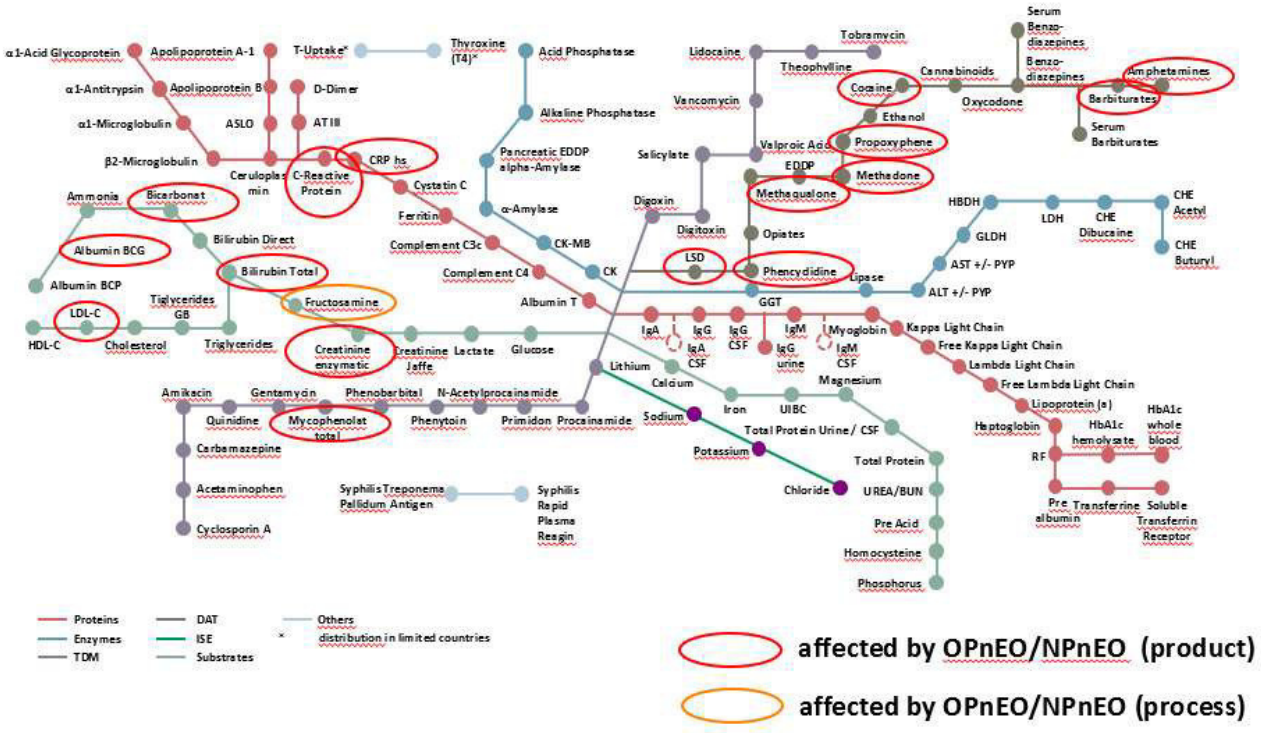


Figure 26. Assays from the CC and DM portfolio (directly or indirectly impacted). Please note that this map is not complete, and some assays affected by this AfA are not shown. Most drug monitoring assays (DAT subway line on the top right) are additionally affected by processes which is not shown.

As another consequence, **these solutions consist of large instrumentation with high investment costs** and considerable efforts to install and implement into the laboratory's infrastructure. In some cases, building structures need to be adjusted, media such as water, high voltage current or data lines have to be installed that fit to the IVD instrumentation.

Therefore, the decision of a central laboratory for a specific solution of an IVD provider is carefully taken. It is the result of a several months decision period during which several offers of competitors are compared and a binding contract for several years (usually 5-7) is closed between the laboratory and the IVD manufacturer. The sales volume of such a contract (or 'tender') can easily comprise several million Euros per year in the case of larger laboratories.

As part of the contract, the **IVD manufacturer guarantees to provide the offered portfolio at constant quality and supply**. In case the IVD manufacturer could not fulfil this guarantee for a (small) part of his portfolio (as would be the case in the non-use scenario), this could not easily be compensated at the customer. This means that if RDG does not provide the complete portfolio to the customer there is no solution for them to fill the 'gap', since the customers are buying a complete

solution from Roche to measure, e.g. all relevant clinical chemistry parameters as described above. Therefore, this whole portfolio is dependent on the use of OPnEO / NPnEO via formulation in products (Use 2&3) as well as use of OPnEO / NPnEO in the production process for enzymes (Use 4) needed for some of the assays.

The **Accutrend**® system **depends on all its components** and will not be functional anymore if one of the components is missing. The system is provided including a meter, test strips and control solutions (Figure 27). The control solutions are impacted by authorisation via Use 2&3 (formulation and products) and the test strips via Use 4 (processes). Not authorising the production of control solutions leads the system to be unusable since quality controls at the customer site are an integral part of the system. These solutions are used in the same way as a drop of blood on a test trip to perform routine quality control testing necessary when a new container of test strips is opened or before using the meter for the first time.

Figure 27. **Accutrend**® Plus system package.

As discussed above, Use 2&3 and Use 4 are for some business units strongly interconnected. In fact, **CC / DM and AT** are affected both by use of OPnEO / NPnEO in products as well as by the use of these substances in the **production of proteins and the conjugation of latex beads** that are either used directly in these assays or used to manufacture further components of the assays. Use 2&3 and Use 4 are differentiated in this dossier because of the function of OPnEO / NPnEO either in the product or in the process. However, it should be kept in mind for the later analysis of impacts in case of the non-use scenario, that these product portfolios depend on both uses and the impacts of the non-

use scenario for Use 2&3 and Use 4 are very similar. This means that if the process use would be authorised and only the product use would have to be stopped, the impacts would remain the same for CC / DM and Accutrend®.

2.8. Definition of 'Applied for Use' Scenario

- ⇨ In the **'applied for use' scenario**, RDG continues to use OPnEO / NPnEO in its products and production processes until substitution is completed.
- ⇨ This scenario is **used as baseline to evaluate the impact for RDG** under the 'non-use scenario'.

In the '**applied for use**' scenario, **RDG continues to use OPnEO / NPnEO** in its products and production processes 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 RDG under the 'non-use scenario' which is described in Section 2.9. To illustrate which product groups are depending on Use 2&3, 4 or combinations of all the 3 uses see Table 3. As IVDs are the most important products affected by this AfA for RDG and for healthcare, the focus of this section is on IVDs and CB downstream products. Some further downstream applications, which depend on Use 4 (processes) such as non-IVD applications (see Section 3.3.2.1), because of their lower importance for RDG's business and for healthcare, are therefore not discussed in detail.

In this scenario RDG will continue to use OPnEO and NPnEO to produce the IVD assays or proteins and MDx Enzymes and conjugate the latex beads. **Substitution projects to replace these substances in all assays and processes will continue** in order to achieve substitution as fast as possible (see further information in the AoAs for Use 2&3 and Use 4). RDG's customers will continue to use the IVD assays with OPnEO / NPnEO until the OPnEO / NPnEO-free assays are available from RDG.

Furthermore, **Roche 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 RDG's IVD assays to provide healthcare services to patients. From an economic point of view, RDG 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.

CC / DM and AT are affected both by use of OPnEO / NPnEO in Use 2& 3 and Use 4. In fact, OPnEO / NPnEO are used in products as well as using these substances in the production of proteins and the conjugation of latex beads that are either used directly in these assays or used to manufacture further components of the assays. Therefore, the 'applied for use' scenario for these product groups (i.e. **CC / DM and AT**) **depends on both, Use 2&3 and 4** of OPnEO / NPnEO directly in the products (Use 2&3) and use in the protein production and latex beads conjugation processes (Use 4).

In addition to these aspects, Roche will be able to **continue the CB business** with industrial customers to supply the proteins based on established long-term contracts. These customers will continue to use RDG's proteins to produce IVD assays or other downstream products such as quality control kits for production in the pharmaceutical industry.

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

- ⇨ Roche is a **leader of the global IVD market** and has **the largest market share in CC and DM**.
- ⇨ RDG is **expecting growth of 4%** CAGR (Compound Annual Growth Rate) of the global IVD market until 2021.
- ⇨ The Diagnostics Division continued to **increase sales** with growth of **5%** at CER (Coupon Equivalent Rate) primarily due to immunodiagnostics sales (13% growth).
- ⇨ The entire portfolios that are depending on the **affected assays contribute to [redacted]% of sales** of the Diagnostics Business.

The aim of this section is to illustrate the economic significance for Roche's Diagnostic Division and specifically for the product groups depending on Use 2&3 and / or Use 4 of OPnEO / NPnEO.

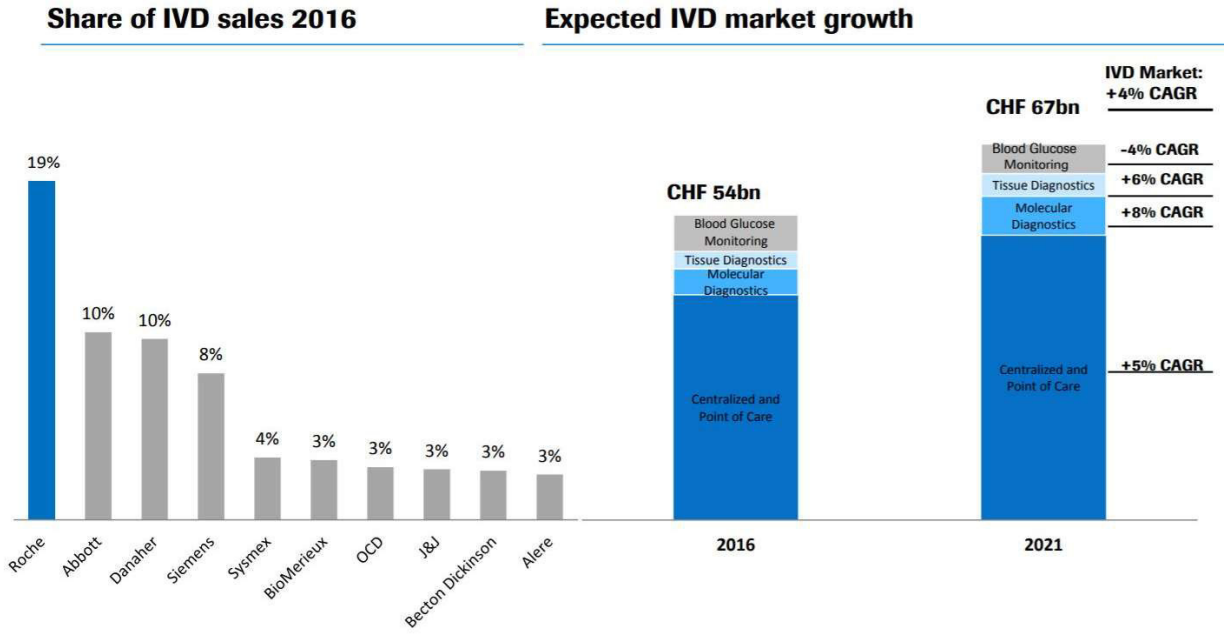


Figure 28. Share of global IVD sales and expected IVD market growth in 2016[30].

As illustrated in Figure 28, Roche is a leader of the global IVD market and has the largest market share in CC and DM (see Table 6). In 2016, Roche had, with **19%**, the highest market share in this market, almost double the market share of its largest competitor (Figure 28). Centralised and Point of Care is the driving Business Unit of the IVD sector, followed by Molecular Diagnostics, Tissue Diagnostics and Blood Glucose Monitoring. As shown in Figure 28, RDG is **expecting growth of 4%** CAGR (Compound Annual Growth Rate) of the global IVD market until 2021. The main competitors of Roche in the IVD business are Abbott, Danaher, and Siemens (Figure 28).

[30] Roche's presentation titled 'Committed to innovation and growth', August 2017: https://www.roche.com/dam/jcr:9a53ce2d-93f0-4751-948e-5028affe5f34/en/irp20170801.pdf

Roche's market share as well as key competitors' market shares differ between the different Business Areas or product groups. In Table 6, Roche's EEA and non-EEA market shares and competitors' market shares per each affected product group or business are given.

Table 6. EEA and non-EEA market share and competitors per product group / portfolio or business (reference year: 2017).

Use	Product group	Market share		Competitors and their market share***	
		EEA (Unless indicated otherwise)	non-EEA (Unless indicated otherwise)	EEA (Unless indicated otherwise)	non-EEA (Unless indicated otherwise)
Use 2&3 Use 4	CC	Enzymes: 31% Proteins: 38%	Enzymes: 17% Proteins: 25%	Enzymes: Competitor1 21% Competitor2 14% Competitor3 9% Proteins: Competitor1 18% Competitor2 14% Competitor3 7%	Enzymes: Competitor1 17% Competitor2 14% Competitor3 5% Proteins: Competitor1 29% Competitor2 18% Competitor3 8%
	DM°	21%	14%	Competitors 1+2+3 71%	Competitors 1+2+3+4+5+6 71%
Use 2&3	HIV	[redacted]%	[redacted]%	EMEA: Competitor1 30.% Competitor2 16% Competitor3 9.8% Competitor4 5.9%	Global: Competitor1 26.5% Competitor2 9.7% Competitor3 8.8% Competitor4 5.5%
Use 3	BGE	12%	7%	Competitor1 30% Competitor2 5% Competitor3 18% Competitor4 15%	Competitor1 30% Competitor2 21% Competitor3 18% Competitor4 15%
Use 2&3 Use 4	AT	4.4%°°° (in dedicated primary markets)	1.1% (in dedicated primary markets)	Competitor1 21% Competitor2 34%	
Use 2&3	UA	18.5%	7%	Competitor1 24.7%	Global: Competitor1 16.8% Competitor2 13%
Use 3	RMD1	10% (EMEA)		Competitors 1+2+3 90%	Not applicable
	RMD2	12% (PCR market only) (Projection for 2021)°°	Not applicable	Competitor1 82% Competitor2 9% Competitor3 4% (PCR market only, 2017)	Not applicable

Use	Product group	Market share		Competitors and their market share***	
		EEA (Unless indicated otherwise)	non-EEA (Unless indicated otherwise)	EEA (Unless indicated otherwise)	non-EEA (Unless indicated otherwise)
Use 3	RTD	42%	23%	Competitor1 25% Competitor2 27% Others 3%	Competitor1 49% Competitor2 17% Competitor3 8%
Use 4	TM	Single analyte of a whole panel. The market share cannot be assessed.	Single analyte of a whole panel. The market share cannot be assessed.	Not applicable	Not applicable
Use 4	CB (proteins)	1-30%* (depending on product and market)	1-30%** (depending on product and market)	CC IVD test material: Competitor1 30% IPC Pharmaceutical manufacturing: Competitor2	
	CB MDx			Competitor1 15-20% Competitor 2 15-20% Competitor3 15-20% Competitor4 15-20%	

°This information is valid for the whole portfolio.
°° Two major technologies make up MRSA testing: Culture & PCR. However, Roche (RMD) historically only looks at PCR competition only thus RMD2 sales will be approximately 12% of PCR MRSA sales.
°°°This information is valid for the whole PoC Business.
*** Note that the terms '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.

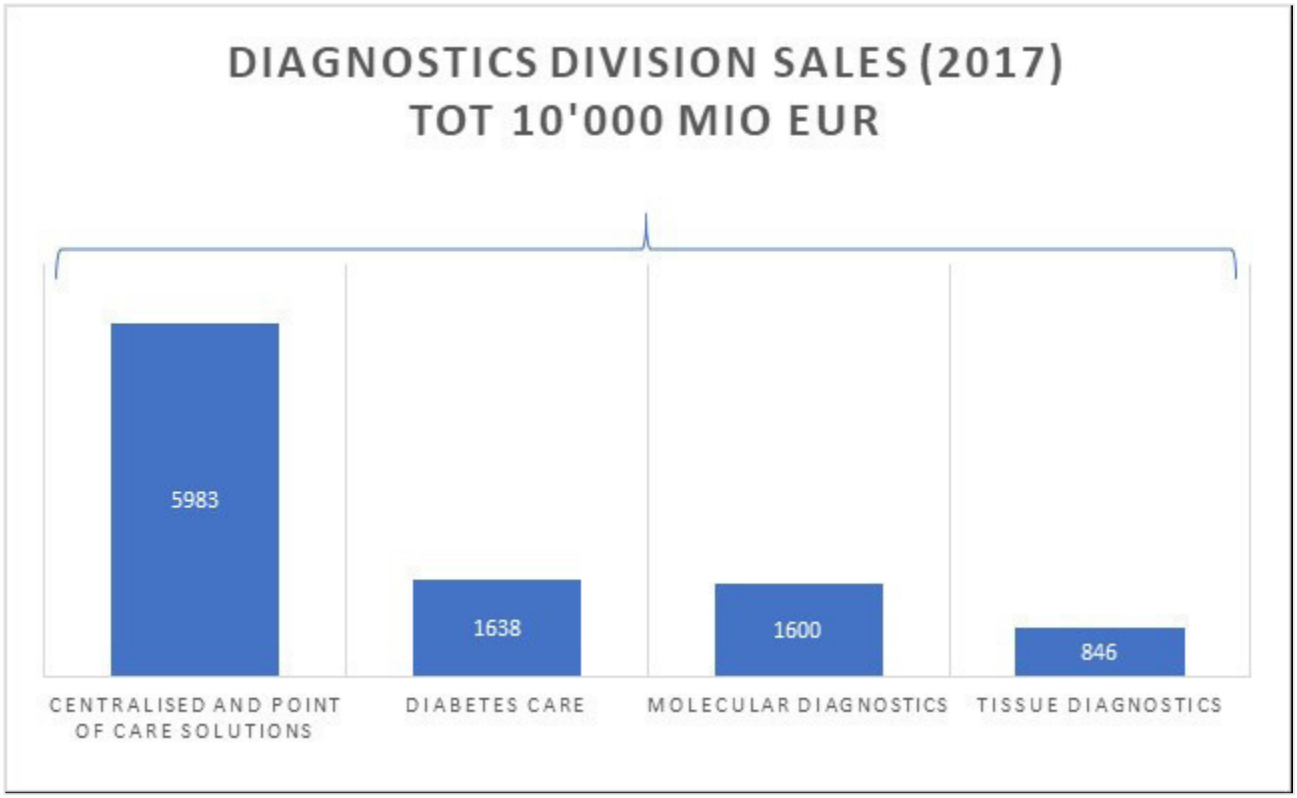


Figure 29. Sales of the Roche Diagnostics Division for 2017 in mio EUR.

Figure 29 shows the results of the Roche Diagnostics Division for 2017. The Diagnostics Division continued to increase sales with growth of **5%** at CER (Coupon Equivalent Rate[31]) to 1010 billion EUR primarily due to immunodiagnostics sales (13% growth) [32].

The Diagnostics Business depends on the use of OPnEO / NPnEO for Use 2&3 and Use 4 which contribute about [redacted]**%** of sales considering the **entire portfolios** that are depending on the affected assays. To illustrate the contribution of the affected portfolios for the EEA and non-EEA market, Table 7 shows the sales per affected group for EEA and non-EEA in mio EUR for the year 2017 (reference year for the baseline data in this SEA). Table 8 shows aggregated earnings before interest, taxes and amortization (EBITA) data per use for EEA and non-EEA for the same year.

[31] CER = ((Market Price - Face Value) / Market Price) * (365 / Days until Maturity).
[32] Roche Website, 'Investor Update', 1 February 2018: https://www.roche.com/dam/jcr:8476522e-ecb4-4c65-b91d-4a8301ccb14b/en/180201_IR_FY_release_en.pdf

Table 7. EEA and non-EEA sales per affected product portfolio for 2017 and percentage of total IVD sales in 2017.

Use	Group name	Sales 2017 (mio EUR)		Total*	% of total sales Diagnostics (2017: 10'000 mio EUR[33])
		EEA	non-EEA		
Use 2&3 Use 4	CC DM	[redacted]	[redacted]	[redacted]	[redacted]
Use 2&3	HIV	[redacted]	[redacted]	[redacted]	[redacted]
Use 3	BGE (**cobas® b** 221 only)	[redacted]	Not relevant***	[redacted]	[redacted]
Use 2&3 Use 4	AT	[redacted]	[redacted]	[redacted]	[redacted]
Use 2&3	UA	[redacted]	[redacted]	[redacted]	[redacted]
Use 3	RMD 1	[redacted]	Not relevant***	[redacted]	[redacted]
	RMD2	[redacted]	Not relevant***	[redacted]	[redacted]
Use 3	RTD	[redacted]	Not relevant***	[redacted]	[redacted]
Use 4	TM	[redacted]	[redacted]	[redacted]	[redacted]
Use 4	CB proteins	[redacted]	[redacted]	[redacted]	[redacted]
	CB MDx	[redacted]	[redacted]	[redacted]	[redacted]
TOTAL		[redacted]	[redacted]	[redacted]	[redacted]

*Totals are rounded figures from the exact sum. rounding of the figures might lead to some inconsistencies

** [redacted]

***As these products are produced outside the EEA, tests in non-EEA are not affected by this AfA; Therefore, no figures are given.

[33] Roche Website, 'Roche Financial Report', 2017; https://www.roche.com/dam/jcr:b70415c0-954f-4a2a-a0e2-47f94bd280e0/en/fb17e.pdf

Table 8. EBITA aggregated per use for 2017 for the affected product portfolios.

Use	EBITA 2017 (mio EUR)		
	EEA	non-EEA	Total
Use 2&3*	[redacted]	[redacted]	[redacted]
Use 4*	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]

*EBITA for portfolios affected by Use 2&3 and Use 4 was attributed equally to each use (i.e. 50:50).

Figure 30 shows the historical, but also predicted sales for the different portfolios demonstrating the expected development assuming the continued use OPnEO / NPnEO. Again, figures are based on entire affected portfolios. For TM, China is the main driver of these sales and this assay accounts for ca. [redacted]**%** of the total Lung Cancer assay **sales** ([redacted] mio EUR). Overall the development over the last 10 years is expected to continue for this assay. For HIV / Infectious Disease (connected with HIV combi PT) [redacted]. The main drivers of the total sales development are CC/ DM and HIV / Infectious Disease. Figure 30 shows the historical, but also predicted sales for the different portfolios without the main driver CC / HIV.

Figure 30. Historical and predicted sales development for the product portfolios affected by Use 2&3 and Use 4.

Figure 31. Historical and predicted global sales development for the product portfolios without the data for CC / HIV.

Figure 32. Historical and predicted global sales development for the affected products.

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 33). Therefore, the core of Roche's business is indeed the sales of the assays.

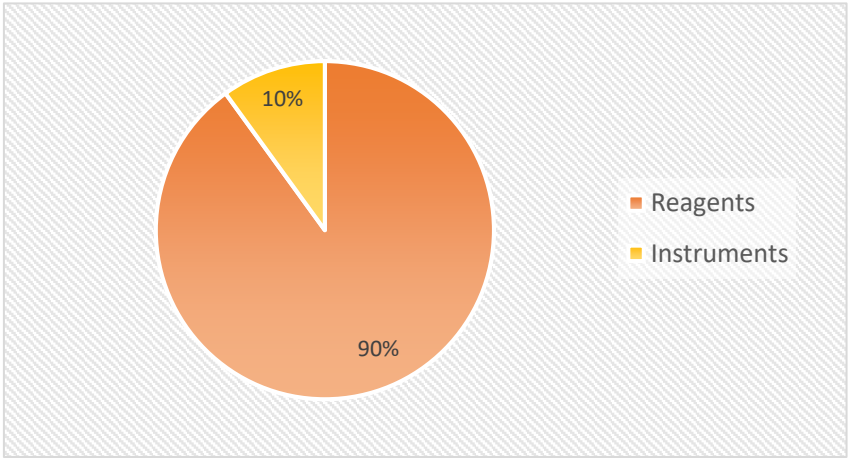


Figure 33. Assays - Contribution of reagents and instruments to the turnover.

2.8.2 Employment

- ⇨ A total of **712 employees** (in EEA and non-EEA) are dedicated to the Diagnostics businesses affected by this authorisation as a conservative estimate.
- ⇨ Under the 'applied for use scenario', RDG will continue to be an important employer in Germany.

RDG has estimated that a total of **712 employees** (in EEA and non-EEA) are dedicated to the **Diagnostics businesses affected** by this AfA (see Table 9). This does not include employees, e.g. at affiliates and only partially includes employees e.g. in the sales organisation or further supporting functions. Therefore, the number is a conservative estimate. Under the applied for use scenario, RDG will therefore continue to be an **important employer in Germany**.

Table 9. Number of employees affected by this AfA.

Use	Product group	Number of employees for Diagnostics (Location)	Additional considerations
Use 2&3 Use 4	CC	54*	Production in Mannheim and Penzberg including protein production processes
	DM		
Use 2&3	HIV		
Use 2	TM		
Use 2&3 Use 4	AT		
Use 3	BGE	70 (Rotkreuz, Switzerland)	Additional 100 indirect employees need to be taken in in account. This is the number of employees at affiliates for Diagnostics sales (data available only for BGE).
Use 2&3	UA	60 (global)	Estimates at the global organization and represents 100% work for the Urinalysis Business
Use 3	RMD1	200 (global)	Additional employees are part of support functions (for examples sales, marketing, training and service personnel in the affiliates).
Use 3	RMD2	0**	Employees may begin to work on another product launching in 2020
Use 3	RTD	28	Includes all positions at RTD; assumption took % of RTD sales that are attributed to ISH products in EEA that would be impacted, used this percentage to define number of employees impacted (EEA ISH product revenue as % of RTD revenue x total number of RTD employees.)

Use	Product group	Number of employees for Diagnostics (Location)	Additional considerations
Use 4	CB (protein)	300	Excluding the production of proteins in Penzberg
Use 4	CB (MDx Enzymes)		Not applicable
TOTAL		**712**	The total number of jobs affected in EEA: 414 (without jobs for BGE, RMD, RTD produced outside the EEA)

* Figure only covers the employees directly involved in production.
**The product was launched in December 2018. The number of employees was not yet available at the time of submission of the dossier.

2.8.3 Customers

- ⇨ Roche offers different types of solutions to a variety of customers such as hospital laboratories, commercial laboratories, blood banks or doctor's practices. 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**. In the EEA, 22 affiliates are covering at least 24 of the EEA countries, among them all larger countries. In the EEA, more than 10'000 instruments are installed.
- ⇨ Under the 'applied for use scenario' CB's customers, i.e. IVD manufacturers and biopharmaceutical manufacturers will also be able to continue to provide IVD-kits and safe medicines to the market based on continued supply of raw materials from Roche.

Roche offers different types of solutions as described in Section 2.6, targeted at **different kinds of customers** such as hospital laboratories, commercial laboratories, blood banks or doctor's practices. Table 10 provides an overview of the type of Roche customers per product group. In the **EEA > 10'000 instruments** are currently installed (for details on instruments per country see supporting document 1 'SD1_SEA_Nr_Instruments_RDG_Use2-4_CONFIDENTIAL'). Depending on the customers, one customer may use a **single** instrument (e.g. for PoC) or have **2 to 15** instruments installed (e.g. for centralised laboratories). Roche's Custom Biotech business unit supplies industrial customers, i.e. IVD manufacturers and biopharmaceutical manufacturers with raw materials such as proteins and MDx Enzymes (depending on Use 4).

Roche sells its products via country **affiliates**. In the **EEA**, **22 affiliates** are covering at least 24 of the EEA countries, among them all larger countries. In **non-EEA**, Roche sells its products through **35 affiliates** worldwide. With a few exceptions, the affected product groups are sold through all EEA affiliates.

Under the 'applied for use scenario', **Roche will be able to continue to supply the market** (hospital laboratories and commercial laboratories), with CC and other IVD assays. Also, Roche will be able to **continue to supply** IVD manufacturers and biopharmaceutical manufacturers with raw materials.

These industrial **customers will be also able to continue their production and sales** of IVD-kits (mainly CC), and further products that depend on the proteins supplied by Roche. Regarding the raw materials used in the pharmaceutical production sold by CB, under the 'applied for use', the biopharmaceutical manufacturers will be able to operate 'as usual' and provide medicines to the healthcare system.

Under the 'applied for use scenario', hospital laboratories, commercial laboratories will be able to operate '**as usual**' and **provide health services** to patients. This is relevant for Use 2&3 and Use 4.

Table 10. Estimation of number of instruments in EEA and non-EEA per each product group (for CB: number of customers).

Use	Group name	Type of customer	Estimation of number of instruments	
			EEA	non-EEA
Use 2&3 Use 4	CC DM	Hospital laboratories commercial laboratories	[redacted]	[redacted]
Use 2&3	HIV	Hospital laboratories commercial laboratories blood banks	[redacted]	[redacted]
Use 3	BGE	Hospital laboratories commercial laboratories doctor's practices	[redacted]	[redacted]
Use 2&3 Use 4	AT	Hospital with ambulatory care settings doctor's practices	[redacted]	[redacted]
Use 2&3	UA	Hospital laboratories commercial laboratories doctor's practices lay users (patients)	[redacted]	[redacted]
Use 3	RMD1	Hospitals Walk-in clinics	[redacted]	Not relevant***
	RMD2	Hospital Microbiology laboratories	[redacted]	Not relevant***
Use 3	RTD	Reference laboratory Hospital laboratories Commercial laboratories	[redacted]	Not relevant***
Use 4	TM	Hospital laboratories commercial laboratories cancer clinics	Same instruments as for HIV	Same instruments as for HIV
Use 4	CB (proteins)	IVD manufacturers Biopharmaceutical manufacturers	[redacted]	[redacted]
Use 4	CB (MDx Enzymes)	IVD manufacturers, Diagnostic service laboratories	[redacted]	[redacted]

*Reference laboratories: is a large laboratory that performs staining for other clinical sites who do not have the infrastructure to do so themselves.
**Visual reading not considered.
***As these products are produced in outside the EEA, tests in non-EEA are not affected by this AfA; Therefore, no numbers are given.

2.8.4 Patients

- ⇨ The overall number of affected tests provided by Roche performed worldwide ranges roughly between **2'000-3'000 mio tests** per year.
- ⇨ This leads to a **benefit for an estimated 200-300 mio patients per year**.
- ⇨ Under Use 4, the benefits to patients are streaming from both the products produced by RDG (e.g. IVD kits) and the ones produced by Roche's industrial customers, all depending on RDG's proteins.

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 and processes. These affected assays are run up **2'000-3'000 mio tests per year** (see Table 11). Assuming on average 10 tests per patient annually, this would result in **200-300 mio patients per year** that benefit from these tests.

For Use 4, it is important to bear in mind that there are additional **benefits streaming** from the products produced by RDG and commercialised by Roche's industrial customers. Among these products are IVD assays, especially in Clinical Chemistry with similar **benefits for healthcare** and therefore patients as described for RDG's CC portfolio. There are some medicines manufactured by Roche's industrial customers, which depend on quality raw material produced with RDG's proteins thus also providing health **benefits for patients** (see Table 12**)**.

Table 11. Current number of tests (directly affected assays only) performed per year.

Use	**Product group**	**Affected assays – current number of tests [mio / a] (in 2017)**	
		EEA	**non-EEA**
Use 2&3 Use 4	CC	[redacted]	[redacted]
	DM	[redacted]	[redacted]
Use 2&3	HIV	[redacted]	[redacted]
Use 3	BGE	[redacted]	Not relevant*
Use 2&3 Use 4	AT	[redacted]	[redacted]
Use 2&3	UA	[redacted]	[redacted]

Use	Product group	Affected assays – current number of tests [mio / a] (in 2017)	
		EEA	non-EEA
Use 3	RMD1	[redacted]	Not relevant*
	RMD2	[redacted]	Not relevant*
Use 3	RTD	[redacted]	[redacted]
Use 4	TM	[redacted]	[redacted]
Use 4	CB (proteins)	No data available**	No data available**
	CB (MDx Enzymes)	No data available**	No data available**
Total		**[redacted] (1'000-1'500)**	**[redacted] (1'000-1'500)**

* As these products are produced outside the EEA, tests in non-EEA are not affected by this AfA; Therefore, no numbers are given.
** Number of IVD assays produced by CB's customers based on RDG's proteins and enzymes are not known to RDG due to confidentiality.

Table 12. Overview of the health benefits for each product group.

Use	Product group	Function	Benefits to society
Use 2&3 Use 4	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. • Used in **screening for drug abuse** in a **working place** or **legal context**.	• Quick diagnosis in life-threatening conditions involving drug abuse. • Workplace drug testing greatly enhances health and safety in the workplace. • 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

Use	Product group	Function	Benefits to society
		• Used for confirming **adherence to replacement drugs**. • Used to **fine-tune therapeutic drug use** in patients.	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.
Use 2&3	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.
Use 3	BGE	• Provides a **critical care test set** required in intensive care units (ICU), emergency departments (ED), neonatology, etc.	• Quick diagnosis in life-threatening conditions.
Use 2&3 Use 4	AT	• Determines important cardiometabolic parameters for the **monitoring of metabolic disorders** and **cardiovascular risk factors** in patients.	• Aids for timely adjustment of treatment in patients, thereby improving quality of life and even life expectancy. • Helps in screening for risk factors, thereby improving early start of treatment and hence patient outcome.
Use 2&3	UA	• Used in the detection of **pathological changes** in **urine** for the screening for e.g. urinary tract infection, kidney dysfunction or diabetes.	• Aids for timely diagnosis and treatment of infections/diseases resulting in changes in urine composition, thereby improving patient outcome and reducing healthcare costs.
Use 3	RMD1	• Quick diagnosis of patients with influenza (Liat® can provide a result in 20 min).	• Prevents the spreading of influenza by diagnosis of patients / allows for the control of epidemies. • Provides information for epidemiologists involved in establishing the composition of influenza vaccines. • Overall contributes to the reduction of influenza-related deaths and influenza-related deterioration of the conditions of patients with poor health condition.
	RMD2	• Allows live cell molecular diagnostics that quickly identifies multidrug-resistant organisms (MDROs) and	• Quicker delivery of result leads to timely treatment which can reduce the risk of mortality due to MDROs.

Use	Product group	Function	Benefits to society
		assesses antibiotic susceptibility.	
Use 3	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.
Use 4	TM	• Provides **early markers** for the detection of lung cancer.	• Allows accurate and quicker delivery of results to the physician leading to an earlier start of treatment.
Use 4	CB (proteins)	• Produced proteins are used in a range of IVD products mainly in Clinical Chemistry.	• Similar benefits to society as the ones listed for Roche's IVD assays.
Use 4	CB (MDx Enzymes)	• Produced enzymes are used in a range of IVD products mainly in Molecular Diagnostics.	• Similar benefits to society as the ones listed for Roche's IVD assays.

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 / processes.
- ⇨ **Total investment cost** for the likely scenario is **ca.** [redacted] **mio EUR** for the products covered under **Use 2&3** and ca. [redacted] **mio EUR** for the processes under **Use 4**.
- ⇨ A **review period of 7 years** is needed from the **sunset date to complete substitutions** taking into account **risks associated with the timelines**.

RDG's R&D department is currently **working on the complete substitution of OPnEO / NPnEO** in Use 2&3 and 4. As described in the AoA substitution projects are already ongoing and OPnEO / NPnEO have already been replaced in several products / processes. In the applied for use scenario, RDG will continue this process until substitution is completed. RDG is and will be investing a large amount of resources into this change process. The estimated **investment costs** for the substitution are given in Table 13 considering the likely and worst-case scenario regarding regulatory requirements for substitution which are an important driver for cost.

Total investment cost for the likely scenario is ca. [redacted] **mio EUR** for the products covered under Use 2&3 and 4. 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 EUR**. The cost includes cost for the required personnel to perform the projects or the clinical studies (e.g. for HIV).

Table 13. Substitution: investment costs including cost for required personnel.

Use	Product group	Cost (mio EUR)	
		Likely scenario	Worst-case scenario*
Use 2&3 Use 4	CC	[redacted]	[redacted]
	DM (incl. process group 3)	[redacted]	[redacted]
Use 2&3	HIV	[redacted]	[redacted]
Use 3	BGE[c]	[redacted]	[redacted]
Use 2&3 Use 4	AT (cost for products based on process change negligible)	[redacted]	[redacted]
Use 2&3	UA	[redacted]	[redacted]
Use 3	RMD1	[redacted]	[redacted]
	RMD2		
Use 3	RTD	[redacted]	[redacted]

Use	Product group	Cost (mio EUR)	
		Likely scenario	Worst-case scenario*
Use 4	Process Group 1 (Use 4), protein processes incl. most important downstream products	[redacted]	No need for a market authorisation / re-registration (except for CYFRA)
Use 4	Process Group 2 (Use 4) MDx Enzyme processes incl. most important downstream products	[redacted]	[redacted]

* Re-registration to obtain market authorisation.
[a] Scenario for a development of an HIV assay on all instruments.
[b] Scenario if there are two developments. [redacted]
[c] Due to phase-out of the affected product based on existing contracts, no additional cost for substitution project.
[d] Cost for likely and worst-case are the same re-registration is needed for these products (AT under Use 2&3).

The following figures summarise the **planned and worst-case substitution timelines** (for more details please consult the respective AoA):

- The estimated timelines for replacement of the Use 2&3 (including the latex bead conjugation for DM assays, Process Group 3 / Use 4) is depicted in Figure 34.
- The estimated required time to complete the substitution program for Process Group 1 / Use 4 is shown in Figure 35.
- The estimated required time to complete the substitution program for Process Group 2 / Use 4 is shown in Figure 36.

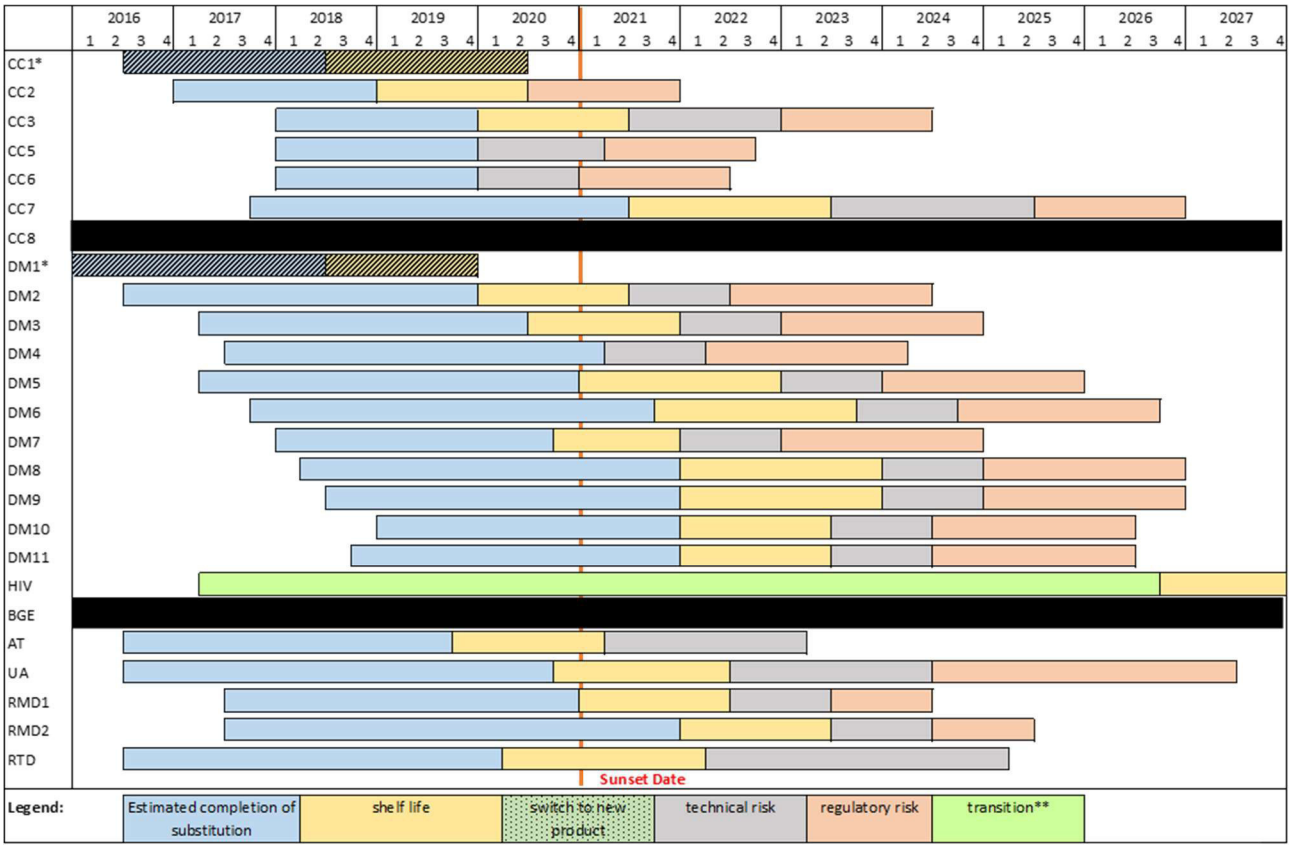


Figure 34. Planned timelines for Use 2&3 (including Process Group 3 / Use 4).

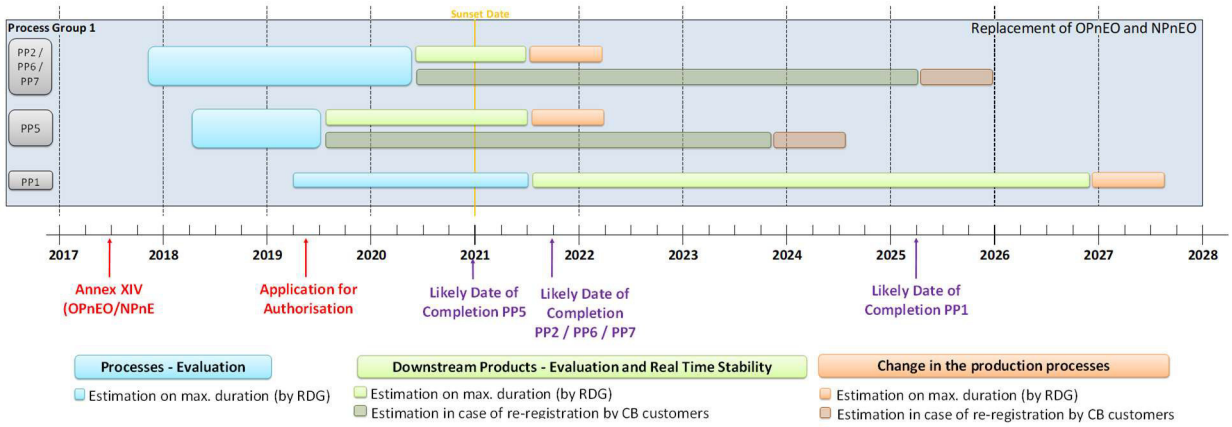


Figure 35. Graphical illustration of the expected maximum durations and worst-case scenarios for replacement of OPnEO / NPnEO within the production processes PP2 / PP6 / PP7 (Roche downstream products: CC / DM), PP5 (Roche downstream products: AT) and PP1 (Roche downstream products: TM) for process group 1 (Use 4).

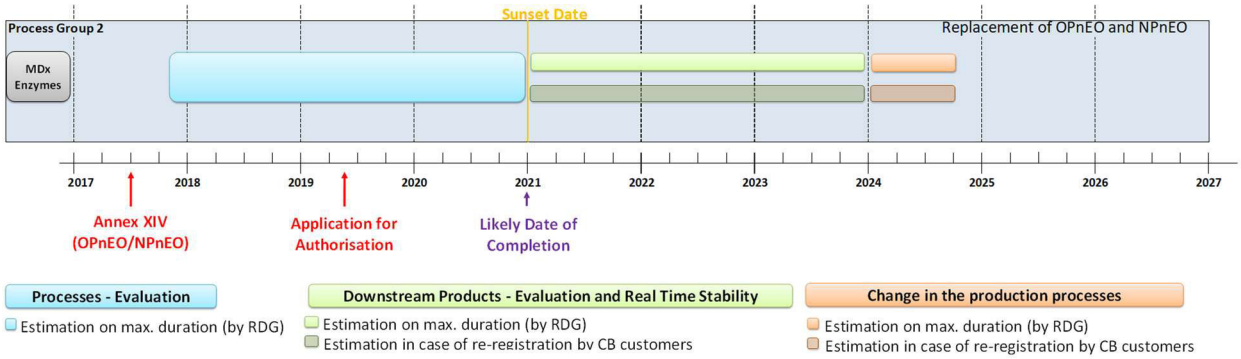


Figure 36. Graphical illustration of the expected maximum duration for replacement of OPnEO/NPnEO within the process group 2 (Use 4).

The timelines include planned substitution dates as well as **technical and regulatory risks** associated with the substitution projects. For substitution in the processes (Use 4), the downstream products must be **validated** and ready for introduction to the market before the corresponding process can be switched to OPnEO / NPnEO-free. If a downstream product fails in the testing, the existing process with OPnEO or NPnEO needs to be maintained to allow further research and development on a process with a suitable substitute.

In conclusion, the AoAs explain the unique technical and regulatory challenges associated with validating alternatives for products (Use 2&3) and processes (Use 4). A **7-year review period** will allow RDG to complete the evaluation of alternatives, validate and assure performance of the affected products, including downstream products of processes, and if necessary, submit change notifications as a regulatory requirement for *in vitro* diagnostic assays. RDG is committed to **substitute OPnEO / NPnEO as fast as possible for each individual product and process**. However, RDG has concluded **that any review period shorter than 7 years** would not be sufficiently long for completing the substitution of OPnEO and NPnEO in all processes and products taking into account the associated risks in the timelines.

.

2.8.6 Emissions and Risk Management Measures

⇨ Under the the 'applied for use scenario', RDG will continue to use OPnEO and NPnEO to produce the IVD assays or proteins and conjugate the latex beads **until substitutions are completed.**

⇨ The maximum yearly used amount and therefore amount applied for is:
- **1434 kg/a OPnEO / 219 kg/a NPnEO for Use 2 and 4** at the production sites
- **646.3 kg/a OPnEO / 54.8 kg/a NPnEO for Use 3** at the downstream users

In the 'applied for use scenario', RDG will continue to use OPnEO and NPnEO to produce the IVD assays or proteins and conjugate the latex beads until substitutions are completed. Substitution projects to replace these substances in all assays and processes will continue in order to achieve substitution as fast as possible (see further information in the AoAs for Use 2&3 and Use 4 and Section 2.8.5). RDG's customers will continue to the use the IVD assays with OPnEO / NPnEO until the OPnEO / NPnEO-free assays are received from RDG. In Table 14 the **maximum used amount of OPnEO and NPnEO after the sunset date** at the production sites of Mannheim and Penzberg and for at downstream user sites is given. This corresponds to the **amount applied for**.

Table 14. Maximum yearly amount of OpnEO and NPnEO used at the production sites of Mannheim and Penzberg (Use 2 and 4) and for downstream uses (Use 3).

Maximum used amount kg/a after the sunset date for formulation (Use 2), products (Use 3) and processes (Use 4)	**OPnEO**	**NPnEO**
Use 2	1326	217.4
Use 4	107.6	2.32
Total production sites	**1434**	**219**
Use 3*	646.3	54.8

*Note that amounts used for Use 3 are a fraction of the amounts employed for Use 2.

Yearly used amounts are not expected to surpass the amounts used at the sunset date due to completed substitutions (see Table 16 and Table 17). An **overview of releases of OP and $NP_{equiv.}$ to surface water** and soil at the sunset date and over the course of the review period from the different uses is given Section 3.1.3. Additionally, an overview of the risk management measures in order to minimise the releases of OPnEO and NPnEO to wastewater from the different uses is provided also in Section 3.1.3.

2.9. Definition of 'Non-Use' Scenario

The purpose of this section is to describe the reaction of RDG in case of refusal of authorisation after the sunset date of 4th of January 2021. In Table 15 an **overview of the non-use scenarios** and their **feasibility** is given.

Table 15. Overview of the feasibility of the non-use scenarios considered in this AfA for Use 2&3 and Use 4, separately.

Option	Feasibility (valid for all uses)	Justification for the feasibility claim	
		Use 2 & 3 (formulation and products)	**Use 4 (processes)**
Stock-building	No	- Where possible only temporary solution (up to few years). - Limitations due to product properties (e.g. product shelf life). - Not possible at short notice.	
		- Difficulties to expand the production capacity - Logistic difficulties	- CB: theoretical stock-building at customer sites feasible but limited (due to e.g. space limitations and shelf life)
		=> not technically feasible	
Relocation of production outside the EEA	No	- Time consuming / not possible at short notice - Required infrastructure not available - Large transfer costs	
		- Market authorisation required	
		=> **not economically and technically feasible / not feasible due to time constraints**	
Replacement by material / product from a third party	No	- Production capacity limitations of third parties - Time constraints	
		- Compatibility problem - Availability - Possible price increase - No certainty to acquire OPnEO / NPnEO free products - Market authorisation required	- Manufacturer with the necessary technical know-how (e.g. quality standards) - Disclosure of proprietary information
		=> **not feasible for compatibility and technical reasons**	
Replacement by other RDG 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 Applicable
		=> **not (yet) feasible option due to time constraints and costs**	
Replacement with an alternative surfactant	No	-Ongoing approach for substitution but cannot be completed before the sunset date for all products and processes	
		=> **not yet feasible due to time requirements**	

2.9.1 Use 2&3

⇨ Under Use 2&3, in case of refusal of authorisation RDG will **not be able to continue the production of the affected products.**

⇨ The following alternatives were analysed:

- **Bridging the period of non-use by stock-building** is not possible for most products due to concentrations ≥ 0.1 % w/w. For the other products it is technically not feasible (due to e.g. logistic problems).
- **Relocation of production outside the EEA** is not possible for most products due to concentrations ≥ 0.1 % w/w. It would also not be economically and technically feasible and is not possible within a short timeframe.
- **Replacement by assays from a third party** is considered unrealistic for compatibility reasons (competitors' products are not suitable for RDG closed systems).
- **Replacement by other RDG 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 alternative surfactants is not yet feasible due to time required for substitution.**

For Use 2&3, upon refusal of authorisation and after the sunset date, RDG will **not be able to continue the production of the affected IVD products** (i.e. the products containing OPnEO / NPnEO). The production will need to be interrupted until the necessary steps to switch to reformulated products (i.e. products in which an alternative surfactant) or in certain cases new-generation products (i.e. completely new products or formulations) are completed. This includes successful changes to existing registrations or successful finalisation of entirely new registrations with health authorities for different markets worldwide. It is expected that this process will extend beyond the sunset date of 4th of January 2021 (see timelines described in the AoA Use 2&3 for the products under consideration). An authorisation refusal would therefore imply that there will be a period during which RDG will be not be able to deliver services 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 and lack 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 RDG will have to interrupt production and supply.

It is anticipated that **bridging the period of non-use by stock-building** is not a feasible solution. Firstly, the supply to the EEA market and the use of products containing OPnEO / NPnEO after the sunset date is only possible for products that are not subject to authorisation themselves, i.e. the use of products with a concentration below 0.1% w/w may be continued if stocks can be built before the sunset date. Non-EEA markets could be supplied from stocks after the sunset date considering the shelf life. Note that this only concerns the supply to the market and the use of such products, not the production. Stock building could thus in theory be at least a temporary solution for some, but not all products. However, it would be hampered by practical issues, such as limited shelf life (between a few months and 2 years), the need to expand production capacity and logistic difficulties. Moreover, it must be assumed that not enough time would be available to build stocks before the sunset date as an authorisation refusal may only be known after the sunset date. Furthermore, products are strongly interlinked as discussed in Section 2.7.3 and a selective, continued supply of some, but not all

products is not a viable solution. A consistent approach for all products is therefore needed. Here below an overview per product type is given:

- For the CC and DM portfolio, stock building would not be possible at all for products with concentrations ≥ 0.1% w/w as the use would not be allowed after the sunset date. Only the DM4, CC5, CC6 and CC8 assays (all < 0.1% w/w OPnEO / NPnEO) could in theory apply for stock-building. However, the shelf life of the assays varies between 12-24 months starting at the bulk production, consequently, only a period of several months could be bridged. All these assays are provided to the market for use in analysers by which a wide spectrum of parameters can be determined (e.g. **cobas**® 6000, **cobas**® 8000), and therefore, as stated above, a consistent approach for all assays would be required (i.e. all tests need to remain available).

- For the HIV combi PT assay, the two affected reagents contain ≥ 0.1% w/w OPnEO / NPnEO and therefore stock-building is not an option for the EEA customers.

- For BGE, stock building would not be possible at all for products such as Hb Calibrator since the OPnEO content is ≥ 0.1% w/w and the use would not be allowed after the sunset date. Since BGE assays are provided to the market for use in bench-top analysers by which multiple parameters can be determined (e.g. **cobas**® b 221 system), it is commercially not viable to omit certain assays and to provide bridging solutions for the other assays. For example, if the HB CALIBRATOR could not be supplied any longer, then customers would not be able to use the **cobas**® b 221 system because it is required to determine all analytes from the same patient sample simultaneously.

- For UA products, the affected products are the strips (Combur, Chemstrip, uPack products) containing the PRO test pad. Considering the shelf lives of these strips, a realistic bridging period would be only 3 months. Therefore, stock-building is not feasible as bridging solution. Since the affected urinalysis strips contain multiple assays, here too, a consistent approach for all assays would be required. Additionally, the products contain ≥ 0.1% w/w OPnEO / NPnEO and therefore stock-building is not an option for the EEA customers.

- Similarly, the affected RMD and RTD assays contain ≥ 0.1% w/w OPnEO / NPnEO and therefore stock-building is not an option for the EEA customers.

Relocation of production outside the EEA would not be a viable solution. All affected RDG products (apart from RMD and RTD products, which are produced in the U.S. and BGE products that are produced in Switzerland) are currently only manufactured in the EEA. Production processes are either too complex to be transferred or the cost associated with a transfer of the complete production of the IVD products outside the EEA would be excessively large. Skilled personnel would have to be hired and trained, production facilities would have to be built, complex equipment would have to be installed and validated. Switching the origin of production would also require various validation and market authorisation efforts. Such efforts are not possible on a short-term notice. An estimated timeline for a transfer is at least 5 to 7 years (including re-registration in the markets). For instance, BGE transfer of production to another site had been done in the years 2010-2014 (from Austria to Switzerland). The overall effort lasted 5 years and cost roughly [redacted] mio EUR (for production only). It required installation of new production facilities (buildings, equipment), hiring and training of personnel for the special production requirements. These activities would also require partly the same employees that are currently working on the re-formulation of products and / or processes and could therefore prolong timelines for substitution projects, which will reduce OPnEO / NPnEO releases into the environment on a short to mid-term time scale rather than transferring them to a different location. Further, as RDG increasingly experiences a volume growth of most parameters over time, existing

production facilities must be utilised more efficiently. Therefore, existing production facilities are constantly close to or at their capacity maximum. Eventually, when efficiency increases cannot compensate volume growth anymore new production facilities are built which involves the acquisition of land, the construction of production buildings, the installation of production equipment and the validation of the processes in the new facility. A new production facility for some CC and **Elecsys**® tests for the Chinese and APAC markets is being built in China. However, as stated above, the capacity of this facility is planned to fulfil the growing demand of the APAC market and does not provide capacity to also supply rest of world with products affected by usage of OPnEO / NPnEO.

For several products where the OPnEO / NPnEO concentration is at or above 0.1% w/w, relocation of production outside the EEA would not be an option in any case as the products themselves are subject to authorisation. Similarly, some products currently produced outside of the EEA (e.g. RTD or RMD products) are nonetheless covered in this dossier as their use is subject to authorisation. Furthermore, as products are strongly interlinked (see Section 2.7.3) and several assays are offered to the market in multi-assay packages, a consistent approach is required.

Replacement by material from a third party is also considered unrealistic for compatibility and capacity reasons. In fact, competitors' products are not suitable for RDG closed systems. Examples teach that it takes 3-4 years in general to apply third party products on RDG systems. Moreover, considering RDG's market share, to equate the production of RDG's products affected by this AfA any competitor would probably need to more than double its current production capacity. Assuming that the competitors are operating at near full capacity a material replacement by a third party would be possible only in a few years. Even a joint-venture between RDG and a third party outside the EU would also not be realistic in the current timeframe and would likely have serious long-term implications on the EU production sites and RDG's entire business model. 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 RDG or the risk for third parties to provide their reagents only at very high transfer prices. Moreover, in the unlikely case that the product could be acquired from a third party, there is no certainty that it would be OPnEO / NPnEO free (or, in case manufactured outside the EEA, contain <0.1% w/w OPnEO / NPnEO) and that it would meet RDG quality / performance standards.

Replacement by other RDG 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 between 10 to 20 years (some details are given below). Note that new-generation products or entirely new formulations might have been developed for other reasons than OPnEO / NPnEO substitution and market authorisation may be ongoing already. In such case the new-generation product or entirely new formulation may also contain OPnEO / NPnEO and therefore face the same problem as the products currently on the market. In the exceptional case of RMD1 an alternative RMD product is available that could replace the affected assay (see below). 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), **Accutrend**®, RTD assays and for Urinalysis strips (containing multiple 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 require at least 15 years with existing 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, and will be on the market for another ca. [redacted] which corresponds to the time necessary for substitution to a new generation product. [redacted]. A newer generation assay (HIV Duo) which is OPnEO / NPnEO free has already been developed to run on the new-generation instruments and is currently being introduced to the market. The successor instrument on which the HIV Duo is running (**cobas**® e801) is already launched worldwide. However, the HIV Duo running on this analyser will need additional country specific approval supported by internal and external evaluations (studies). [redacted] launch of this product will depend on the approval from [redacted] that impose a high level of regulations when it comes to HIV testing products. [redacted]. This new solution is only suitable for laboratories requiring high throughput. [redacted]

- For **BGE** products, the HB Calibrator in **cobas**® b 221 system cannot be replaced by another product as it is dedicated to the **coba**s® b 221 system. It is expected that [redacted]% of the **cobas**® b 221 system market in the EEA would be affected if authorisation was not granted. Replacement of all **cobas**® b 221 systems on the market by **cobas**® b 123 POC systems is not feasible because of the cost burden on customers associated with validation of the new system in the hospitals, and because the **cobas**® b 123 POC system addresses a different customer segment. It is expected that only [redacted]% of the customers could be switched to **cobas**® b 123 POC. In addition, this would not be feasible before the sunset date based on existing contracts for **cobas**® b 221 system.

- For Liat® (**RMD1**), the assay can be replaced by another RMD assay, **cobas**® Influenza A / B & RSV (Respiratory Syncytial Virus) which does not contain OPnEO surfactants and is currently available on the EEA market. However, switching to **cobas**® Influenza A / B & RSV is an option that may not be supported by Roche's customers due to higher cost. Therefore, customers may prefer to switch to a competitor's product instead.

A **replacement 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 are ongoing. However, only replacement in some products may be completed by the sunset date (4th of January 2021) for the reasons as outlined in the AoA for Use 2&3.

2.9.2 Use 4

- ⇨ Under Use 4, in case of refusal of authorisation RDG will **not be able to continue the production of proteins and MDx Enzymes and the conjugation of latex beads**.
- ⇨ **Stock-building** to ensure supply for a limited amount of time would need sufficient time to prepare and is therefore in most cases not feasible at short notice.
- ⇨ **Outsourcing** the processes to non-EEA countries is **not considered** as a feasible option due to:
  - Lack of infrastructure for the processes in non-EEA countries.
  - Complexity of the outsourcing process.
  - Time and cost required for a transfer.
- ⇨ **Subcontracting** the production to a third party is **not considered** possible because of:
  - Disclosure of process and pipeline information.
  - Lack of manufacturers that are technically able to take over the production process.
  - Time-consuming re-evaluation of downstream applications.
- ⇨ The alternative considered to be the **most feasible** is **replacement with an alternative surfactant**. However, replacement in all processes cannot be completed until the sunset date.

Under Use 4, in the 'non-use' scenario, RDG will **not be able to produce and supply different enzymes and proteins as well as latex beads for drug monitoring produced with processes requiring OPnEO or NPnEO**. The production / processes will need to be interrupted until the necessary steps to switch to an alternative surfactant are completed. This includes - where required – validation and possibly adapted or new registrations for the different markets, e.g. for IVD assays that rely on the produced enzymes (in the case of CB, this does not apply to the CB Business Area but rather to CB's customers). Therefore, an interruption of the supply of the products relying on the processes is expected until substitution will be completed.

It is expected that completion of validation and possibly new market authorisation for products depending on affected processes (Process Group 1) will become reality, as a worst-case, in 6.5-9.5 years from 2018 (i.e. a few years beyond the sunset date, see timelines described in the AoA). Considering the sunset date (4th of January 2021) this would imply a period of up to 3.5-6.5 years in which RDG would not able to deliver services to the market. It should be noted that the timeline for substitution of OPnEO / NPnEO in the production processes or enzyme formulations will be governed by the downstream products with the longest timelines to complete the change (incl. regulatory requirements). Other alternatives to an interruption of supply, such as relocation (or partial relocation) of production processes outside the EEA, replacement by material from a third party, are not realistic because of reasons listed here below.

However, in the case of no authorisation, RDG would try to **build a stock** to bridge the time period until the substitution is completed. Obviously, this is only possible for processes where the final product does not intentionally contain OPnEO / NPnEO at or above 0.1% w/w. Therefore, this is not possible for the bead conjugation processes. How much time could be bridged by stocks produced before the sunset date is depending on the shelf life of the material resulting out of the process and of the shelf life of the material(s) derived from that by further processing (usually 12 months from

production date). In any case, building bridging stocks would result only in postponing supply shortages, because it will not be possible to create bridging stocks for more than an estimated period of 12 to 24 months. Therefore, based on the timelines for substitution given in the AoA, there would still be up to 2.5-5.5 years of lack of supply to the market.

Furthermore, in order to build a stock to bridge the time period, it would be necessary to know approximately 12 months before the sunset date that stock building is required. If stock building was possible, the period of lack of supply would be reduced by a maximum of 1-2 years. It must be assumed that not enough time would be available to build stocks before the sunset date as an authorisation refusal may only be known after the sunset date. Therefore, lack of supply to the market up to a maximum of 6.5-7 years has to be expected in case the full review period is required to complete substitution (see AoA). In case of the Custom Biotech products, it could be discussed / negotiated with customers how to build a stock at the customer site. However, this would be possible only to a certain degree and would again be limited by shelf life.

A **switch of the processes / formulation to a non-EEA site** is also not possible. Roche has some facilities in non-EEA countries (e.g. U.S.). However, most of the processes could not be transferred to another site since the infrastructure required is not available in terms of certain sizes of bioreactors, reaction vessels, filter units, etc. Moreover, this is a very complex and thus time-consuming and a costly process. The timeline of a transfer, if ever feasible, would be comparable with or longer than the substitution of OPnEO / NPnEO with an alternative surfactant. Therefore, relocation of the processes / formulation is technically not possible and building a new facility outside EEA is not an economically viable option and could not be completed within the required timeline.

To **bridge the period of lack of supply**, it might in principle be considered to subcontract the production of some materials (e.g. enzymes) to a **third party**. It would not be possible to identify in a short period of time a manufacturer with the capacity, technical capability and the quality standards required to produce the material. In addition, RDG would have concerns about performing a technical transfer and disclosing proprietary process and pipeline information to a third party. Even if a suitable third-party manufacturer / supplier could be identified, in most cases, a re-validation of the downstream applications would have to be performed, which would lead to timelines beyond the sunset date. The effort and thus the time needed to switch to the alternative material in this case is estimated to be higher than that required for evaluation of a switch of the established RDG material to an alternative surfactant. Therefore, subcontracting production to a third party is not a feasible option.

Replacement with alternative surfactants is the chosen approach, but not feasible within a short timeframe. Projects to substitute OPnEO / NPnEO by alternative surfactants in the different processes are ongoing. However, only replacement in some processes may be completed by the sunset date (4th of January 2021) for the reasons outlined in the AoA for Use 4.

2.9.3 Conclusion on the Non-Use Scenario for Use 2&3 and 4

- ⇨ Under Use 2&3 and Use 4 upon refusal of authorisation and after the sunset date, RDG will **not be able to continue** the production of the affected products under Use 2&3 and the production based on processes under Use 4 including their downstream applications.
- ⇨ Production and supply to the market will need to be interrupted **until substitutions are completed**.

Under Use 2&3 and Use 4 upon refusal of authorisation and after the sunset date, RDG will **not be able to continue the production of the affected products (Use 2&3) and the production of proteins and MDx Enzymes and the conjugation of latex beads relying on the affected processes (Use 4) including their downstream applications**. The production and 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 - where required - adapted or new registrations for the different markets e.g. for IVD assays that currently contain OPnEO or NPnEO or rely on the produced proteins, enzymes or latex beads. 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

- ⇨ RDG is applying for an authorisation to use OPnEO / NPnEO for a period of **7 years** starting from the sunset date: 4th of January 2021.
- ⇨ **Use 2&3**
  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.
- ⇨ **Use 4**
  All production processes can only be switched when validation of the downstream products is completed, and regulatory approval has been obtained where 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 processes and assays.
- ⇨ **Any review period shorter than 7 years** would not be sufficiently long for completing the substitution of OPnEO and NPnEO in **all processes and products** taking into account the associated risks in the timelines.

RDG is applying for an authorisation to use OPnEO / NPnEO for a period of 7 years starting from the sunset date: 4th of January 2021. This period of time is justified in detail in the AoAs.

Use 2&3

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. In addition, in some cases, change of specific **IVD market authorisations or re-registration** will be needed before OPnEO / NPnEO can be substituted in the products. If a **validation test** for an assay fails, the existing product with OPnEO or NPnEO needs to be maintained to avoid a market gap and allow further research and development on a product with a suitable substitute. Due to the quality and regulatory requirements outlined above, identified alternatives cannot be implemented even if considered in principle 'technically feasible' until validation is completed and, where required, regulatory approval is obtained by the corresponding health authorities.

For most products, the substitution of the OPnEO / NPnEO in the IVD assays by an **alternative surfactant**, is expected to be a **technically and economically feasible alternative**.
Many of these **replacement projects are currently on track** and are expected to be completed on time (see Figure 34 for timelines) with a high likelihood (e.g. RTD and some CC assays). For some CC and DM assays, there is a possibility that the timelines of the **substitution projects** could be **prolonged** until close to the **end of the review period** due to **technical or regulatory difficulties**. In the other cases, a prolongation until the end of the review period cannot be excluded if further difficulties arise but is not very likely. Therefore, it is highly unlikely that the full review period will be needed for substitution in all assays. However, as a worst-case it is assumed in the assessment in the SEA and CSR that all substitutions could be delayed until the end of the review period.

For **two assays** that employ a small portion of the overall amount of OPnEO / NPnEO, **different alternatives are being implemented**.

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

In one other case, **BGE**, support for the complete system will end by [redacted]. Replacement of OPnEO in the HB CALIBRATOR before removal of the market of the cobas® b 221 system may not be possible due to the time required and is not economically viable because of the large efforts involved in verification (including potential technical risks), implementation in production and change registration in China. Roche can provide an alternative system to a part of his clients, but this system is not suitable for all laboratory settings. Due to contractual obligations and to ensure availability of IVD assays for Blood Gas and Electrolyte measurements, the cobas® b 221 system HB CALIBRATOR needs to be supplied until the planned date of removal from the market. This will allow customers to replace their instruments with an alternative provided by Roche or to identify a new suitable alternative system based on their needs.

Use 4

A **large number of potential alternative substances are available** to replace the OPnEO / NPnEO in the processes. In **process group 2**, OPnEO / NPnEO will be **omitted** without replacement. For the processes in **process group 1 and 3**, feasibility studies have **identified technically suitable alternatives**, or it is expected that such alternatives will be identified. Due to the complexity of requirements for the produced proteins and conjugation of latex beads and especially even further requirements for downstream products containing or using the proteins, a **considerable effort** is needed for **process evaluatio**n and performance and **stability testing** of the downstream products (see Figure 35 and Figure 36 for timelines). For some downstream products, changes in the specific **market authorisation** (e.g. IVD authorisation) or possibly **re-registrations** are needed before OPnEO / NPnEO can be substituted in the processes. Therefore, it is not possible to switch processes to OPnEO / NPnEO-free processes even if an identified alternative is considered in principle 'technically feasible' until validation of the downstream products is completed, and regulatory approval has been obtained where required. In case a downstream product containing the protein or the latex beads from the changed process fails in the testing, the existing process with OPnEO or NPnEO needs to be maintained to avoid a market gap and allow further research and development on a suitable substitute in the process.

In conclusion, the AoAs explain the unique technical and regulatory challenges associated with validating alternatives for products (Use 2&3) and processes (Use 4). A **7-year review period** will allow RDG to complete the evaluation of alternatives, validate and assure performance of the affected products, including downstream products of processes, and if necessary, submit change notifications

as a regulatory requirement for *in vitro* diagnostic assays. RDG is committed to **substitute OPnEO / NPnEO as fast as possible for each individual product and process**. However, RDG has concluded **that any review period shorter than 7 years** would not be sufficiently long for completing the substitution of OPnEO and NPnEO in all processes and 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 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.

Further, in the note published by the socio-economic analysis committee (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 RAC and the SEAC, the **following information will be summarised / discussed** in the following subsections:

- Total annual use of OPnEO / NPnEO at production sites and 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 risk management measures.
- 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 CSRs (separate documents for Uses 2, 3, and 4) 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 Production Sites and Downstream User Sites Over Time

- ⇨ The total annual usage at the sunset date was estimated based on **data collected in 2016-2017** and considering the evolution planned between 2017 and 2021.
- ⇨ Since the possibility exists that the ongoing substitution projects run into delays, **two cases** were considered:
  - Case 1 - Decrease in total used amount of OPnEO / NPnEO as expected considering the **planned substitutions** at the production sites.
  - Case 2 - Expected development of total used amount of OPnEO / NPnEO over time considering that **all substitutions at the production sites are delayed** until the end of the review period.
- ⇨ Considering the planned substitutions with no substantial delays, the total annual use of OPnEO and NPnEO **could reach zero in 2022** at the production site of **Mannheim** (which uses the largest amounts of OPnEO and NPnEO). The amount of OPnEO could also reach **almost 0 by 2022** in **Penzberg**. Use of NPnEO in Penzberg will reach 0 by the end of the review period.
- ⇨ At **downstream user sites**, **complete elimination** of the use of OPnEO and NPnEO **is expected by 2024 and by the end of the review period**, respectively.
- ⇨ In case of delays of all substitution projects, the total annual use of OPnEO and NPnEO may only reach zero by the end of the review period.

For the CSRs, the **total annual usage at the sunset date**, considering the worst-case that all substitutions are delayed, serves as a **basis for the exposure assessment**. This was estimated based on **data collected in 2016-2017** and considering the evolution planned between 2017 and 2021. The estimation was also further **extrapolated** to the end of the review period **considering expected sales** development. The total annual usage for both production and downstream user sites is expected to **decrease** over time from 2021 to **reach 0** at the latest **by the end of the review period** due to completion of planned substitutions in the activities covered in the present dossier.

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

- **'All substitutions completed as planned'**: Expected decrease in the total used amount of OPnEO / NPnEO over time considering the planned substitutions at the production sites (see AoA for details).
- **'All substitutions delayed'**: Expected development of total used amount of OPnEO / NPnEO over time considering that all planned substitutions at the production sites (with the exception of the formulation of CC1 and DM1, which were substituted in 2018) are delayed to the end of the review period as a worst-case.

Use 2 – Formulation

Figure 37 and Figure 38 give an overview of the **evolution** of the **total annual use** of OPnEO and NPnEO (respectively) under **Use 2** for each **production site** under both cases (delayed substitutions versus substitutions as planned). Note that there is no production using OPnEO in Penzberg under Use 2.

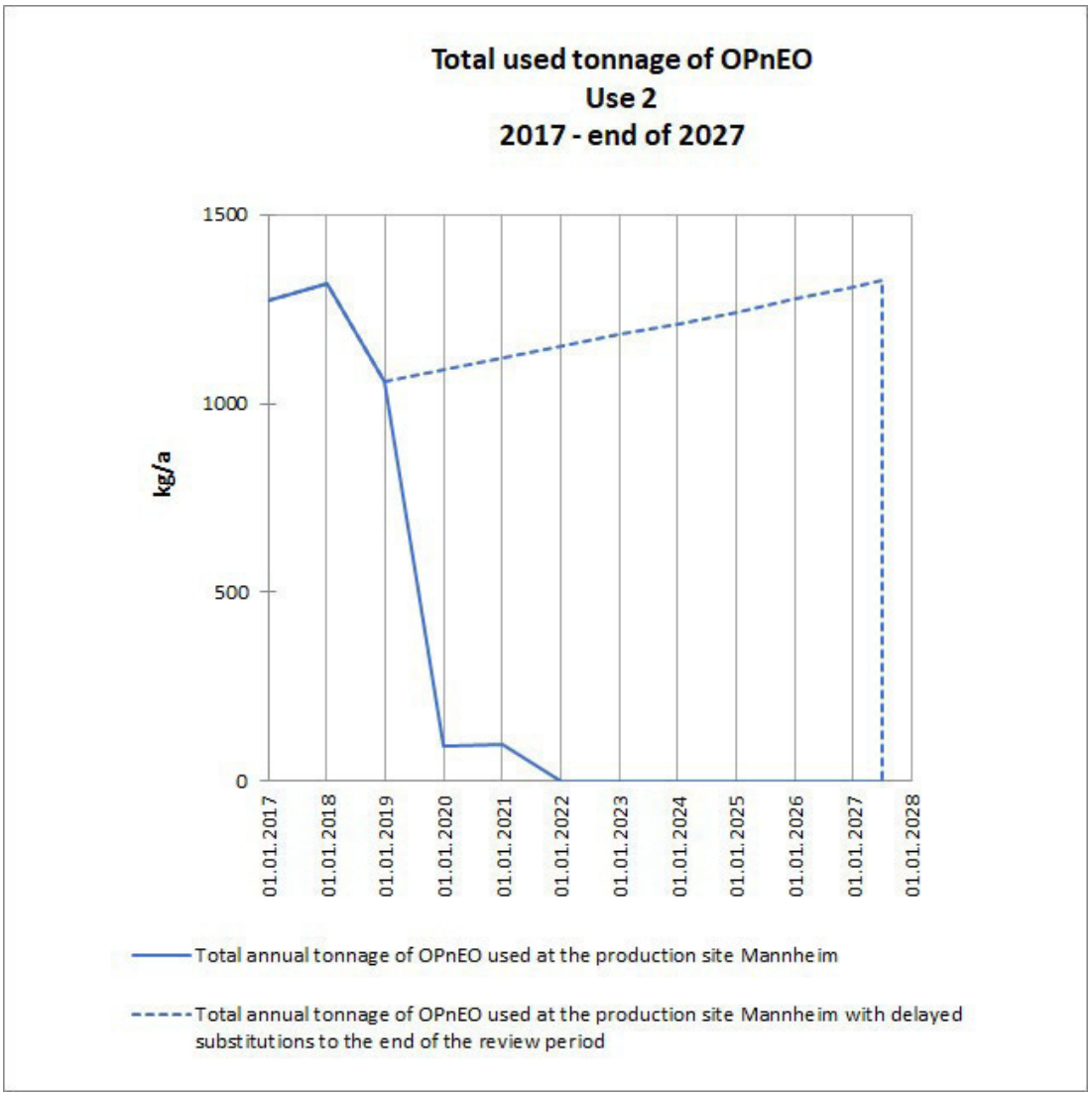


Figure 37. Evolution of the total annual use of OPnEO under Use 2 between 2017 and end of 2027 for the production site of Mannheim, respectively considering planned substitutions and expected sales development.

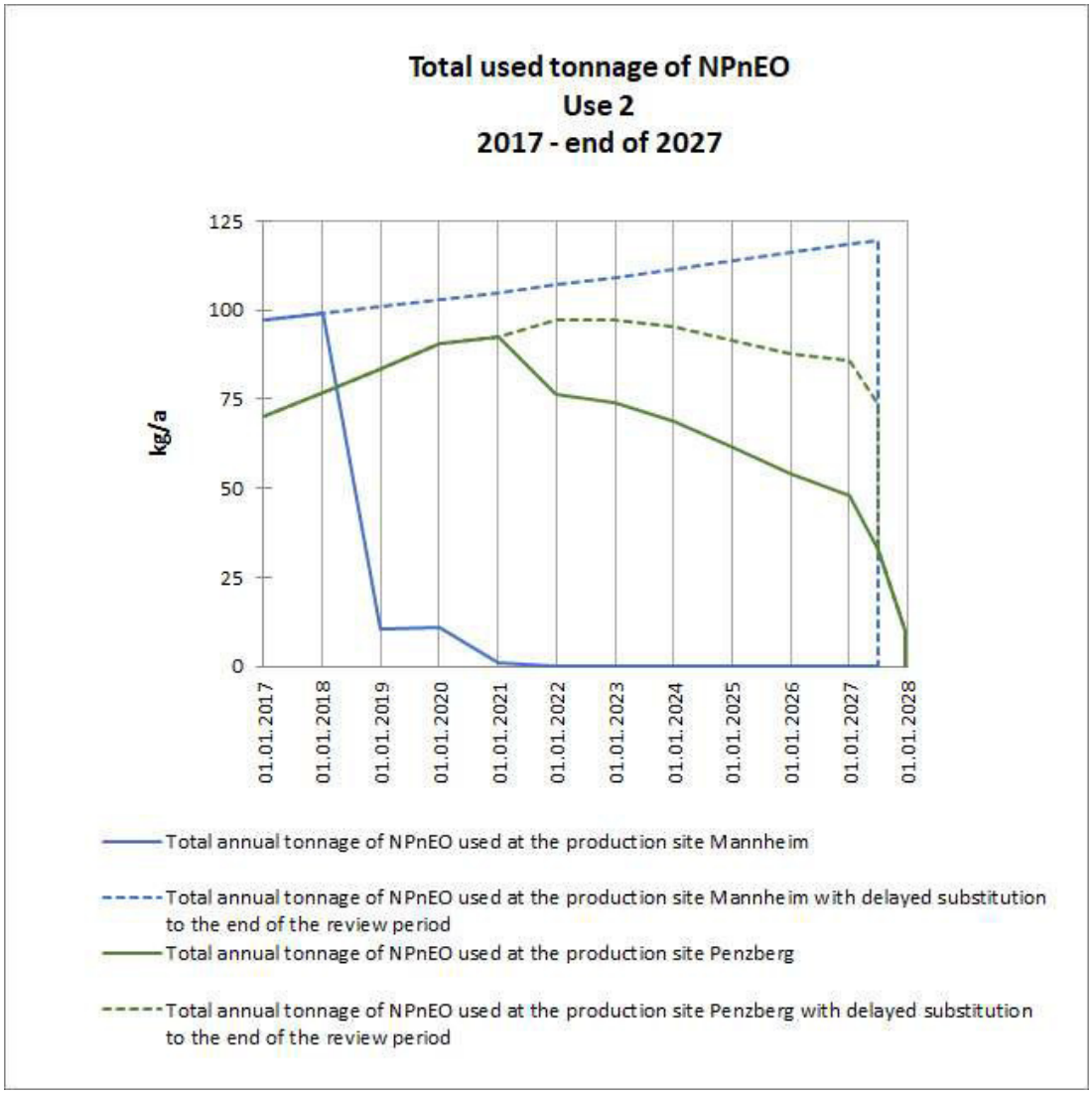


Figure 38. Evolution of the total annual use of NPnEO under Use 2 between 2017 and end of 2027 for both production sites considering planned substitutions and expected sales development.

Use 3 – Products

Figure 39 and Figure 40 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. Note that part of the affected IVD assays are exported outside of EEA. The amounts used in production ending up in final products used in the EEA correspond to the use at downstream user sites in the figures below. However, Use 3 only concerns products that contain OPnEO or NPnEO at or above the cut-off concentration limit for authorisation of 0.1% w/w.

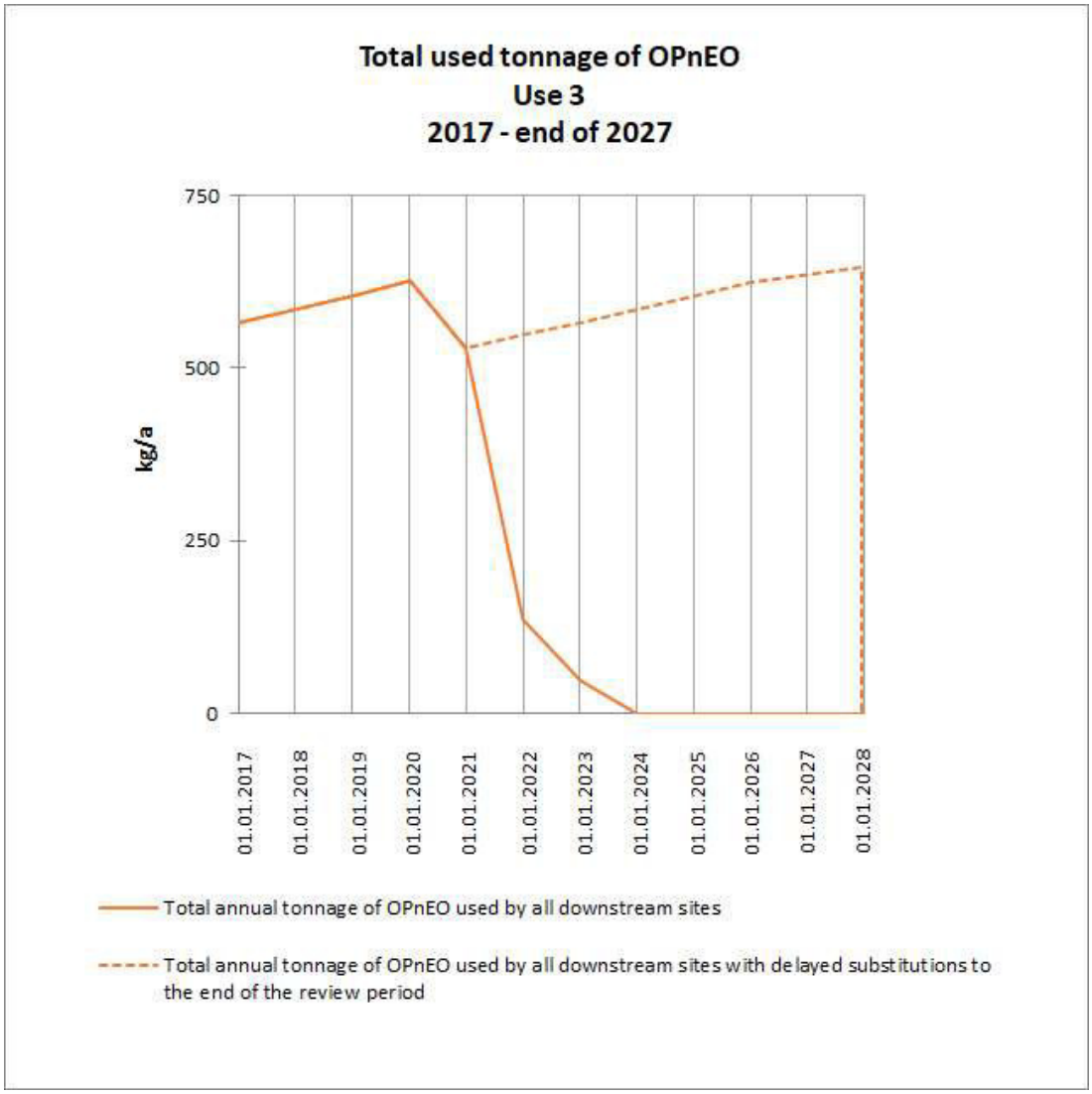


Figure 39. Evolution of the total annual use of OPnEO under Use 3 between 2017 and end of 2027 for the downstream user sites considering planned substitutions and expected sales development.

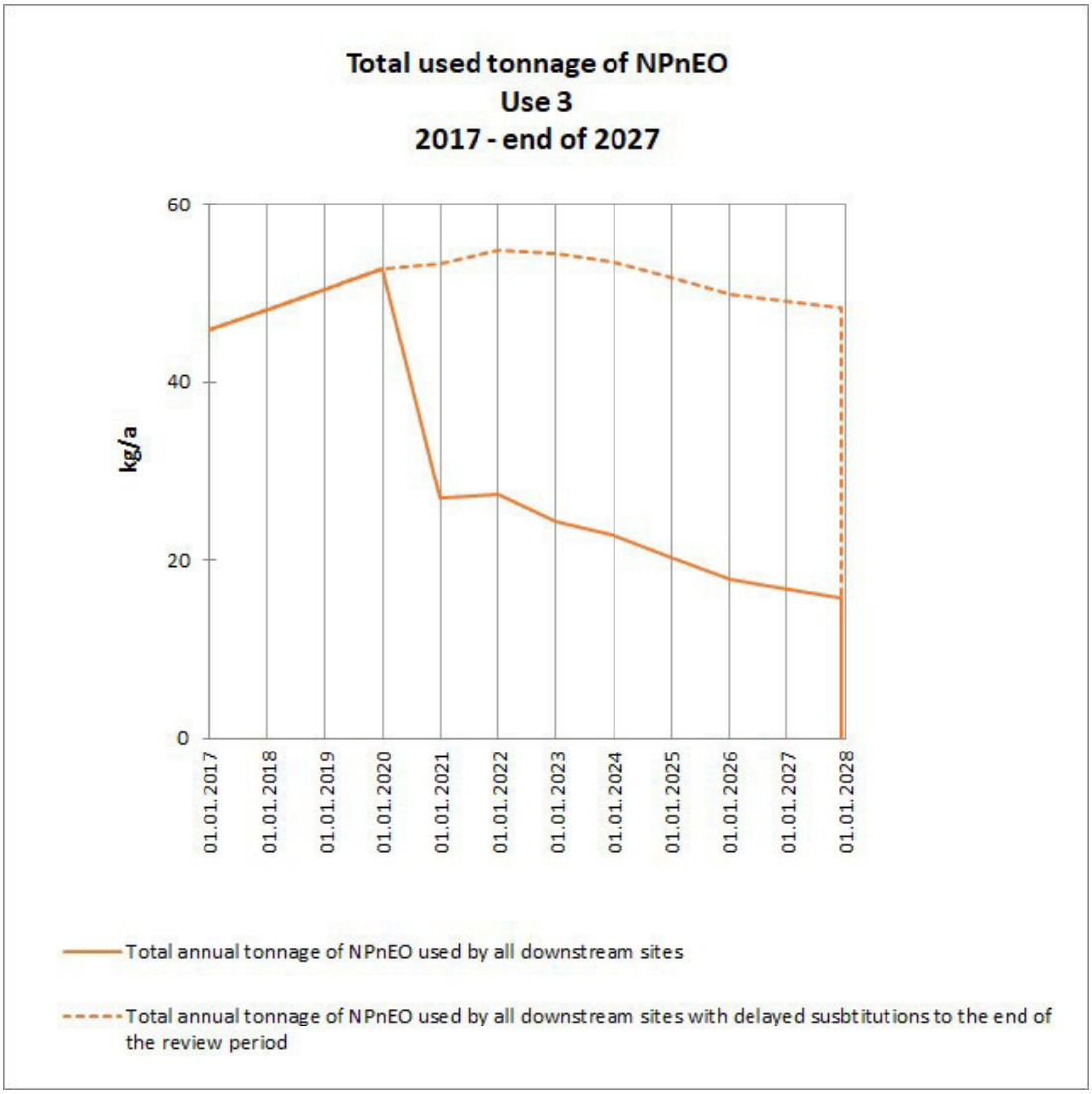


Figure 40. Evolution of the total annual use of NPnEO under Use 3 between 2017 and end of 2027 for the downstream user sites considering planned substitutions and expected sales development.

Use 4 – Processes

Concerning **Use 4**, which covers processes in which OPnEO or NPnEO are used at both of RDG's production sites, the **evolution** of the **total annual use** of OPnEO and NPnEO at the **production sites** of Mannheim (OPnEO only) and Penzberg (OPnEO as well as NPnEO) under the two cases (substitutions delayed or substitutions as planned) is shown in Figure 41 (OPnEO) and Figure 42 (NPnEO). Note that no processes using NPnEO take place in Mannheim under Use 4.

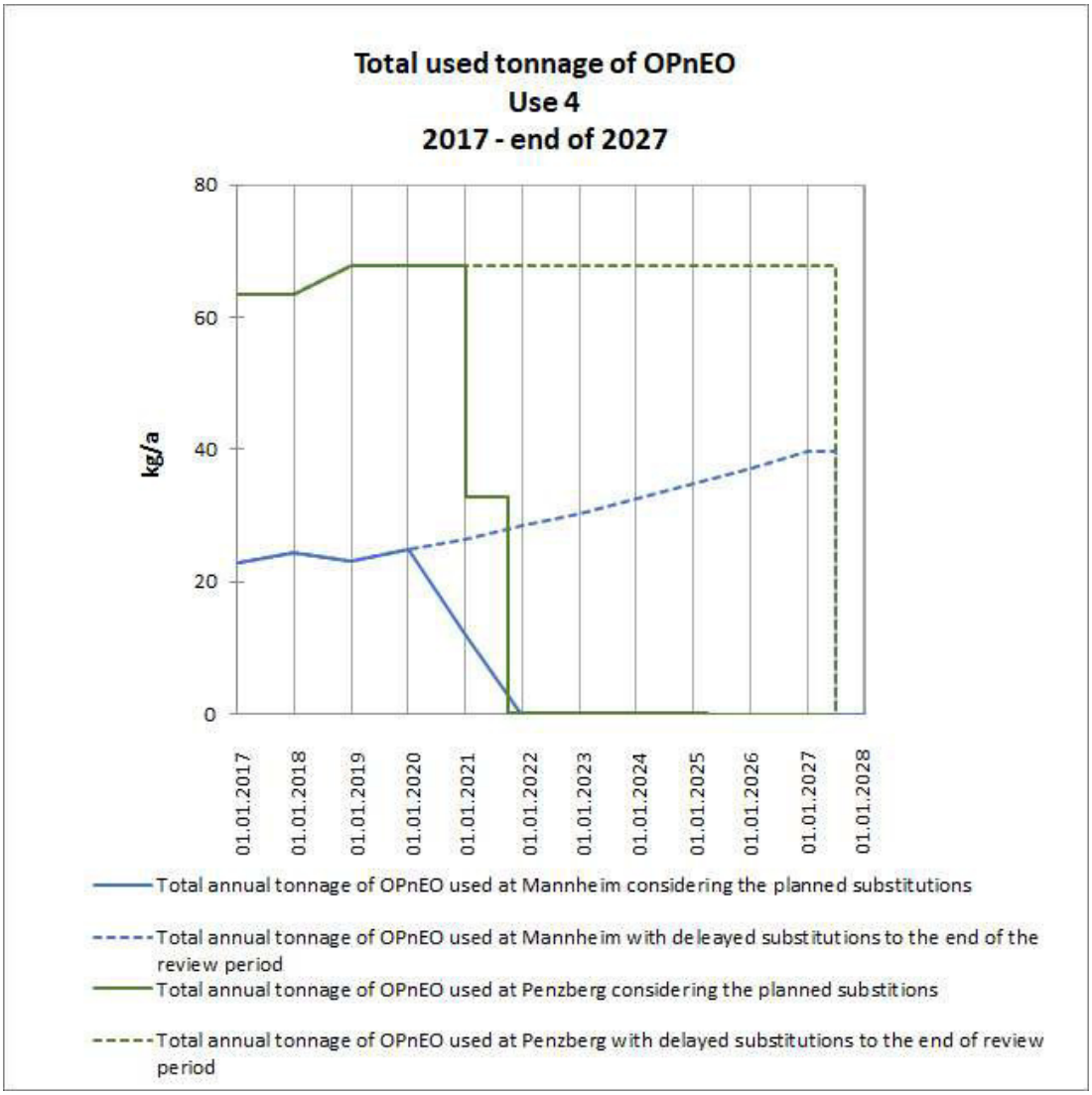


Figure 41. Evolution of the total annual use of OPnEO under Use 4 between 2017 and end of 2027 for the production sites of Mannheim and Penzberg considering planned substitutions and expected sales development.

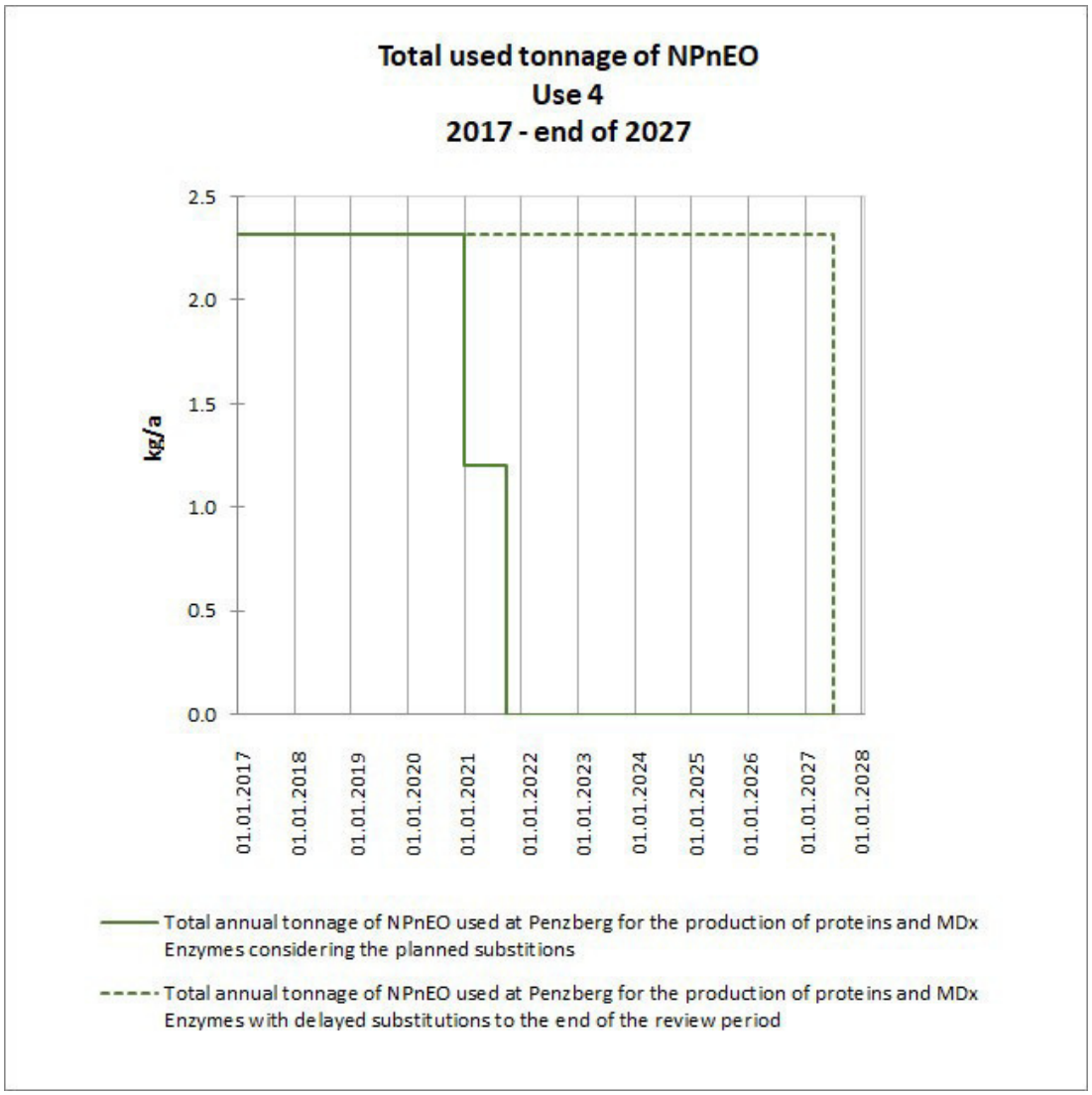


Figure 42. Evolution of the total annual use of NPnEO under Use 4 between 2017 and end of 2027 for the production site of Penzberg considering planned substitutions and expected sales development.

The **total annual use at different times** and predicted for the **two cases** (substitution as planned or delayed) for **Uses 2, 3, and 4** are also displayed below in Table 16 for OPnEO and Table 17 for NPnEO. Lower used amounts in production (Use 2) compared to the used amounts at downstream users (Use 3) at the sunset date for OPnEO can be explained by the fact that a number of substitution projects for OPnEO are planned to be completed by the sunset date, but phase-out of the downstream uses will not yet be achieved by the sunset date due to shelf life of the products (see also Figure 37 and Figure 39).

Table 16. Overview of evolution of tonnages over time for OPnEO for Use 2 (production at Mannheim), Use 3 (downstream uses) and Use 4 (production at Penzberg and Mannheim) under the two cases (substitutions as planned or delayed).

	Case 1				**Case 2**			
	(substitution as planned)				**(all substitution projects delayed)**			
	Use 2	**Use 3**	**Use 4**		**Use 2**	**Use 3**	**Use 4**	
	Mannheim	**Downstream use**	**Mannheim**	**Penzberg**	**Mannheim**	**Downstream use**	**Mannheim**	**Penzberg**
Total annual tonnage in 2017 (kg / a)	1275	566	23	64	1275	566	23	64
Total annual tonnage at sunset date (kg / a)	99	529	12	33	1121	529	27	68
Maximum annual tonnage after sunset date (amount applied for)	n.a.	n.a.	n.a.	n.a.	1326	646	40	68
Year when usage reaches 0	2022	2024*	2022	2022**	4th. Jan. 2028	4th. Jan. 2028	4th. Jan. 2028	4th. Jan. 2028

n.a.: not applicable
*2024: 0.1 kg/a, reaches 0 in 2026
**2022: 0.1 kg/a, reaches 0 in 2025

From the information presented above, it is clear that thanks to the planned substitutions, provided no substantial delays occur, the total annual use of OPnEO could **reach zero in 2022 already** (i.e. one year after the sunset date) **at the production site of Mannheim, which uses the highest amounts of OPnEO**. At the production site of **Penzberg**, the total annual use is expected to reach almost zero in **2022 (2022: 0.1 kg/a) and 0 in 2025**. The total annual use at **downstream user sites** could reach **close to zero in 2024** already (i.e. later than at the production site of Mannheim due to shelf life of OPnEO-containing products). In case all scheduled substitutions would be delayed until the end of the review period, the total annual use of OPnEO would only **reach zero** by the end of the review period (**4th of January 2028**), after reaching a maximum about 6 months before the end of the review period.

Table 17. Overview of evolution of tonnages over time for NPnEO for Use 2 (production at Penzberg and Mannheim), Use 3 (downstream uses) and Use 4 (production at Penzberg only) under the two cases (substitutions as planned or delayed).

	Case 1				**Case 2**			
	(substitution as planned)				**(all substitution projects delayed)**			
	Use 2		**Use 3**	**Use 4**	**Use 2**		**Use 3**	**Use 4**
	Mannheim	**Penzberg**	**Downstream use**	**Penzberg**	**Mannheim**	**Penzberg**	**Downstream use**	**Penzberg**
Total annual tonnage in 2017 (kg / a)	97	70	46	2	97	70	46	2
Total annual tonnage at sunset date (kg / a)	1	92	27	1	105	92	53	2
Maximum annual tonnage after sunset date (amount applied for)	n.a	n.a.	n.a.	n.a.	120	97	55	2
Year when usage reaches 0	2022	4th. Jan. 2028	4th. Jan. 2028	2022	4th. Jan. 2028	4th. Jan. 2028	4th. Jan. 2028	4th. Jan. 2028

n.a.: not applicable

For NPnEO, the substitutions as scheduled would result in **complete reduction** of its use **by 2022 at the production site of Mannheim, which uses the largest amount of NPnEO**. At the production site of **Penzberg**, and consequently also at **downstream user sites**, the use would only become zero by the **end of the review period** (**4th of January 2028**). In case substitutions were delayed until the end of the review period, the use (at both production sites as well as downstream user sites) would be reduced to zero by the end of the review period. However, the reduction would not be as gradual as in the case where all substitutions are completed as planned.

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

3.1.3 Releases of OPnEO / NPnEO at Production Sites and Downstream User Sites Over Time in OP / $NP_{equiv.}$, and Discussion on Risk Management Measures

⇨ The predominant receiving compartments considered in this assessment are **surface water** and **agricultural soil**, the latter due to sludge application to soil from STPs in Use 3.

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

⇨ In both cases the same level of **risk management measures** will be implemented. This will be done before the submission date at the production sites and by the sunset date at the downstream user sites.

⇨ Releases at downstream user sites are responsible **for 100% of releases to soil and > 99% and > 90% of total release to surface water** in OP and $NP_{equiv.}$, respectively, over the review period.

⇨ Additional risk management measures are determined based on feasibility and include **collection of additional waste fractions** at the production sites for subsequent incineration as well as **disposal of solid waste** containing OPnEO / NPnEO from downstream uses as if it was 'hazardous waste'.

⇨ Due to the additional risk management measures as well as completion of planned substitutions before the sunset date, **drastic reductions of releases are expected to occur already before / by the sunset date**, especially at the production sites. Further reduction after the sunset date is expected as the result of further **completed substitutions**.

Release pathways

- **Wastewater**: For processes, formulation and 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 (only Use 3). 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 (from Use 3). Releases to the environment can also occur from waste assumed to be landfilled under Use 3. 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 decrease in the total release to the environment in OP / $NP_{equiv.}$ by the activities covered in Uses 2, 3, and 4 over time until the end of the review period. In both cases expected sales development and the implementation of risk management measures by the submission date at the production sites / by the sunset date at the downstream user sites is considered:

- '**All substitutions completed as planned'**: Expected decrease in the total release to surface water and – for Use 3 – soil in OP / $NP_{equiv.}$ over time considering that substitutions are completed as planned.

- '**All substitutions delayed'**: Expected decrease in the total release to surface water and – for Use 3 – soil in OP / NP_{equiv}. over time considering that all planned substitutions at the production sites 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 for Use 3.

Use 2 – Formulation

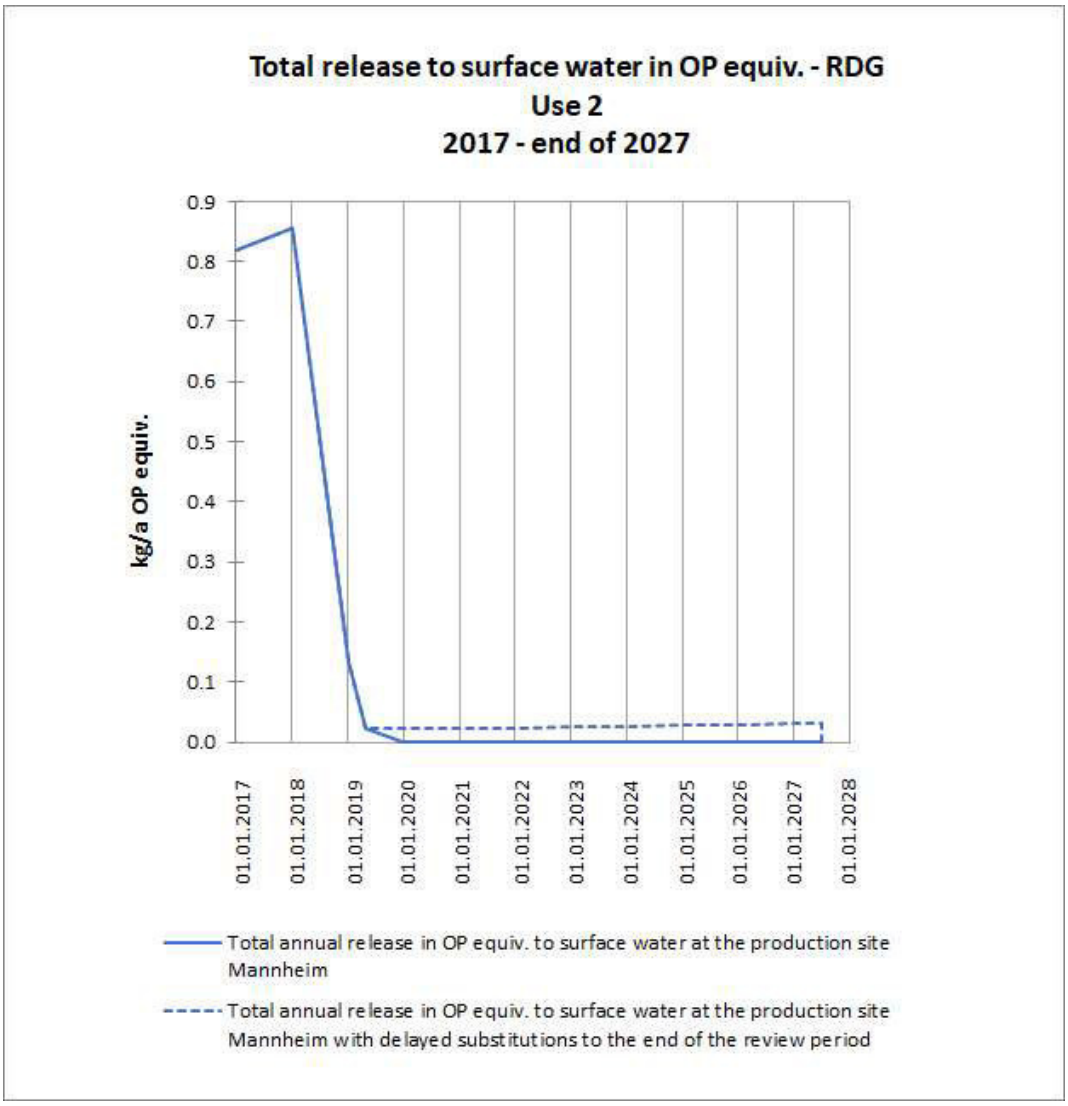


Figure 43. Evolution of the total annual release to surface water in $OP_{equiv.}$ under Use 2 between 2017 and end of 2027 for the RDG production site in Mannheim considering planned substitutions, implementation of risk management measures and expected sales development.

As shown in Figure 43, if the substitutions are completed as planned and the identified additional risk management measures are implemented by the submission date, the total release to surface water in $OP_{equiv.}$ should decrease to **0.98 g/a $OP_{equiv.}$** at the sunset date to reach 0 in 2022. However, if the substitutions are delayed until the end of the review period for all formulation activities but CC1, a maximum total annual release of **31 g/a $OP_{equiv.}$** to surface water could be reached as a worst-case about 6 months before 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.

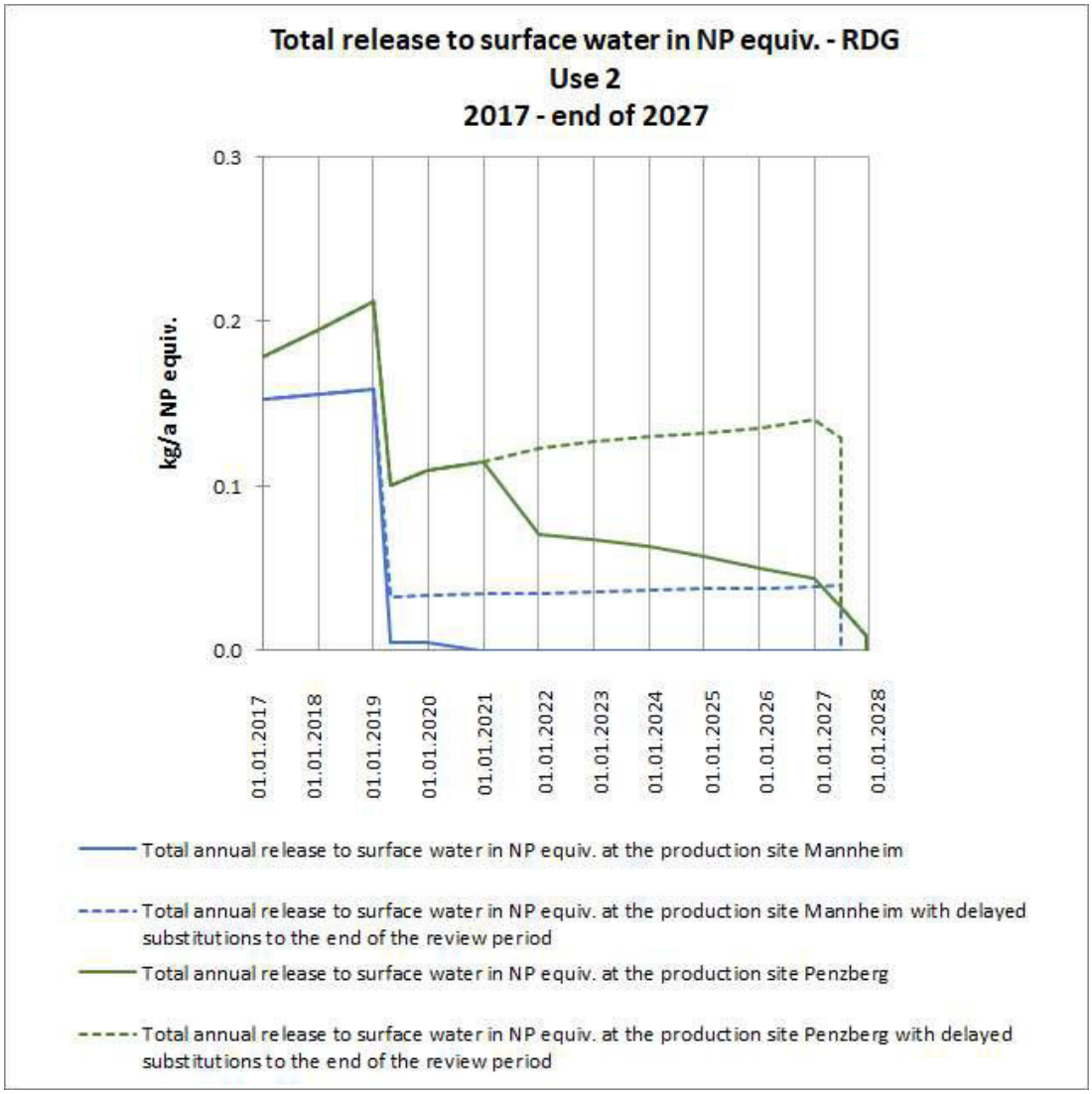


Figure 44. Evolution of the total annual release to surface water in $NP_{equiv.}$ under Use 2 between 2017 and end of 2027 for the RDG production sites (Mannheim and Penzberg) considering planned substitutions, implementation of risk management measures and expected sales development.

As shown in Figure 44, if the substitutions are completed as planned and the identified additional risk management measures are implemented by the submission date, the total release to surface water in $NP_{equiv.}$ should decrease from **0.1 g/a $NP_{equiv.}$** at Mannheim and **115.3 g/a $NP_{equiv.}$** at Penzberg at the sunset date to zero in 2022 and end of 2027, respectively. However, if the substitutions are delayed to the end of the review period for all formulation activities, a maximum total annual release to surface water of **39.5 g/a $NP_{equiv.}$** at Mannheim and **140.5 g/a $NP_{equiv.}$** at Penzberg could be observed as a worst-case about 6 months before the end of the review period and beginning of 2027 at Mannheim and Penzberg, respectively. 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, a delay of all projects until the end of the review period is highly unlikely.

Use 3 – Products

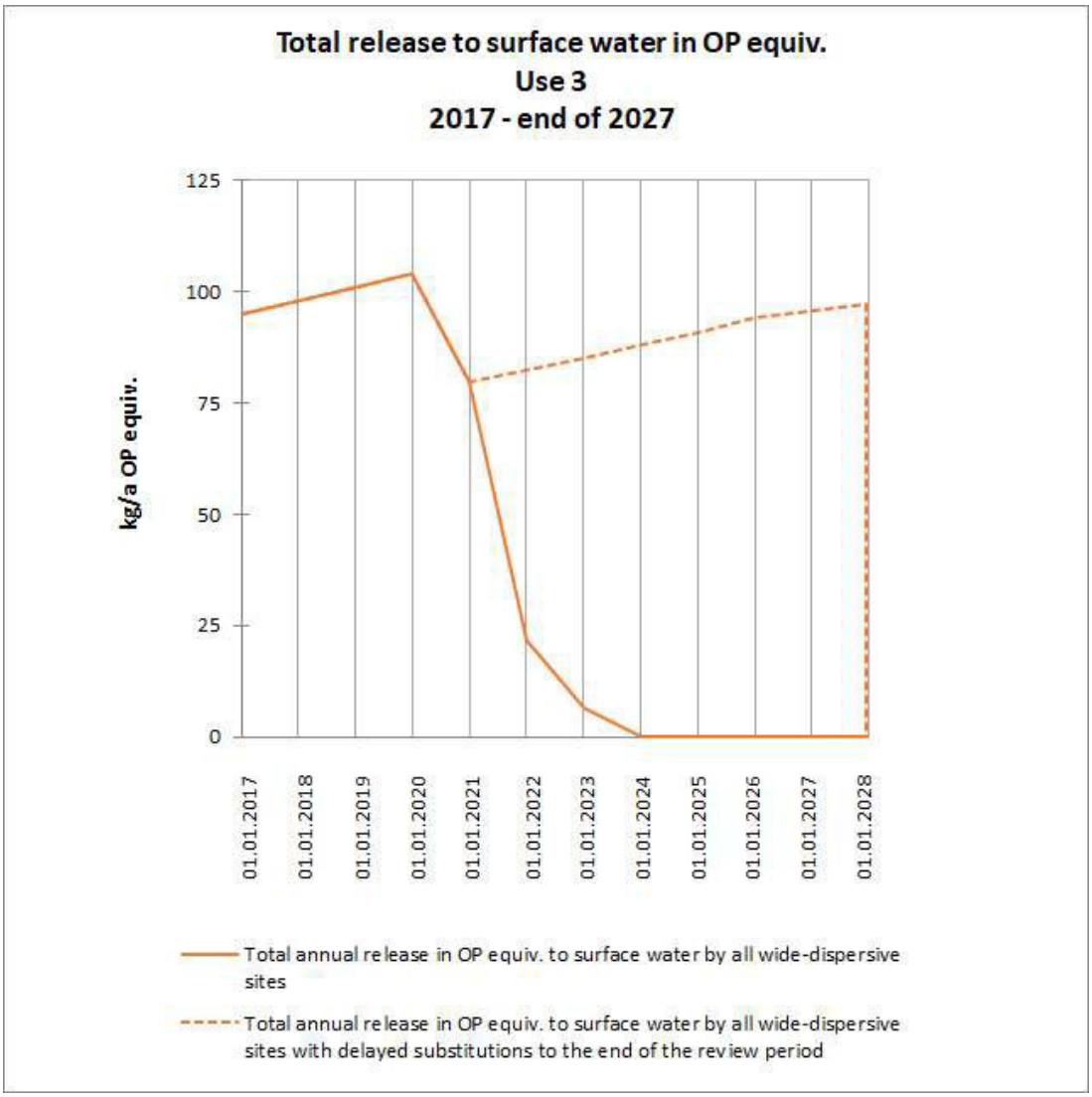


Figure 45. Evolution of the total annual release to surface water in OP_{equiv} under Use 3 from 2017 until the end of 2027 for the downstream user sites considering planned substitutions, implementation of risk management measures, expected sales development as well as the shelf life of reagents.

As shown in Figure 45, 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 should decrease from **79.6 kg/a OP_{equiv}** at the sunset date to reach 0 in 2024 in line with the delay due to the shelf life of the products. However, if the substitutions are delayed until the end of the review period for all formulation activities, a maximum total annual release of **97.4 kg/a OP_{equiv}** to surface water from all wide-dispersive uses could potentially be reached as a worst-case at 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.

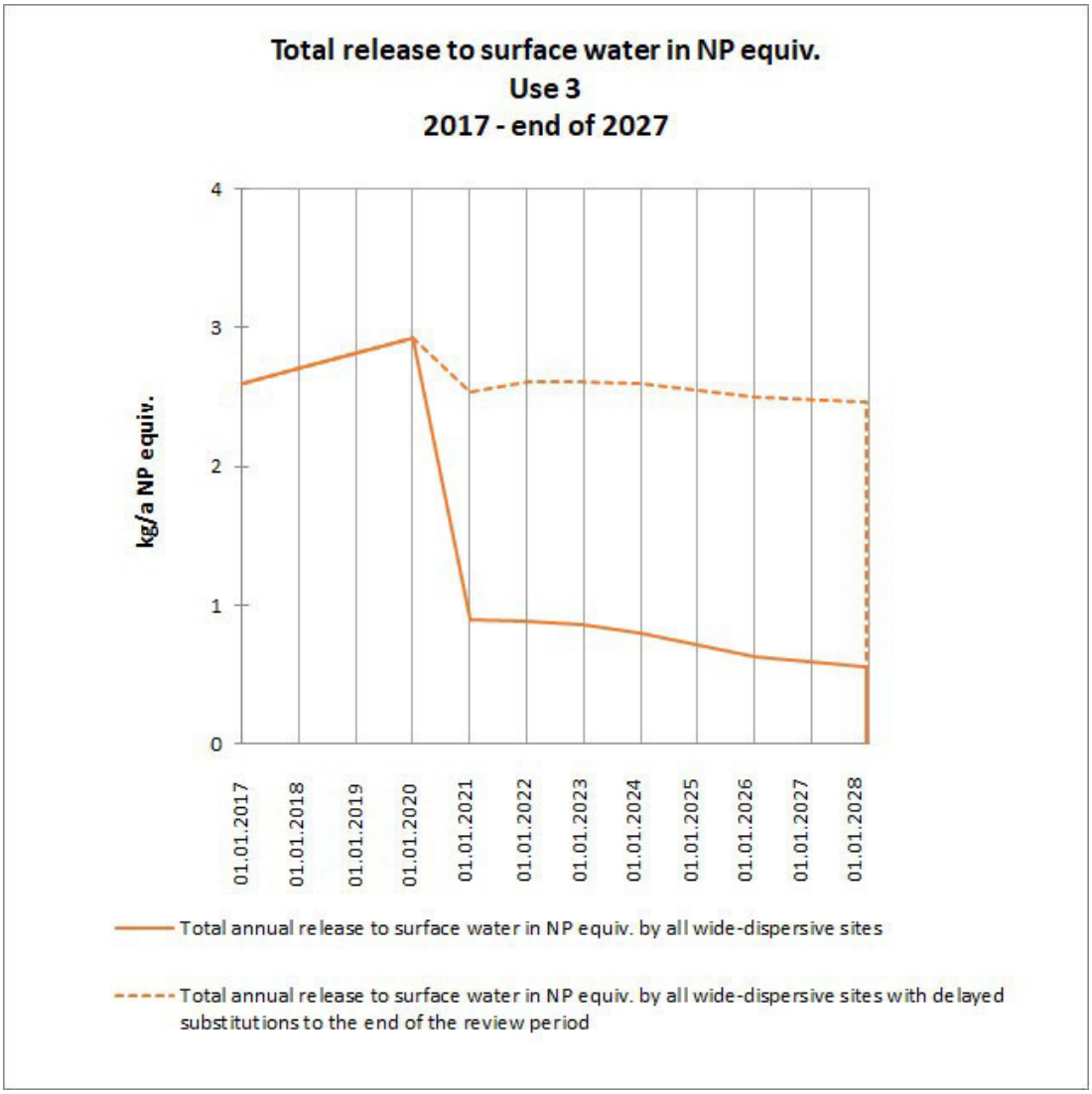


Figure 46. Evolution of the total annual release to surface water in $NP_{equiv.}$ under Use 3 from 2017 until the end of 2027 for the downstream user sites considering planned substitutions and implementation of risk management measures, expected sales development as well as the shelf life of the products.

As shown in Figure 46, if the substitutions are completed as planned, the total release to surface water in $NP_{equiv.}$ at the downstream user sites should decrease from **0.89 kg/a $NP_{equiv.}$** at the sunset date to zero 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 **2.6 kg/a $NP_{equiv.}$** to surface water from all wide-dispersive uses could potentially be reached as a worst-case in 2023. 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.

Use 4 – Processes

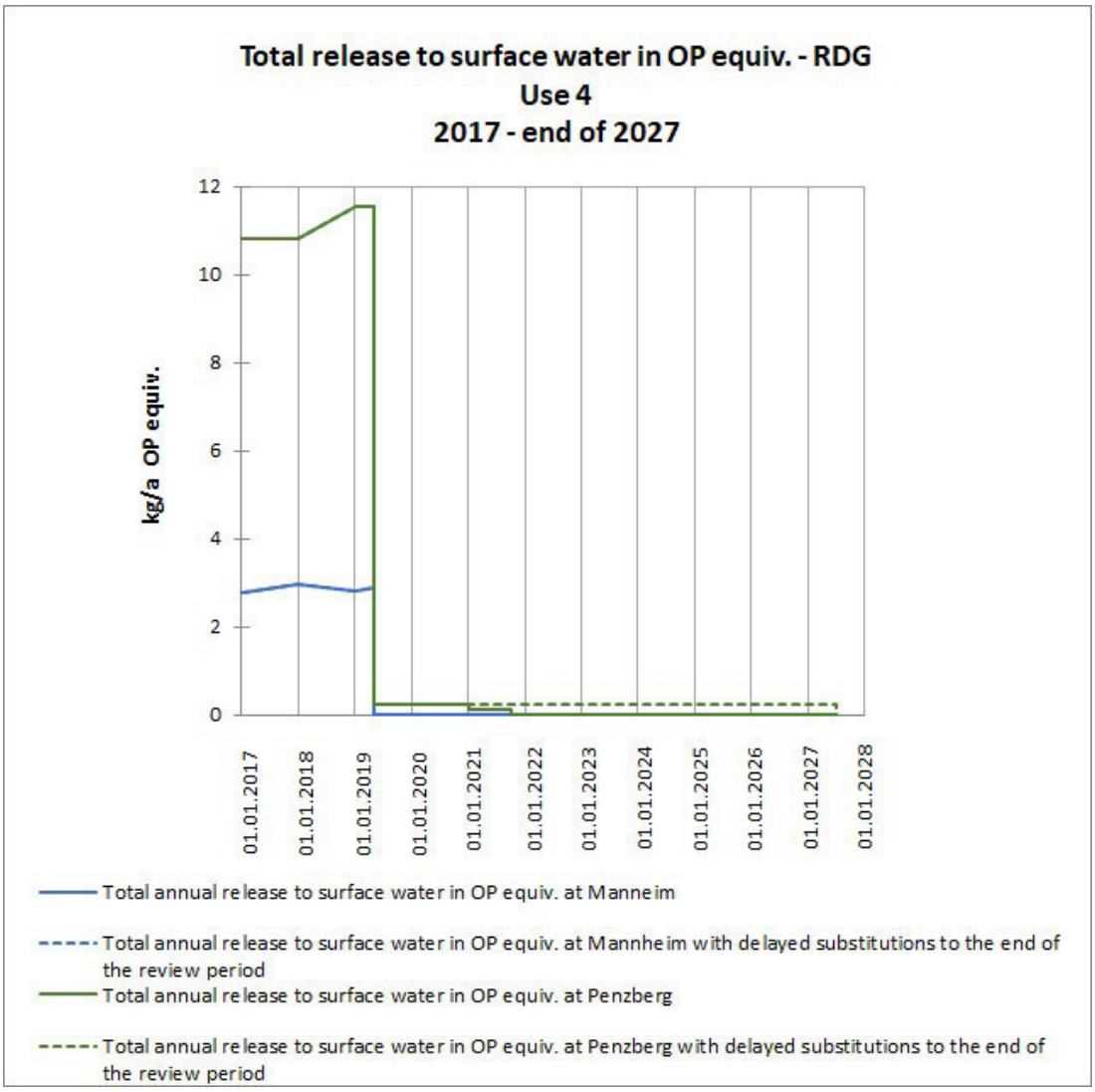


Figure 47. Evolution of the total annual release to surface water in OP_{equiv} under Use 4 from 2017 until the end of 2027 for the production sites (Mannheim and Penzberg) considering planned substitutions and implementation of risk management measures.

As shown in Figure 47, if the substitutions for all processes are completed as planned and the identified additional risk management measures are implemented by the submission date, the total release to surface water in OP_{equiv}. should decrease from **3 g/a OP_{equiv}** at the production site of Mannheim and **0.112 kg/a OP_{equiv}.** at the production site of Penzberg at the sunset date to reach 0 in 2022 and even before 2022, respectively. However, if the substitutions are delayed until the end of the review period for all activities, a maximum total annual release to surface water of **5.5 g/a OP_{equiv}.** at the production site of Mannheim and **0.231 kg/a OP_{equiv}.** at the production site of Penzberg could be observed as a worst-case about 6 months before 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.

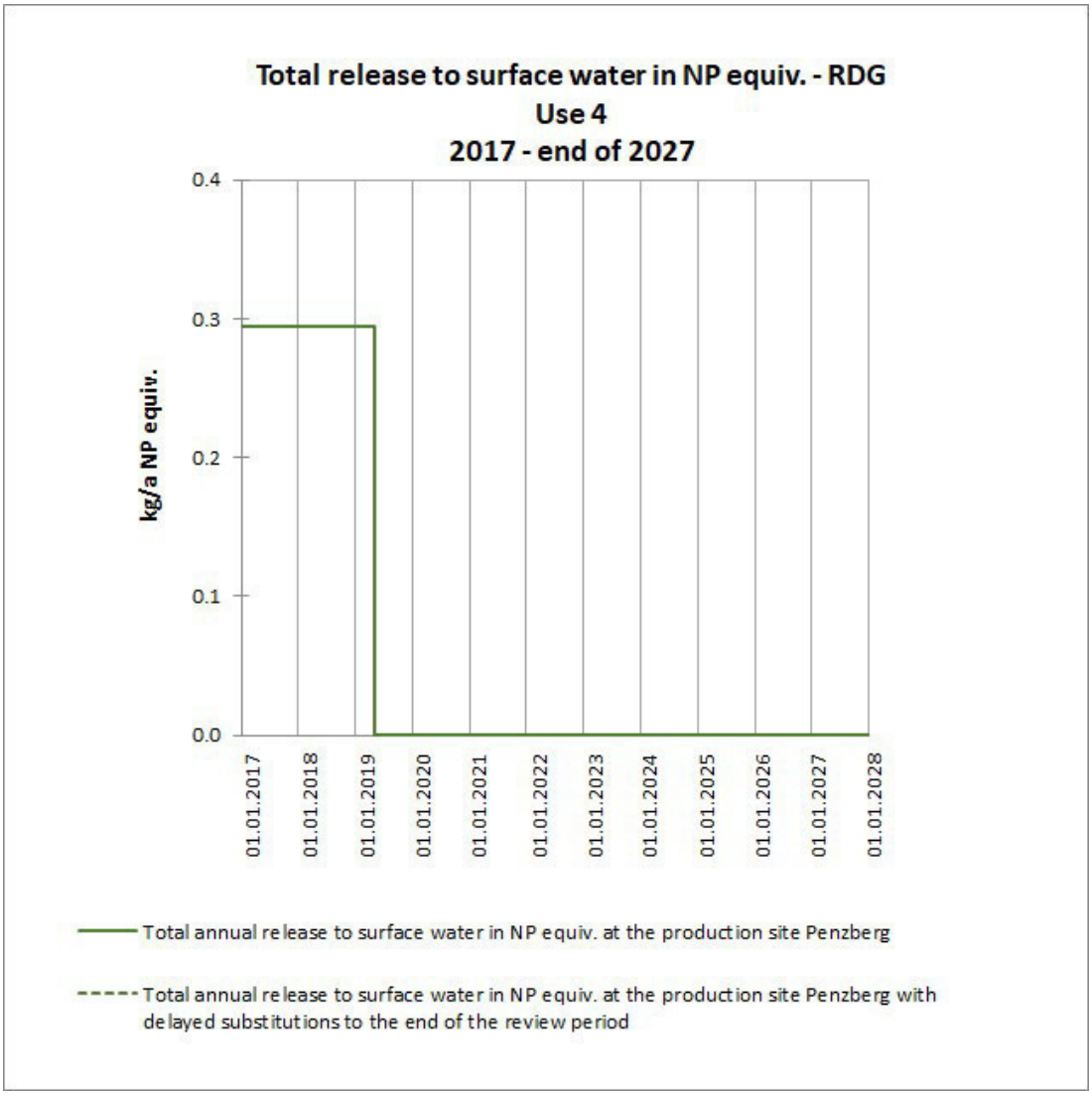


Figure 48. Evolution of the total annual release to surface water in $NP_{equiv.}$ under Use 4 from 2017 until the end of 2027 for the RDG production site in Penzberg considering planned substitutions, implementation of risk management measures and expected sales development.

As can be shown in Figure 48, if the substitution is completed in time and the identified risk management measures are implemented by the submission date, the total release to surface water in $NP_{equiv.}$ should reach 0 in 2019 in both scenarios. If the substitutions are delayed to the end of the review period for all processes, the use of NPnEO would continue (with 0 emissions to surface water) until about 6 months before the end of the review period at Penzberg.

Table 18 **Fehler! Verweisquelle konnte nicht gefunden werden.**and Table 19 respectively give an overview of the total annual release of $OP_{equiv.}$ and $NP_{equiv.}$ to surface water (for downstream uses: also to soil) under current conditions, 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 (2021 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 18. Current and expected releases to surface water and to soil after STP in kg/a $OP_{equiv.}$ and integrated releases over the review period (2021 to end of 2027). Data are summed for Uses 2, 3, and 4.

Uses 2, 3 and 4	Case	Unit	Releases to surface water					Releases to soil (Use 3 only, rounded)*
			RDG - Penzberg	RDG - Mannheim	RDG - TOTAL	Down-stream uses	TOTAL (rounded)	
Current release to surface water / soil after STP (2016-2017)	**Expected release considering current situation (no substitutions and no additional RMMs yet)**	kg/a $OP_{equiv.}$	10.809	3.583	14.392	94.853	**109**	**79**
Release to surface water / soil after STP at sunset date (04.01.2021)	**Expected release considering substitutions and RMMs**	kg/a $OP_{equiv.}$	0.112	0.004	0.116	79.622	**80**	**67**
	Max total release with delayed substitutions	kg/a $OP_{equiv.}$	0.231	0.027	0.258	79.630	**80**	**67**
Release to surface water / soil after STP 6 months before the end of review period (04.07.2027)	**Expected release considering substitutions and RMMs**	kg/a $OP_{equiv.}$	0	0	0	0	**0**	**0**
	Max total release with delayed substitutions	kg/a $OP_{equiv.}$	0.23	0.037	0.267	97.417	**98**	**81**
Total release to surface water / soil after STP over the review period (2021-end of 2027)	**Expected release considering substitutions and RMMs**	kg/7a $OP_{equiv.}$	0.112	0.004	0.116	107.872	**108**	**90**
	Max total release with delayed substitutions	kg/7a $OP_{equiv.}$	1.615	0.218	1.832	617.760	**620**	**515**

* 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).

Table 18**Fehler! Verweisquelle konnte nicht gefunden werden.** shows that the total release to surface water in $OP_{equiv.}$ is dominated by the release at the downstream user sites at all time from 2016-2017 until the end of the review period. Indeed, from the sunset date, the **downstream user sites are responsible for > 99% of the total release to surface water** in $OP_{equiv.}$ over the review period. Downstream uses are also responsible for 100% of releases to soil.

The release to surface water in $OP_{equiv.}$ will decrease from **3.583 kg/a $OP_{equiv.}$** at the production site of Mannheim and **10.809 kg/a $OP_{equiv.}$** at the production site of Penzberg in 2016-2017 to **0.027 kg/a $OP_{equiv.}$** and **0.231 kg/a $OP_{equiv.}$** (without substitutions) at the sunset date, respectively. This decrease in release to surface water in $OP_{equiv.}$ is **due to the risk management measures implemented** by the submission date. Implementing risks management measures (RMMs) at the production sites will thus allow significantly reducing the total release of $OP_{equiv.}$ to surface water from 2016-2017 to the sunset date **by about 99% and 98%** at Mannheim and Penzberg, respectively. At the downstream user sites, RMMs are assumed to be implemented by the sunset date. The reduction of releases at downstream user sites by the sunset date is however mainly due to completed substitutions including phase-out of products before the sunset date. See further below for discussion on implementation of RMMs.

Six months before the end of the review period, the release to surface water in $OP_{equiv.}$ would have already ceased if substitutions are completed as planned (see Table 18). If all substitutions are delayed, a maximum of **98 kg/a $OP_{equiv.}$** (81 kg/a $OP_{equiv.}$ for release to soil) could be reached at this time. In this case, an overall maximum amount of $OP_{equiv.}$ 5.7 times higher than if the substitutions would be completed as planned, would be released over the 7 years of the review period (i.e. **620 kg $OP_{equiv.}$** for surface water; **515 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 45% in the EEA, the release to soil is likely lower [5].

Table 19. Current and expected releases to surface water and to soil after STP in kg/a $NP_{equiv.}$ and integrated releases over the review period (2021 to end of 2027). Data are summed for Uses 2, 3, and 4.

Uses 2, 3 and 4	**Case**	**Unit**	**Releases to surface water**					**Releases to soil (Use 3 only, rounded)***
			RDG - Penzberg	**RDG - Mannheim**	**RDG - TOTAL**	**Down-stream uses**	**TOTAL (rounded)**	
Current release to surface water / soil after STP (2016-2017)	**Expected release considering current situation (no substitutions and no additional RMMs yet)**	kg/a NP_{equiv}	0.473	0.152	0.625	2.595	**3.2**	**8.0**
Release to surface water / soil after STP at sunset date (04.01.2021)	**Expected release considering substitutions and RMMs**	kg/a NP_{equiv}	0.115	0	0.115	0.890	**1.0**	**2.7**
	Max total release with delayed substitutions	kg/a NP_{equiv}	0.115	0.034	0.149	2.541	**2.7**	**7.8**

Uses 2, 3 and 4	Case	Unit	Releases to surface water					Releases to soil (Use 3 only, rounded)*
			RDG - Penzberg	RDG - Mannheim	RDG - TOTAL	Down-stream uses	TOTAL (rounded)	
Release to surface water / soil after STP 6 months before the end of review period (04.07.2027)	**Expected release considering substitutions and RMMs**	kg/a NP_{equiv}	0.044	0	0.044	0.550	**0.6**	**1.7**
	Max total release with delayed substitutions	kg/a NP_{equiv}	0.140	0.039	0.180	2.467	**2.6**	**7.5**
Total release to surface water / soil after STP over the review period (2021-end of 2027)	**Expected release considering substitutions and RMMs**	kg/7a NP_{equiv}	0.467	0	0.467	5.311	**5.8**	**16**
	Max total release with delayed substitutions	kg/7a NP_{equiv}	0.904	0.257	1.161	17.878	**19**	**55**

* 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).

Table 19 shows that the total release to surface water in $NP_{equiv.}$ is dominated by the release of the downstream user sites at all time from 2016-2017 until the end of the review period. Indeed, the **downstream user sites are responsible for > 90% of the total release to surface water** in $NP_{equiv.}$ over the review period. Downstream uses are also responsible for 100% of releases to soil.

The release to surface water in $NP_{equiv.}$ will decrease from **0.152 kg/a $NP_{equiv.}$** at the production site of Mannheim and **0.473 kg/a $NP_{equiv.}$** at the production site of Penzberg in 2016-2017 to **0.034 kg/a** $NP_{equiv.}$ and **0.115 kg/a $NP_{equiv.}$** (without substitutions) at the sunset date, respectively. This decrease in release to surface water in $NP_{equiv.}$ is due to the risk management measures implemented by the submission date. Implementing RMMs at the production sites will thus allow significantly reducing the total release of $NP_{equiv.}$ to surface water from 2016-2017 to the sunset date **by about 78% and 76%** at Mannheim and Penzberg, respectively. At the downstream user sites, RMMs are assumed to be implemented by the sunset date which will lead to a small decrease of the total release per year from downstream user sites between 2016-2017 and the sunset date, as shown in Table 19.

The release to surface water in $NP_{equiv.}$ is expected to decrease by about 40% 6 months before the end of the review period in comparison with the emission at the sunset date if the substitutions are completed as planned. If all substitutions are delayed, a maximum of **2.6 kg/a $NP_{equiv.}$ (7.5 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 3 times higher than if the substitutions would be completed as planned, would be released over the 7 years of the review period (i.e. **19 kg $NP_{equiv.}$** for surface water; **55 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 45% in the EEA, the release to soil is likely lower [5].

Overview of risk management measures and discussion on additional risk management measures

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 **risk management measures** already in place or implemented by the submission date at the production sites / to be implemented by the sunset date at the downstream user sites. Below an overview is given of the current and newly implemented risk management measures at the sites of Mannheim and Penzberg as well as the planned risk management measures for the downstream user sites. By implementation of these additional RMMs, the release to wastewater will be reduced from 601.4 kg/a OPnEO and 37.2 kg/a NPnEO in 2016-2017 to 428.3 kg/a OPnEO and 32.2 kg/a NPnEO at the sunset date for the uses covered by this application (Uses 2, 3 and 4). This corresponds to an overall reduction of releases to wastewater of 29% for OPnEO and 13% for NPnEO. This reduction is based on the assumption that all substitutions are delayed apart from the already implemented replacement of OPnEO in assays CC1 and DM1. In the CSRs it is demonstrated that emissions and releases to the environment to and after STP from the activities covered in the Uses 2, 3 and 4 **are minimised as far as practically and technically feasible** by implementation of the additional RMMs as discussed below.

<u>Production sites (Mannheim and Penzberg)</u>

At the production sites of RDG in Mannheim and Penzberg, the releases to wastewater at the time of preparation of this dossier were mainly due to the introduction of liquid waste (i.e. surplus / dead volumes / rinsing waters) to wastewater.

Concerning solid waste containing OPnEO or NPnEO, all waste streams were already collected and incinerated. Only for the use of OPnEO in proteins production processes and one MDx Enyzme process under Use 4 taking place at Penzberg, additional measures have been identified. For these processes, separate collection and incineration of all biomass / precipitation and other solid waste was implemented by the submission date.

In the CSRs, **additional measures** considered regarding liquid waste are the collection and incineration of **1) the generated surplus / rest buffers**, and **2) the rinsing waters**.

The absolute and relative contribution of these liquid waste streams with respect to the total annual releases of OPnEO to wastewater as well as the total incineration cost in EUR / g of emissions saved are shown in Table 20 (Use 2), Table 21 (Use 4 – latex beads conjugation), and Table 22 (Use 4 – proteins production and one MDx Enzyme production process). For Use 2, approximately 85% of releases are already eliminated by substitution in the formulation of assay CC1. It is clear from these tables that for both Use 2 and Use 4 the liquid waste stream consisting of surplus / rest buffers is by far contributing the most to the remaining total annual release to wastewater in absolute and relative terms. As available infrastructure for collection of liquid waste from processes could be used, it was possible to implement the separate collection and incineration of the surplus and used buffers by the submission date as an additional measure to eliminate the large part of releases of OPnEO to wastewater.

Considering the total volume of this liquid waste to be collected, this results in small incineration costs per gram of OPnEO emissions saved. This was not the case for the rinsing waters, which represent much higher volumes and lower concentrations of OPnEO.

Table 20. Total releases to wastewater per year in kg OPnEO / a in different liquid waste streams for Use 2 (Mannheim) at the time of the dossier preparation based on data from 2016-2017, relative contribution to total release, and incineration cost.

Use 2			
	Total amount of OPnEO in the liquid waste fractions in kg/a	**Percentage of the total annual OPnEO release**	**Total incineration costs in €/g of OPnEO emissions saved**
Surplus/rest buffers	0.817	12.5 %	0.72
Rinsing waters	0.160	2.4 %	1113
Product CC1*	5.574	85.1 %	not applicable
TOTAL	**6.550**	**100 %**	**-**

* OPnEO was successfully substituted in 2018 for this formulation process at the production site. The amounts eliminated by substitution were not included in the discussion on reduction of releases by implementation of additional RMMs and therefore, are shown separately in the table.

Table 21. Total releases to wastewater per year in kg OPnEO / a in different liquid waste streams from the latex beads conjugation processes (Use 4, Mannheim) at the time of the dossier preparation based on data from 2016-2017, relative contribution to total release, and incineration cost.

Use 4 – latex beads conjugation processes			
	Total amount of OPnEO in the liquid waste fractions in kg/a	**Percentage of the total annual OPnEO release**	**Total incineration costs in €/g of OPnEO emissions saved**
Surplus / used buffers	22.1	96.89%	0.72
Rinsing waters	0.03	0.13%	1113
Final products	0.68	2.98%	-
TOTAL	**22.81**	**100%**	**-**

Table 22. Total releases to wastewater per year in kg OPnEO/a in different waste streams from the protein production processes and one MDx Enzyme production process (Use 4, Penzberg) at the time

of the dossier preparation based on data from 2016-2017, relative contribution to total release, and incineration cost.

Use 4 – proteins production processes and one MDx production process			
	Total amount of OPnEO in the liquid waste fractions in kg/a	**Percentage of the total annual OPnEO release**	**Total incineration costs in €/g of OPnEO emissions saved**
Surplus/rest buffers	66.44 assumed	97.94 % assumed	0.72
Rinsing waters	1.36 assumed	2 % assumed	1113
Solid (Biomass/precipitation & other solid waste)	Unknown	unknown	unknown
Amount in final products*	0.04	0.06 %	-
TOTAL	**67.8**	**100 %**	**-**

* as impurities (in proteins)

Similar information is given below for NPnEO for Use 2 (Table 23) and Use 4 (Table 24). The conclusions are similar as for OPnEO and therefore the separate collection and incineration of the surplus / rest buffers by the submission date as an additional measure to eliminate the large part of releases of NPnEO to wastewater was implemented. In addition, for Use 4, it was also considered possible to implement the collection and incineration of rinsing waters, because of the low volume of the rinsing waters generated during the processes using NPnEO.

Table 23. Total releases to wastewater per year in kg NPnEO / a in different liquid waste streams for Use 2 at the time of the dossier preparation based on data from 2016-2017, relative contribution to total release, and incineration cost.

Use 2					
	Total amount of NPnEO in the liquid waste fractions in kg/a			**Percentage of the total annual NPnEO release for Mannheim and Penzberg**	**Total incineration costs in €/g of NPnEO emissions saved**
	Mannheim	**Penzberg**	**TOTAL**		
Surplus/rest buffers	1.533	0.742	**2.275**	68.0 %	0.25
Rinsing waters*	0.412	0.659	**1.071**	32.0 %	1342
TOTAL	**1.945**	**1.401**	**3.346**	**100 %**	**-**

* filling included in the rinsing waters

Table 24. Total releases to wastewater per year in kg NPnEO / a in different liquid waste streams for Use 4 (Penzberg) at the time of the dossier preparation based on data from 2016-2017, relative contribution to total release, and incineration cost.

Use 4 – proteins and MDx Enzyme production processes			
	Total amount of NPnEO in the liquid waste fractions in kg/a	**Percentage of the total annual NPnEO release**	**Total incineration costs in €/g of NPnEO emissions saved**
Surplus/used buffers	2.27 estimated	98 % estimated	0.77
Rinsing waters	0.035 estimated	1.5 % estimated	1510
Amount in final products*	0.012	0.5 %	-
TOTAL	**2.32**	**100 %**	**-**

* as impurities (in protein)

After **implementation of the additional RMMs** (collection and incineration of the generated surplus / rest buffers), **rinsing waters are the remaining source for OPnEO and NPnEO emissions** from the production processes at the production sites. The collection of rinsing waters is not considered practically and technically feasible for processes with high volumes of rinsing waters for several reasons. For example, in many cases, the **current set up of installation does not allow collection of rinsing waters**. The required reconstruction would be associated with high cost and, based on expected timelines, it can be assumed that a major part of the substitutions will be finalised before a reconstruction of the water system would be implemented. In addition, due to the large volumes and low concentrations of OPnEO / NPnEO in rinsing waters, **incineration of the rinsing water would mean high cost large energy consumption** per g of OPnEO / NPnEO. For further details please refer to the respective CSRs.

Other risk management measures (which are currently already in place) are summarised below for the production sites of Mannheim and Penzberg:

Mannheim (STP)

- First, all wastewater enters a storage basin of 1'000 m^3 on RDG's Mannheim site before being transferred to a communal STP with additional nitrification step. About 90% of the wastewater is treated with activated carbon (additional effort to remove micropollutants).

- The sludge of the wastewater treatment plant is treated in 4 steps and dried. The dried granules (ca. 10'000 t/a) are used thermally in cement industry (incineration). There is no application of sludge to agricultural land.

Penzberg (STP)

- All wastewater is directed to an on-site industrial STP, receiving only wastewater from RDG, after passage via a storage basin (neutralisation basin). The STP consists of an activated sludge biological step with pure oxygen, nitrification, denitrification, and microfiltration (membrane filter hollow fiber, PVDF, pore size: 0.04 µm).

- The sludge of the wastewater treatment plant is concentrated to 22-25% solid content. Removed water is directed again into the biological treatment step of the STP. The concentrated sludge is incinerated by an authorised company.

Monitoring

A validated method is not available to measure NPnEO and all its degradation products in wastewater or STP effluent at the expected low concentrations. As such a method has been developed for OPnEO, emissions to wastewater or **concentrations in STP effluents after implementation of RMMs will be verified for OPnEO**. As operational conditions and RMMs are the same or very similar for formulation activities with both substances, results from OPnEO can be considered valid also for NPnEO. For processes, release of NPnEO have been eliminated by the submission date.

Mannheim:

A monitoring campaign at the STP Mannheim was not envisaged because the production site is connected to a very large communal STP and measurements would not only reflect emissions from the RDG site but likely be a mixture of several sources.

Regarding releases to wastewater, **monitoring is planned to be performed after the implementation of RMMs**, i.e. after the submission date, **in wastewater from the site**. Such monitoring will be performed for OPnEO for which recently a method has become available that is sufficiently sensitive to perform such measurements.

Penzberg:

Due to the on-site STP in Penzberg, releases to surface water from the site can be directly measured in the STP effluent.

Water from the STP outlet was sampled during five production events relevant for Use 4 using OPnEO at the RDG site at Penzberg before the implementation of risk management measures. In order to verify emissions after implementation of RMMs by the submission date **an additional monitoring campaign will be conducted** to measure OPnEO and degradation products including OP in the STP effluent of the on-site STP in Penzberg. Such a campaign will be aligned with the occurrence of the relevant formulation activities (Use 2) and protein production processes (Use 4) at the site.

Downstream uses

The downstream uses (Use 3) represent uses only of products containing OPnEO or NPnEO at or above the cut-off concentration level of 0.1% w/w for authorisation. These uses take place in medicinal laboratories, hospitals, blood banks and ambulatory points of care such as physicians' practices or emergency rooms (point of care uses). The generation of liquid and solid waste streams from these uses, and potential risk management measures to avoid / reduce releases of OPnEO and / or NPnEO from these waste streams, are further discussed below.

Waste from some assays containing OPnEO and / or NPnEO such as closed tubes in which assays were performed (e.g. RMD), cuvettes still containing reagents (e.g. Integra 400+) and test strips (e.g. UA) are **generally disposed of as solid hazardous waste**. Teststrips used directly by patients are disposed of as municipal waste. As an additional risk management measure, empty cartridges and flasks, which may still contain a dead volume of unused reagent or calibrator solution, will be

disposed of as if they were hazardous solid waste by the sunset date. Note that most of the solutions under consideration are actually not classified as hazardous waste according to the waste regulations. However, instructions for waste disposal in safety data sheets are being adapted to indicate to dispose of this waste 'as if it was hazardous'. At the time of preparation of this dossier, handling of waste from cartridges and flasks was not yet managed in a harmonised way across RDG's EEA customers. This will be achieved by changes in the safety data sheets and, if necessary, additional/separate communication to customers.

Releases to wastewater mainly take place via liquid waste streams from the IVD modules, which may be directly connected to the sewer system. Although it may be standard practice in some countries to collect certain liquid waste streams from IVD modules for disposal via waste management companies, in other countries the liquid waste streams may be directed to wastewater. Due to large variations between countries and the uncertainty regarding the efficiency of treatment methods towards OPnEO and NPnEO, 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. 81% for OPnEO and 58% for NPnEO. Implementation of further risk management measures 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 RDG'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 10 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**. Due to national legislation, this is a measure already in place in some countries (e.g. Italy). However, in other countries where this is not required, space for liquid waste containers and facilities for collection by waste management companies are not foreseen during installation of laboratories. 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. Total **incineration cost** for the generated concentrated liquid waste, based on incineration cost in Germany, was estimated to

range between 22 and 126 mio EUR 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 15'000 to 30'000 EUR. Thousands of 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 in countries where this is not common practice 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 / blood bank / point of care 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 and reference values

- ⇨ Releases are generally well-spread over the year. The majority of releases, originating from Use 3, are spread throughout the EEA as RDG's instruments are installed throughout the EEA.

- ⇨ The demonstrated **broad margin of safety** at most times and locations when comparing local PECs with reference values such as EQS and / or PNEC can serve as an indication that the overall releases from RDG's activities and downstream uses to the environment **are not expected to cause issues** in the receiving environmental compartments.

Geographical and temporal considerations

Production sites

Figure 49 shows a map pinpointing the two production sites in Mannheim and Penzberg in Germany.

The municipal STP treating wastewater from the production site of Mannheim is discharging to the River Rhine, whereas the on-site STP from the production site of Penzberg is discharging to the River Loisach. The Loisach is a tributary of the Isar, which is in its turn is Germany's second largest tributary of the Danube.

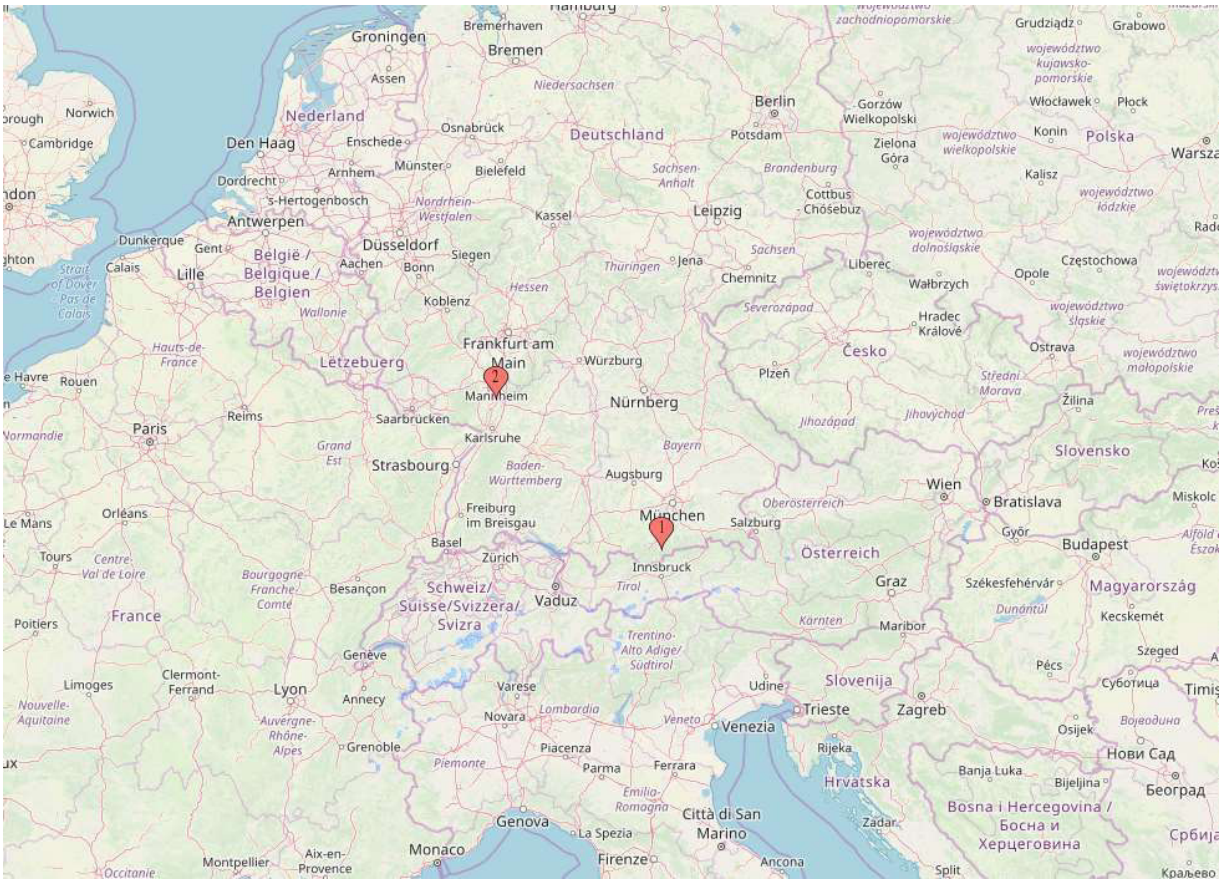


Figure 49. Map pinpointing the production sites in Penzberg (1) and Mannheim (2).

Mannheim is situated along the upper Rhine where industrialisation along the river is not as high as in the Ruhr area which is situated a few 100 km downstream of Mannheim, yet chemical (and pharmaceutical) industry is remarkably present in cities such as Karlsruhe, Mannheim, Worms, Darmstadt, Mainz, Heidelberg etc. This is also the case in Frankfurt am Main, which is situated close to the confluence of the Main and the Rhine. 612 km downstream of Mannheim, the Rhine debouches into the North Sea. The Rhine has an average discharge of about 2'900 m^3/s (whereas at the discharge point of the municipal STP in Mannheim it has a flow rate of about 664 m^3/s (MNQ)).

Some temporal variation could be expected in the release of OPnEO and NPnEO after treatment of the wastewater of RDG's production site in the municipal STP of Mannheim, since all production processes take place in batches, the maximum number of emission days varying between 20 and 39 days/year over the different exposure scenarios. However, since the different batch processes are spread over the year and since the wastewaters of RDG pass firstly via a storage basin and are released gradually to the STP, the **surface water releases can be assumed to be well-spread over the year**. Predicted environmental concentrations (PECs) further discussed below are given for the sunset date assuming that all substitutions are delayed as a worst-case. As shown in Figure 43, Figure 44, and Figure 47, emissions are expected to decrease already drastically due to implementation of risk management measures before the submission date as well as due to planned substitutions before the sunset date (the latter is not yet considered in PEC calculations). They will further decrease to zero during or at the end of the review period due to further completion of substitutions.

Penzberg is situated around 50 km south from Munich. The local river to which the on-site STP of RDG's production site is discharging into is the Loisach (average flow rate of about 17.1 m^3/s (Mittlerer Niedrigwasser Abfluss (MNQ)), which confluences with the Isar only around 30 km downstream of Penzberg. The Loisach is not a highly industrialised river. The Isar's main industrialised area is around Munich (about 50 km from Penzberg). This river is only around 200 km long between the confluence of the Loisach and its debouching into the Danube. The Danube in its turn debouches almost 2'000 km further in the Black Sea.

As for the production site in Penzberg, **some temporal variation** could be expected in the release of OPnEO and NPnEO after treatment of the wastewater of RDG's productions site in Penzberg in its on-site industrial STP. Here too, all production processes take place in batches, the maximum number of emission days varying between 11 and 28 days/year over the different exposure scenarios. However, here as well, since the different batch processes are spread over the year and are released gradually to the STP after passage via a storage basin, the **releases to surface water can be assumed to be well-spread over the year**. At the same time, it has to be taken into account that the highest releases leading to the (maximum PEC values (as discussed below) are only occurring on 3 to 4 days a year. This is because only a few production batches using the respective largest amounts of OPnEO occur per year (see supporting documents SD4a/b_CSR_Usage_Releases_OPnEO_RDG_Use4_CONFIDENTIAL of CSR for Use 4). Predicted environmental concentrations (PECs) are given for the sunset date assuming that all substitutions are delayed as a worst-case and will be further discussed below. As shown in Figure 44, Figure 47, and Figure 48, emissions are expected to decrease drastically already due to implementation of risk management measures before the submission date as well as due to planned substitutions before the sunset date (the latter is not yet considered in PEC calculations). They will further decrease to zero during or at the end of the review period due to further completion of substitutions.

Downstream user sites

The downstream users are medicinal laboratories, hospital laboratories, blood blanks and ambulatory points of care (e.g. physicians' practices). The number of instruments currently installed in the EEA is > 10'000 giving an indication of the high number of customers in the EEA. These **customers are well-spread across the EEA**. The number of instruments installed per EEA country provides more detailed information on the distribution of customers across the EEA (See supporting document SD1_SEA_Nr_Instruments_RDG_Use2-4_CONFIDENTIAL). As explained in the CSR (Use 3) as well as above, due to the many differences in national legislation, the exposure scenario had to be developed using a worst-case assumption that liquid waste in all countries (except the fraction disposed of as solid waste, see above) is introduced to the wastewater and treated in a municipal wastewater treatment plant. Similary, 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 risk management measures 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 respectively 79.6 and 2.5 kg / a at the 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 365 days / year. Fluctuations may however be expected between weekends (lower releases) compared to working days. Predicted environmental concentrations (PECs) are given for the sunset date assuming that all substitutions are delayed as a worst-case and will be further discussed below. As shown in Figure 45 and Figure 46, emissions are expected to decrease already before the sunset date due to planned substitutions (including some which are already implemented, e.g. for CC1 and DM1) and are then expected to further decrease over time after the sunset date due to further planned substitutions. 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 66.6 kg / a $OP_{equiv.}$ and 7.8 kg / a $NP_{equiv.}$ at the sunset date (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** (predicted no-effect concentration) values [8] 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 Framework Directive [8] 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 0.004, 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 25) and $NP_{equiv.}$ (Table 26) 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 25. Comparison of combined local and regional PECs (in $OP_{equiv.}$) with available background and reference values for fresh waters at the sunset date.

Sites/Region	**Combined Freshwater PEC [µg/l]**	**Background values [µg/l]**	**EQS [µg/l]**	**PNEC[3] [µg/l]**	**Ratio PEC / EQS**	**Ratio PEC / PNEC**
Mannheim	0.000506	0.021[1]	0.1	0.034	0.005	0.015
Penzberg	0.0533	0.02-0.7[2]	0.1	0.034	0.53	1.57 [< 1 based on monitoring data]
Wide-dispersive uses						
Average-size laboratory	0.00306	0.02-0.7[2]	0.1	0.034	0.031	0.09
Large laboratory	0.0184	0.02-0.7[2]	0.1	0.034	0.184	0.54
Regional	0.000448	0.02-0.7[2]	0.1	0.034	0.0045	0.013

1 Rhine at Koblenz

[2] Range for surface and groundwaters

[3] PNEC value as determined in the hazard assessment of the CSRs ('Derivation of the PNEC or dose-response-relationship for endocrine disrupting properties of 4-(1,1,3,3-tetramethylbutyl) phenol, ethoxylated (OPNEO)', December 18, 2018, Patricia Janz, Christiane Brandt); see supporting document to the CSRs 'SD1_CSR_Hazard_assessment_OPnEO_RDG_Use1-4'

Table 26. Comparison of combined local and regional PECs (in $NP_{equiv.}$) with available reference values for fresh waters at the sunset date.

Sites/Region	**Unit**	**Combined Freshwater PEC [µg/l]**	**Background values (range)[1] [µg/l]**	**EQS [µg/l]**	**Ratio PEC / EQS**
Mannheim	µg/l	0.0000586	0.05-0.1	0.043	0.0014
Penzberg	µg/l	0.0124	0.05-0.1	0.043	0.29
Wide-dispersive uses					
Average-size laboratory	µg/l	0.0000882	0.05-0.1	0.043	0.002
Big blood bank	µg/l	0.00206	0.05-0.1	0.043	0.05
Regional	µg/l	0.0000143	0.05-0.1	0.043	0.0003

[1]Range for surface and groundwaters

Production site of Mannheim – OP

Earlier measurements at the outlet of the secondary clarifier of the municipal STP of Mannheim showed levels of approximately 20 ng/L OP (median of 7 measurements on 7 days in March 2012). After sand filtration and treatment with activated carbon, these levels were reduced to below 5 ng/L.

In comparison, modelled data in the STP Mannheim effluent amount to 0.0335 µg/L $OP_{equiv.}$ or 33 ng/L $OP_{equiv.}$ for the sum of Uses 1-4, which is higher than the measured OP concentration in the municipal STP effluent (5 ng/L). The reason that modelled data are higher than the measured data is that the modelling assumptions were very conservative and furthermore, the reported concentration only represents the measured concentration of OP in the effluent. However, additional compounds which ultimately could be degraded into OP are expected to still be present in the STP effluent, i.e. remaining OPnEO and further intermediate degradation products of OPnEO. This contribution to the total $OP_{equiv.}$ concentration was taken into account in the modelling calculations performed in the CSR. If the measured concentration of OP in the STP effluent is extrapolated to total $OP_{equiv.}$ (a factor of 15 between the OP concentration and the total $OP_{equiv.}$ concentration was determined in the model), the reported concentration of about 5 ng/L OP in the STP effluent would correspond to a total concentration of 75 ng/L. $OP_{equiv.}$ This concentration would be higher than the predicted effluent concentration of 33 ng/L $OP_{equiv.}$ at the STP in Mannheim. The latter value already represents a maximum as it is assumed that all different activities are taking place on the same day. As the municipal STP receives wastewater from different sources, the **higher measured concentrations in the municipal STP effluent** are in agreement with the fact that **RDG's site may not be the only contributor** to the release of $OP_{equiv.}$ to the municipal STP.

The local PEC in surface water at Mannheim (i.e. the Rhine) was calculated to be 0.000506 µg/L, i.e. 0.506 ng/L (Uses 1-4 + regional; $OP_{equiv.}$; see Table 25). This concentration is a factor of 40 lower than the measured concentration of OP in the Rhine at Koblenz (which is downstream of Mannheim) of 21 ng/L (average 2016). In reality, the relative contribution of RDG's emissions to OP concentrations in the Rhine will be even lower as the modelled PEC values are $OP_{equiv.}$ (i.e. the sum of OP and all of its precursors) and the measured concentrations are OP concentrations only. Despite these conservative assumptions, the comparison of modelled $OP_{equiv.}$ with measured OP concentrations already shows that the local PEC is much smaller than the measured values. Hence, the **contribution of Mannheim RDG** site including regional exposure covered in the CSR **to current concentrations of OP in surface waters is small**.

The local PEC in surface water at Mannheim (0.506 ng/L, see above) is also approximately 200 times lower than the AA-EQS of 100 ng/L for OP, resulting in a PEC / EQS ratio of 0.005 (see Table 25). Furthermore, the local PEC in surface water at Mannheim is also approximately 67 times lower than the PNEC of 34 ng/L for OP, resulting in a PEC / PNEC ratio of 0.015 (see Table 25). PEC / PNEC ratios of <0 usually indicate that no potential risk exists. However, since it is assumed in the CSR that no threshold value can be assigned to OPnEO and its degradation products, the calculation of the ratios is for illustration purposes only. Since the modelling assumptions were demonstrated to be very conservative, it can be assumed that the **'true' contribution of the RDG site in Mannheim** to the environmental OP concentrations **will likely be much lower than the EQS value or the PNEC value**.

Production site of Mannheim – NP

Earlier measurements at the outlet of the secondary clarifier of the municipal STP of Mannheim showed levels of approximately 50 ng/L NP (median of 7 measurements on 7 days in March 2012).

After sand filtration and treatment with activated carbon, these levels were reduced to below 40 ng/L.

In comparison, modelled data in the STP Mannheim effluent amount to 0.0255 µg/L $NP_{equiv.}$ or 25.5 ng/L $NP_{equiv.}$ (Use 2), which is lower than the measured NP concentration in the STP effluent (40 ng/L), but within the same order of magnitude. However, the modelling assumptions were very conservative. Furthermore, the reported concentration only represents the measured concentration of NP in the effluent. In addition, further compounds which could be degraded to NP are expected to still be present in the STP effluent, i.e. remaining NPnEO and further intermediate degradation products of NPnEO. This contribution to the total $NP_{equiv.}$ concentration was taken into account in the modelling calculations performed in the CSR. If the measured concentration of NP in the STP effluent is extrapolated to total $NP_{equiv.}$ (a factor of 38 between the NP concentration and the total $NP_{equiv.}$ concentration was determined in the model), the reported concentration of about 40 ng/L NP in the STP effluent would correspond to a total concentration of 1520 ng/L $NP_{equiv.}$. This concentration would be a factor of approximately 60 higher than the predicted effluent concentration of 25.5 ng/L $NP_{equiv.}$ at the STP in Mannheim. The latter value already represents a maximum as it is assumed that all different activities are taking place on the same day. As the municipal STP receives wastewater from different sources, the **higher measured concentrations in the municipal STP effluent** are in agreement with the fact that **RDG's site may not be the only contributor** to the release of $NP_{equiv.}$ to the municipal STP.

The local PEC in surface water at Mannheim (i.e. the Rhine) was calculated to be 0.0000586 µg/L, i.e. 0.0586 ng/L (Use 2 + regional; $NP_{equiv.}$; see Table 26). This concentration is a factor of 800-1'700 lower than the measured concentration of NP in surface waters of 50-100 ng/L (range for surface and groundwaters). In reality, the relative contribution of RDG's emissions to NP concentrations in the Rhine will even be lower as the modelled PEC values are $NP_{equiv.}$ (i.e. the sum of NP and all of its precursors) and the measured concentrations are NP concentrations only. Despite these conservative assumptions, the comparison of modelled $NP_{equiv.}$with measured NP concentrations already shows that the local PEC is much smaller than the measured values. Hence, the **contribution of Mannheim RDG** site including regional exposure covered in the CSR **to current concentrations of NP in surface waters is small**.

The local PEC in surface water at Mannheim (0.0586 ng/L, see above) is also approximately 700 times lower than the AA-EQS of 43 ng/L for NP, resulting in a PEC / EQS ratio of 0.0014 (see Table 26). Since the modelling assumptions were demonstrated to be very conservative, it can be assumed that the **'true' contribution of the Mannheim RDG site** to environmental NP concentrations **will likely be much lower than the EQS value**.

<u>Production site of Penzberg – OP</u>

The only measurements available in effluent of the STP at Penzberg are those obtained from the monitoring campaigns performed in February / March and November / December 2018. The monitoring data were compared with the modelling results for Use 4 in the CSR (see Section 9.4.5 of the CSR for Use 4). The data confirmed that the assumptions used in the model 'Multifate' were very conservative (e.g. assumption of no complete mineralisation). Because there is no additional contribution of the activities involving OPnEO covered in Uses 1, 2 and 3 to the combined exposure at Penzberg, further comparison is not required.

The local PEC in surface water at Penzberg (i.e. the Loisach) was calculated to be 0.0533 µg/L, i.e. 53 ng/L (Use 4 + regional; $OP_{equiv.}$; see Table 25). This concentration is in the same range as measured environmental concentrations (rivers and groundwaters across the EEA show concentrations in the

range of 20-700 ng/L). In reality, the relative contribution of RDG's emissions to OP concentrations in the Loisach will be lower as the modelled PEC values are $OP_{equiv.}$ (i.e. the sum of OP and all of its precursors) and the measured concentrations are OP concentrations only. From the modelling calculations, a factor of 15 between the OP concentration and the total $OP_{equiv.}$ concentration could be determined. Using this factor, the reported OP concentrations of 20-700 ng/L in surface water would correspond to a total concentration of 300-10'500 ng/L $OP_{equiv.}$, which is higher than the modelled local PEC in the surface water at Penzberg. As surface waters receive wastewater from different sources, the **higher observed concentrations in receiving surface waters** are in agreement with the fact that **RDG's site is not the only contributor** to the release of $OP_{equiv.}$.

The local PEC in surface water at Penzberg (53 ng/L) is approximately half the AA-EQS of 100 ng/L for OP, resulting in a PEC / EQS ratio of 0.5 (Table 25). Furthermore, the local PEC in surface water at Penzberg is higher than the PNEC of 34 ng/L for OP, resulting in a PEC / PNEC ratio of 1.57 (Table 25). Since the modelling assumptions were demonstrated to be very conservative (see comparison with monitoring data in the CSR for Use 4), it can be assumed that the 'true' contribution of the Penzberg RDG site to environmental OP concentrations will likely be lower than the modelled PEC value. Furthermore, for PEC calculation it was assumed that all rinsing water from the processes is released to the STP in one day (worst-case) and such a release would only occur 3 to 4 times per year (see Appendix 2 to the CSR for Use 4). Therefore, very likely, the PEC / PNEC ratio will be below 1 for surface water in Penzberg. This is supported by monitoring data in STP effluent for large processes without RMMs where the maximum concentration reached 0.84 µg/L $OP_{equiv.}$ in the STP effluent, corresponding to a concentration of 1.14 ng/L in surface water (Loisach) when applying a dilution factor of 740. This concentration is **well below the PNEC of 34 ng/L** (see above).

Production site of Penzberg – NP

No measurements are available for NP in effluent of the STP at Penzberg based on processes or formulation activities covered in this AfA. The only measurements available for the STP effluent in Penzberg are those for OPnEO obtained from the monitoring campaign performed in February / March and November / December 2018 for processes covered in the CSR of Use 4 (see Section 9.5.6 of CSR Use 4 and see above under 'OP').

The local PEC in surface water at Penzberg (i.e. the Loisach river) was calculated to be 0.0124 µg/L, i.e. 12.4 ng/L (Use 2 + Use 4 + regional; $NP_{equiv.}$; see Table 26). This concentration is a factor of 4-8 lower than the measured environmental concentrations (rivers and groundwaters across the EEA show concentrations in the range of 50-100 ng/L). In reality, the relative contribution of RDG's emissions to NP concentrations in the Loisach will be lower as the modelled PEC values are $NP_{equiv.}$ (i.e. the sum of NP and all of its precursors) and the measured concentrations are NP concentrations only. From the modelling calculations, a factor of 38 between the NP concentration and the total $NP_{equiv.}$ concentration could be determined. Using this factor, the reported NP concentrations of 50-100 ng/L in surface water would correspond to a total concentration of 1'900-3'800 ng/L $NP_{equiv.}$, which is higher than the modelled local PEC in the surface water at Penzberg. As surface waters receive wastewater from different sources, the **higher observed concentrations in receiving surface waters** are in agreement with the fact that **RDG's site is not the only contributor** to the release of $NP_{equiv.}$.

The calculated local PEC in surface water at Penzberg (12.4 ng/L, see above) is approximately 4 times lower than the AA-EQS of 43 ng/L for NP, resulting in a PEC / EQS ratio of 0.25 (Table 26). Since the modelling assumptions were demonstrated to be very conservative, it can be assumed that

the **'true' contribution of the Penzberg RDG site** to environmental NP concentrations **will likely be much lower than the EQS value**.

Wide-dispersive uses - OP

The local PEC in surface water for wide-dispersive uses was calculated to be 0.00306 µg/L for an average-size laboratory to 0.0184 µg/L for a large laboratory, i.e. 3.06 ng/L to 18.4 ng/L (Use 3 + regional; $OP_{equiv.}$; see Table 25), respectively. This concentration is lower than measured environmental concentrations (rivers and groundwaters show concentrations across the EU in the range of 20-700 ng/L).

Local $OP_{equiv.}$ in soil porewater of 0.12 pg/L, i.e. 0.00000012 µg/L (which, according to the guidance document, are assumed to be identical to groundwater concentrations) are by a factor of 30'000 lower than calculated surface water concentrations of 0.00351 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 (3.06-18.4 ng/L, see above) is also approximately 5-32 times lower than the AA-EQS of 100 ng/L for OP, resulting in a PEC / EQS ratio of 0.031-0.184 (Table 25). Furthermore, the local PEC for wide-dispersive uses in surface water is also approximately 2-11 times lower than the PNEC of 34 ng/L for OP, resulting in a PEC / PNEC ratio of 0.09-0.54 (Table 25). 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 0.0000882 µg/L for an average-size laboratory and 0.00206 µg/L for a big blood bank, i.e. 0.0882-2.06 ng/L (Use 3 + regional; $NP_{equiv.}$; see Table 26). These concentrations are a factor of 24-1'100 lower than the measured concentration of NP in surface waters of 50-100 ng/L.

Local $NP_{equiv.}$ in soil porewater of 0.027 pg/L, i.e. 0.000000027 µg/L (which, according to the guidance document, are assumed to be identical to groundwater concentrations) are by a factor of 3'800 lower than calculated surface water concentrations of 0.000103 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 (0.0882-2.06 ng/L, see above) is also approximately 20-490 times lower than the AA-EQS of 43 ng/L for NP, resulting in a PEC / EQS ratio of 0.002-0.05 (Table 26). 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 the different uses. For this comparison, it should be kept in mind that regional exposure was estimated based on releases at downstream user sites from Use 3 as the main source of release with the assumption that 10% of the total amount is released in one 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. In addition, 100% of the releases from the two production sites was also assumed to be released in the same region. However, as was discussed above, **releases from production sites are small in comparison to releases from wide-dispersive uses**.

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 $OP_{equiv.}$ at Penzberg and for local wide-dispersive use. At Mannheim, regional exposure (due to releases from wide-dispersive uses) was higher than local exposure for OP. 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

Contribution of regional exposure (0.45 ng/L) to total local exposure at Mannheim (Uses 1, 2 and 4 + regional; $OP_{equiv.}$) of 0.058 ng/L is larger than the contributions of the respective uses 1, 2 or 4. Hence, the local uses of OPnEO (1, 2 and 4) do not contribute much to the total exposure of surface waters with $OP_{equiv.}$ at Mannheim.

Contribution of regional exposure (0.448 ng/L) to local exposure at Penzberg (Use 4 + regional; $OP_{equiv.}$) of 52.8 ng/L is much lower than the contribution of the respective Use 4. Hence, the main contribution to total exposure of surface waters with $OP_{equiv.}$ at Penzberg is Use 4. However, under the modelling assumptions used, such a high release would only occur 3 to 4 times per year (see supporting document SD4a_CSR_Usage_Releases_OPnEO_RDG_Use4_CONFIDENTIAL of CSR for Use 4). Normal release is expected to be much lower.

Contribution of regional exposure (0.45 ng/L) to wide-dispersive uses (Use 3; $OP_{equiv.}$) of 3.06 ng/L is much lower than the contribution of the respective Use 3. Hence, the main contribution to total local exposure of surface waters with $OP_{equiv.}$ due to wide-dispersive uses is Use 3.

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 five thousand lower than calculated surface water concentrations and hence, are not assumed to contribute to $OP_{equiv.}$ in surface water (e.g., Table 32 in CSR use 2).

Regional exposure – NP

Contribution of regional exposure (0.0143 ng/L) to total local exposure at Mannheim (Use 2 + regional, $NP_{equiv.}$) of 0.0586 ng/L is smaller than the contribution of the respective Use 2. Hence, the local use of NPnEO (Use 2) contributes to a greater extent than regional exposure to the total exposure of surface waters with $NP_{equiv.}$ at Mannheim.

Contribution of regional exposure (0.0143 ng/L) to total local exposure at Penzberg (Uses 2, 4 + regional; $NP_{equiv.}$) of 12.4 ng/L is much lower than the contribution of use 2. Hence, the main contribution to total exposure of surface waters with $NP_{equiv.}$ at Penzberg is Use 2 (12.3 ng/L).

Contribution of regional exposure (0.0143 ng/L) to total local exposure from wide-dispersive uses (Use 3; $NP_{equiv.}$) of 0.103 ng/L is approx. a factor of 10 lower than the contribution of the respective Use 3. Hence, the main contribution to total exposure of surface waters with $NP_{equiv.}$ due to wide-dispersive uses is Use 3.

Regional $NP_{equiv.}$ in soil porewater (0.15 pg/L) (which, according to the guidance document, are assumed to be identical to groundwater concentrations) are by a factor of at least seven hundred lower than calculated total surface water concentrations and hence, are not assumed to contribute to $NP_{equiv.}$ in surface water (e.g., Table 41 in CSR Use 2).

Overall conclusion

Comparison of data from newly set up monitoring campaigns in the effluent of the on-site STP in Penzberg with modelled concentrations **confirmed the robustness of the exposure scenario modelling** as modelled concentrations were higher than measured concentrations. For Mannheim, the wastewater from production at the RDG site is likely not the only source of OP or NP. For this reason, modelled and measured OP / NP (equivalent) concentrations cannot be directly compared and a new monitoring campaign at the outlet of the STP was not conducted at Mannheim. However, **monitoring is planned to be performed after the implementation of RMMs**, i.e. after the submission date, in wastewater from the site. Also, an additional campaign will be conducted in the STP effluent in Penzberg. This monitoring will be performed for OPnEO (and its degradation products) for which recently a method has become available that is sufficiently sensitive to perform such measurements. It will serve to confirm the effectiveness of RMMs that were implemented to minimize emissions at the production sites. Similar to Mannheim, no monitoring campaign was conducted at a laboratory / hospital / blood bank / point of care or an associated STP since measurements would not only reflect emissions from the downstream user site but likely be a mixture of several sources. As amounts of OPnEO and NPnEO contained in the assays and the fractions that are released are known, 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.

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 **most concentrations were well below the EQS / PNEC values**, with one exception at Penzberg, where modelled concentrations for $OP_{equiv.}$ in surface water exceeded the PNEC value for maximum daily releases occurring on 3-4 days per year. However, due to very conservative assumptions in the modelling, very likely, the PEC / PNEC ratio will also be below 1 for surface water in Penzberg. This is supported by monitoring data in STP effluent for large processes without RMMs where the maximum concentration reached 0.84 µg/L $OP_{equiv.}$ in the STP effluent, corresponding to a concentration of 1.14 ng/L in surface water (Loisach) when applying a dilution factor of 740. This

concentration is **well below the PNEC of 34 ng/L**. This **broad margin of safety** at most times and locations can serve as an indication that the overall releases from RDG's activities and downstream uses to the environment are not expected to cause issues in the receiving surface waters or agricultural soil.

Finally, 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 RDG's activities and downstream uses is small**.

Qualitative description of impacts

Taking all abovementioned information into account, the **impacts** of the releases from RDG's activities and 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 (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.

⇨ These impacts would occur due to interruption of the IVD production either due to non-authorisation of Use 2& 3 and / or Use 4 as most portfolios are depending on two or three of these uses.

As described in the non-use scenario, RDG will not be able to continue to formulate the IVD assays (Use 2), to produce the proteins and conjugate the latex beads (Use 4) and to produce the respective downstream products at the sites in Germany in case of non-authorisation. RDG will thus not be able to continue to deliver these products to their customers worldwide. At the same time, Roche's customers, i.e. laboratories, hospitals and doctors' practices within the EEA will not be able to perform the full portfolio of IVD assays, with immediate effect for the assays covered under Use 3. In non-EEA countries, this impact will be somewhat delayed as assays available on stock could still be performed. However, customers will also not be able to perform assays in non-EEA countries as soon as the customers' and RDG's stocks are depleted.

To **evaluate the impacts** in case of the non-use scenario, it is important to consider possible assumptions regarding the situation of RDG's competitors, i.e. the situation on the EEA and global 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 RDG'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 50).

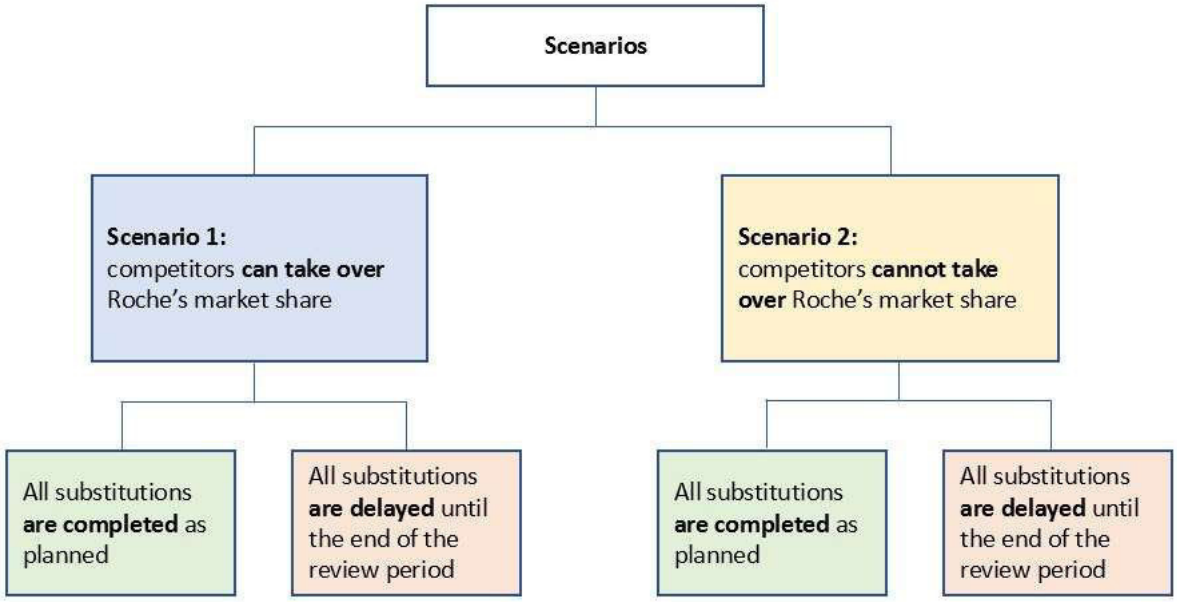


Figure 50. Overview of the two scenarios considered in the impacts assessment with two sub-scenarios depending on the completion of substitution projects.

As indicated, Scenario 1 and 2 are extremes and the likely impacts are expected to be in-between. The following factors render it **unlikely that competitors can fully take over Roche's market share**:

a) Some IVD manufactures depend on proteins provided by RDG depending on Use 4 and are thus directly affected by this dossier and

b) From sector evaluations within the trade association medtech, it is known that other IVD manufactures are using opneo in their assays even though information on the details are not available.

On the other hand, it is **expected** that at least **some competitor** systems that are not affected **will be available to replace a part of RDG's systems** considering the worldwide market of IVD manufactures. 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. Roche is expected to face compensation claims for this investment.

The impacts summarised above would occur due to interruption of Use 2&3 as well as Use 4. Additionally, supply interruptions of the market with products from CB's industrial customers are expected under Use 4 due to the inability of RDG to deliver the proteins and MDx Enzymes needed by these customers to produce IVD assays. Additionally, further healthcare services will be impacted as the production of some medicinal products depends on CB's proteins.

In the following sections, the **details of these impacts are first described for the different product groups**. The following three groups of assays are discussed separately due to some differences in consequences of the non-use scenario:

- Assays used in centralised laboratories:
    - Clinical chemistry
    - Drug monitoring
    - HIV
    - Urinalysis (automated solutions)
    - Tumour Marker
    - Roche Tissue Diagnostics

- Assays used at the location of treatment:
    - Blood gas and electrolytes
    - **Accutrend®**
    - Urinalysis

- Assays with alternative products but technological advantages:
    - Roche molecular diagnostics

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 51 based on the assumption that all substitutions are delayed. Note that not all impacts are shown.

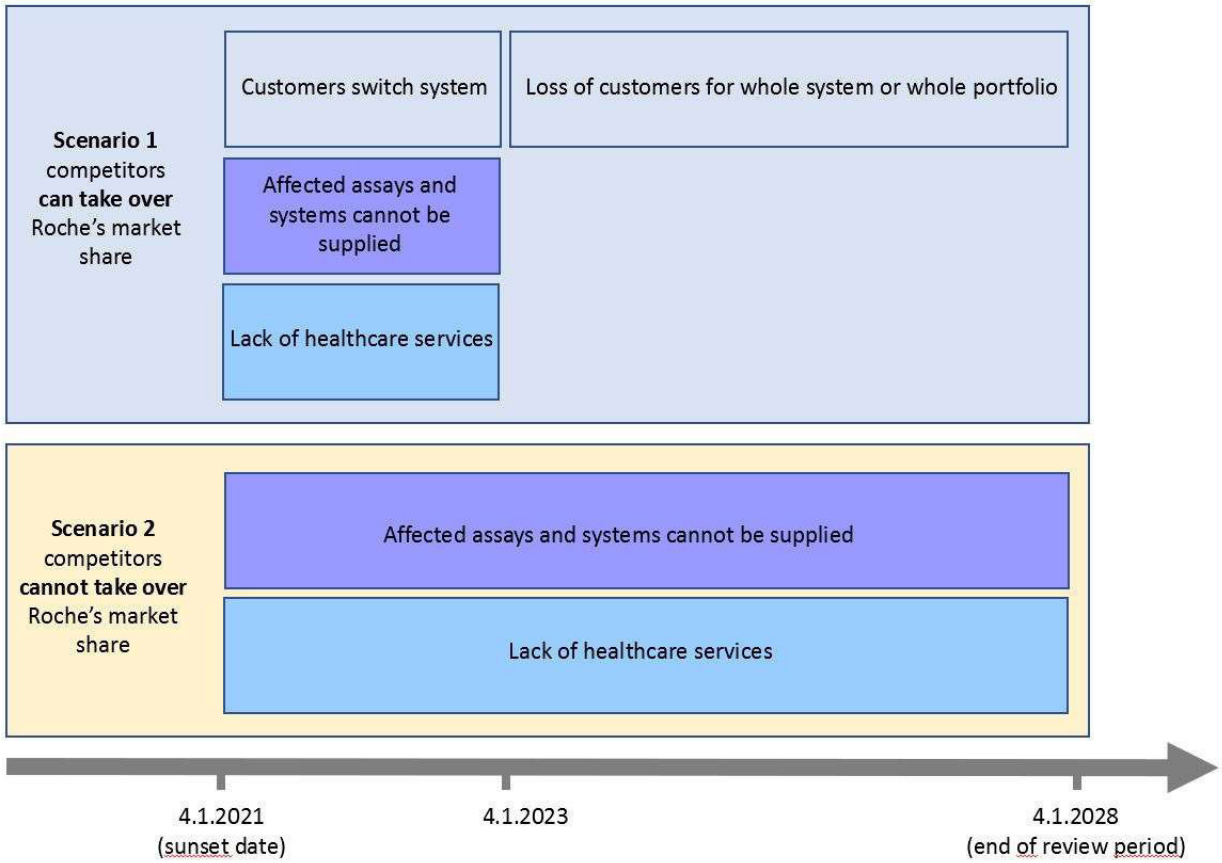


Figure 51. Most important direct consequences and the occurrence of impacts on healthcare services in the two scenarios over the course of the review period if all substitutions are delayed. (Not all impacts are shown).

Subsequently, impacts are quantified and summarised per Use and 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 Roche can no longer supply certain assays, this will lead to **gaps in the parameter portfolio** and **a breach of 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**.
- ⇨ 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 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 **compensation claims** due to breach of delivery 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 and
  - The lack of competitor assays as a significant part of **Roche's competitors depends on the proteins produced by Roche** for their CC assays.

As described in the non-use scenario, RDG will not be able to continue to formulate the IVD assays (Use 2), to produce the proteins, to conjugate the latex beads (Use 4) and produce the respective downstream products at the sites in Germany in case of non-authorisation. RDG will thus not be able to continue to deliver these products to their customers (hospitals, laboratories, blood banks) leading to a breach of contracts. For the product portfolios of CC, DM and TM these customers are mainly large centralised private laboratories or centralised laboratories in hospitals (see further description in Section 0) and for HIV centralised laboratories and in addition, blood banks. UA assays based on automated solutions are also run in centralised laboratories and similar considerations as discussed below apply. However, UA assays are discussed in more detail in Section 3.2.3. 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 26 in Section 2.7.3), the RDG portfolio of clinical chemistry (incl. drug monitoring) comprises ~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) etc.. 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**. If the TM assay is not available, an important marker in oncology, part of Roche's lung cancer tumour panel to diagnose lung cancer is missing. Indeed, RDG is **the only diagnostic company** that can provide a **full lung cancer tumour marker panel**. 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. Apart from the additional costs and efforts (which for certain would be charged to Roche by the customer), 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 in markets where Roche is the **market leader** as is the case in many EEA countries (see Table 6 for Roche's market share in EEA countries, e.g. > 30% 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), 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 any more. 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 would likely be informed of a non-authorisation decision only shortly before or even 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 that fall under Use 2&3 and / or Use 4 would jeopardize 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, RDG is therefore expected to face **losses** based on affected assays that cannot be sold. RDG forecasts also **compensation claims** from Roche's customers due to breach of delivery contracts, which are normally in place for a duration of 5-7 years (see Section 3.3.3 for further information on penalties). This indemnity will be needed to compensate for the inability to perform tests or additional costs for testing certain parameters in other laboratories (if at all feasible; see above). If some of these costs could not or would not be claimed from Roche, the customers themselves - and thus ultimately insurance schemes and the healthcare system – would have to face the financial consequences.

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. For some projects, even the likely timelines (not considering any additional risks) go beyond a timeframe of 12-24 months after the sunset date (see

AoA Use 2&3 and Use 4). Therefore, 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, 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. Therefore, Roche may be **faced with additional compensation claims** from customers for such a switch. In the further assessment of Scenario 1, it is assumed that all laboratories could be switched within **24 months** assuming sufficient capacities from competitors.

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 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 or doctor's practices). 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 EEA as well as non-EEA countries. The case of the HIV assay and the associated infectious disease portfolio differs from the CC/DM portfolio as Roche is offering a new-generation analyser with a new HIV assay, which is currently introduced to the market for high-throughput customers. At this moment, the old system still has a strong position on the market [redacted]. Ca. [redacted]% of the market is actually based on small to mid-throughput analysers for which an alternative system is not yet available. Therefore, Roche may be able to switch only a small fraction of the existing customers, and in particular blood banks, to the new system. This replacement is already ongoing for high-throughput analysers. However, in the case of the non-use scenario, it remains open, if customers would be willing to invest into a new Roche infectious disease system despite 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 and Roche may face further compensation claims from customers. Indeed, a severe lack of CC services may occur as a significant part of **Roche's competitors also depend on the proteins produced by Roche using OPnEO** (covered under Use 4) for their CC assays. Competitors will thus be directly affected by a non-authorisation decision for this AfA, Use 4. Therefore, it is unlikely that competitors will be able to cover the lack of CC assays on the EEA, but also on the world market.

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 2.7.1.1.8) 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 Description of Impacts for IVD Assays Used in Point of Care Units Including Urinalysis

- ⇨ For AT, UA and BGE impacts will occur for the **entire system** and not only for the specific assays or elements of the kits.
- ⇨ Due to the **short-term stability of samples** or the need for **immediate measurements**, sending out samples to other laboratories is not an option.
- ⇨ Since the usage of competitor assays or reagents is also not possible (closed system) the **only possibility** is the **replacement by a competitor system**.
- ⇨ For all UA and AT systems that are hand-held devices or test strips for manual reading the switch is expected to be **relatively quick** if competitor systems are not affected by the OPnEO / NPnEO ban.
- ⇨ Instruments in UA and BGE, will be more easily switched than whole laboratory installations, but **6 - 12 months** are still required for each instrument and a total of 24 months would likely be needed to switch all customers.
- ⇨ A non-authorisation will result in the unavailability of critical BGE assays in Intensive Care Units and Emergency Rooms.

For assays mainly used in Point of Care Units, impacts will occur for the **entire system** rather than only for the specific assays or elements of the kits affected (e.g. control solution). This is due to one of two reasons (see also Section 2.7.3 for explanation on interrelations of assays)

1) The entire system is not usable without the affected element, e.g. the control solution, like for the **Accutrend**® system or

2) A whole range of parameters is measured in the same sample with one system, like for the test strips for Urinalysis or BGE so that a measurement of only a part of the parameters does not provide any benefit and would not be performed.

Therefore, for these products an alternative system would have to be available instantly. This, is however not, or only partially, feasible similar to centralised laboratories, but with some differences specific to these kinds of assays. Due to the **short-term stability of samples** or the need for **immediate measurements**, sending out samples to other laboratories is not an option. According to test instructions, for UA, measurements have to be performed within 2 hours, for BGE within 0.5 h and for **Accutrend**® even within minutes. Usage of competitor assays or reagents is also not possible (the systems are closed as described for the centralised laboratories). Therefore, the only possibility for laboratories and physician's practices in case of the non-use scenario is the replacement by a competitor system which is not concerned by the OPnEO / NPnEO ban. In the case of UA (test strips used in PoC) and AT, it is expected that customers can substitute **relatively quickly** all systems as these are hand-held devices or test strips for manual reading. Whether competitor systems are affected by REACH authorisation requirements or not will determine if competitors can actually take over Roche's market share (Scenario 1) or not (Scenario 2). In Scenario 1, Roche's customers would need to invest resources to implement the switch to the competitor system.

For instruments such as UA instruments placed in laboratories or BGE instruments in laboratories or intensive care / emergency units a switch cannot be achieved immediately even though they will be more easily switched than whole laboratory installations. Especially, a switch of thousands of installed instruments cannot be achieved on short notice. The time required for one instrument is **6 months for UA and 6 -12 months for BGE**. For both systems it is estimated that approx. **24 months** would be needed to replace all systems considering expected capacities of competitors. The time required to switch will additionally depend on the resources of the laboratory (time / money / manpower) and the contract situation.

A non-authorisation will therefore **result in the unavailability of critical assays in intensive care units and emergency departments** as well as in Urinalysis assays run on laboratory-based instruments.

As described for centralised laboratories, RDG will face **losses from the assays / systems not sold** as well as **compensation claims and penalties** for the described assays mainly used in Point of Care Units.

3.2.4 RMD

- ⇨ For RMD1 customers could switch to another RMD assay or a competitor system, but **without the advantages** of this product such as receiving quick, accurate, definitive results that require no additional confirmation testing.
- ⇨ For RMD2, patients would not be able to benefit from the new Smarticles technology, which, among other benefits, yields **faster results**.

In the case of RMD **cobas**® Influenza A/B (Liat) (RMD 1), customers could easily switch to another RMD assay, **cobas**® Influenza A/B & RSV test, which is used for in vitro qualitative detection and discrimination of Influenza A virus, Influenza B virus and respiratory syncytial virus (RSV) RNA in nasopharyngeal swab specimens. This alternative RMD assay does not contain OPnEO surfactants and is currently available on the EEA market. However, switching to **cobas®** Influenza A/B & RSV is an option that may not be supported by Roche's customers due to **higher cost**. Therefore, customers may prefer to **switch to a competitor's product** instead. Similar competitor assays using other molecular diagnostics amplification and detection technologies are also available. However, availability of these products cannot be predicted. Overall, no unavailability of assays to detect Influenza A/B is expected for the market in case of the non-use scenario, but patients would not be able to **benefit from receiving quick, accurate, definitive results** that require no additional confirmation testing that leads to **same day treatment for the patient**. This easy to use automated LIAT platform qualitatively detects and differentiates Influenza type A and type B viral RNA using RT-PCR nucleic acid testing in 20 minutes.

RMD's other OPnEO containing assay (RMD2), vivoDx MRSA utilises Smarticles technology, an innovative technology that creates an amplified luminescent signal only in viable (live) MRSA cells that was CE-IVD launched in December 2018. It has advantages with respect to both

a) Classic identification by culture and / or PCR for screening and

b) Antimicrobial susceptibility testing.

Cobas® vivoDx MRSA has significant turnaround time and workflow advantages over culture, as its direct detection technology does not require the growth of bacterial cells in culture, leading to **faster results for the patient**. In addition, **cobas**® vivoDx MRSA does not depend on detecting known genetic markers for mechanisms of bacterial resistance as PCR competitors do, making the test valuable in instances where bacteria might develop new mechanisms of resistance over time.
VivoDx MRSA is intended to be a **unique offering in the market that confers both the phenotypic detection benefits of culture** (i.e. the benefit to only detect viable (i.e. live) antibiotic resistant cells) and the **rapid turnaround time** benefits of PCR (rapid detection of the presence of the genetic material). In case of the non-use scenario, RDG would not be able to keep this new product on the market. As this assay has been newly introduced to the market, customers could easily switch to another RMD assay or a competitor system, but **patients would not be able to benefit from this new technology**.

3.2.5 Market Position and Competitiveness for the IVD Business

- ⇨ Not being able to provide core systems (i.e. CC assays) renders **RDG no longer competitive** and may **reduce the sales** of other systems or portfolios (i.e. not affected by this authorisation).
- ⇨ Loss of part of Roche's IVD business and expected growth could lead to a **shift of revenues of the IVD business outside of the EEA**.
- ⇨ However, it is unlikely that competitors outside the EEA will be able to meet the increased demand in both EEA and non-EEA markets.
- ⇨ RDG expects to experience **loss of reputation and trust** gained in the past as IVD supplier.

As an IVD supplier, to provide all relevant products is a strong sales argument and often a requirement in tenders. Roche's business model (see Section 2.6) 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, HIV assays for mid-throughput systems, or more specialised products such as Drug Monitoring assays will render **RDG no longer competitive**. Therefore, the effects described above may go beyond the directly affected products (via Use 2&3 or Use 4) 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 ; Figure 30) **will be lost** during several years in addition to the possible loss of existing customers both leading to a gain at Roche's competitors. If all or some of those competitors are located outside the EEA, this could lead to a **shift of revenues** of the IVD business **outside of the EEA**. At least a partial shift outside of the EEA is expected as some competitors are located e.g. in Asia and the US and non-EEA competitors will not be affected by the OPnEO / NPnEO ban in production. However, given that Roche's customers worldwide will be affected (including non-EEA countries), it is unlikely to expect that competitors with a stronger presence in non-EEA countries will be able to fully meet the increased demand on the EEA market. This is unlikely as Roche's customers in non-EEA countries will likely also want to switch systems increasing the demand worldwide. To still **win tenders**, Roche might be forced to reduce prices or include competitor products in tenders to complete the portfolio at a high 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 dependency on proteins provided by RDG depending on Use 4, the competitors themselves being affected by the OPnEO / NPnEO ban or limited production capacities.

Beside losing competitiveness on the market, RDG expects to experience **loss of reputation and trust** gained in the past as IVD supplier. Losing customer trust can prove disastrous for any company but can be even worse for a leading company as Roche. Due to loss of trust, it is unlikely that the customer 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 3.2.3), 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, winning back customers after completed substitution or getting new customers in the future, leading to further economic losses. As stated above, at least **part of this business will likely be lost to companies outside of the EEA**.

3.2.6 Description of Impacts for Custom Biotech

- ⇨ The only possibility for RDG's industrial customers will be to **switch to another supplier of raw materials**. It is unclear if competitors would have sufficient capacity.
- ⇨ A switch to a new supplier implies capacity for re-validation and registration of the final assay which takes **from 2 up to 5 years**. Therefore, impacts on patients are expected through **lack of IVD assays**.
- ⇨ For the CB pharmaceutical customers, a switch to a new supplier might imply **unavailability of their medicinal products** on the market.

Under the non-use scenario Roche will **not be able to sell the Custom Biotech products to customers** (please see Section 2.7.2 for a complete list of the affected downstream products).

As for the IVD business (see section before) this will lead Roche not being able to fulfil customer contracts. Given the impossibility for Roche to supply the raw materials (proteins / MDx Enzymes based on Use 4), the only possibility for industrial customers will be to **switch to another supplier** as a lack of supply of a maximum of 3-6 months may be acceptable for customers. Beside the fact that it is unclear if Roche's competitors have enough capacity to take over Roche's large market share, a switch to a competitor product (i.e. enzyme / proteins) will mean that some steps need to be undertaken to re-validate and possibly re-register the final products (e.g. in the case of IVD). This includes a great effort from the industrial customers perspective in terms of time and resources and is expected to take **at least 2 years**, and if real-time stability studies for the IVD assays are needed, **up to 5 years**. Until such changes are completed, **impacts on patients** are expected through **lack of IVD assays** on the market as hospitals and laboratories depending on CB customers' IVD assays will face a similar situation as described above in Section 3.2. In the same way as described for Roche, CB customers' will risk losing their customers and their customers' trust damaging their market position and their reputation.

CB sells raw material for cell cultures in pharmaceutical manufacturing. Raw materials are often part of a validated process and as soon as the medicinal product is on the market a change in manufacturing processes is very critical. This is due to the fact that a change may require re-validations and re-registrations of the medicinal products by CB's customers. Most important for CB customers in the pharmaceutical industry is a **100% reliable supply** for a long period (>10 years) without changes to the products. Therefore, CB has established long-term contracts with these customers with very strict terms and conditions which could not be fulfilled in case of non-authorisation likely **leading to unavailability of the medicinal products** on the market.

Failure by Roche to supply the products to customers will lead to a significant number of claims for compensation by affected CB customers which poses an inacceptable financial risk for Roche. In fact, **liability is not limited** in the contracts, meaning that compensation might hypothetically be unlimited (see Section 3.3.3.2). Breach of contracts will lead to substantial **loss of trust** in Roche as a reliable business partner with a substantial customer loss because the customers will be forced to switch to different suppliers to minimise damages. The lost customers would probably not come back in the future and Roche, which is a leading supplier of high-quality raw materials and reagents worldwide, might lose its competitiveness on this market completely.

Also, customers of generic products (i.e. products without specific contracts freely available on the market for other customers) might switch to similar products purchased from competitors (if available without OPnEO / NPnEO). For the generic market, it is estimated that a period between **3 and 6 months** may be tolerated by customers as periods of supply interruption of such a duration are common in this business. As substitution is expected to take longer, at least for the proteins (see AoA), customers of the generic biochemical reagents business are also expected to be lost.

3.3. Quantification of Economic Impacts Per Use

3.3.1 Approach for Quantification of Impacts

- ⇨ Financial losses are estimated for **RDG** based on affected assays / systems not sold and existing and new customers that are expected to be lost.
- ⇨ The economic impact analysis is done **combined for Use 2&3 and separately for Use 4** based on the above described expected impacts of a non-authorisation.
- ⇨ Estimates are provided separately with respect to **EEA and non-EEA customers** due to some delay of impacts at non-EEA customers.
- ⇨ 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)**.
- ⇨ For portfolios with different assays affected by Use 2&3 or Use 4, impacts occurring at the level of the portfolio are divided **50:50** between these two use groups.
- ⇨ Roche customers are expected to **claim compensation for financial losses** from Roche based on breach of contracts turning customers' losses into **additional cost for Roche**.
- ⇨ This cost is roughly estimated based on affected assays not sold 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 2021 until the end of 2027 in case the authorisation was not granted. This **analysis is done for Use 2&3 and separately for Use 4** based on the above described expected impacts for RDG (in case of non-authorisation for use of OPnEO / NPnEO) for the different product groups. 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 product groups CC / DM and AT are affected by both the use of OPnEO / NPnEO in products (Use 2&3) as well as the use of these substances in the production of proteins and the conjugation of latex beads (Use 4) that are either used directly in these assays or used to manufacture further components of the assays. 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. Therefore, the impacts would remain the same for CC / DM and AT even if the product uses (Use 2&3) were authorised and only the production processes (Use 4) would have to be stopped or vice versa. The AT system will not be functional anymore if one of the components is missing and the CC portfolio will not be useful for customers if important parameters cannot be measured. The DM assays cannot be produced if the latex beads (based on Use 4) are missing. For Scenario 1, impacts for these assays (see Section 3.2) are therefore distributed **50:50** between Use 2&3 and Use 4. Only the impacts from the direct loss from sales of affected CC assays (individual assays are affected either by Use 2&3 or

Use 4, but not by both) and potential direct compensation are specifically assigned to the two use groups. Direct loss from sales of affected DM assays and the AT system are divided 50:50 between Use 2&3 and Use 4 as almost all DM assays and the AT system depend on both uses.

For **Scenario 2**, i.e. assuming that competitors cannot take over Roche's market share, impacts are assigned specifically to Use 2&3 and Use 4. Direct loss from sales of affected DM assays and the AT system are divided 50:50 between Use 2&3 and Use 4 as almost all DM assays and the AT system depend on both uses. All other individual assays can be either assigned to Use 2&3 or Use 4.

For **both scenarios**, impacts are estimated combined for Use 2&3 as these two uses cover one supply chain and impacts are the same whether an assay cannot be produced at RDG (Use 2) or cannot be used at the customers (Use 3). Some assays are only in scope of either Use 2 (due to final concentrations below 0.1 % w/w) or Use 3 (assays imported from outside of EEA). However, it was not deemed to improve the analysis if impacts were further differentiated between Use 2 und Use 3. In any case, at least for Scenario 1, the main impacts occur at the level of the portfolio.

To assess the impacts in case of the non-use scenario, RDG'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 RDG itself, Roche's customers will be directly affected in case of the non-use scenario as described above. RDG will not be able to supply the affected products, materials and customers in the EEA will themselves 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 (Use 3). However, Roche's customers are expected to **claim compensation for financial losses from Roche** based on supply contracts turning customers' losses into additional costs for Roche. Compensation claims are difficult to estimate due to a large variety of contractual provisions. As an indication, this cost is roughly estimated based on affected assays not sold (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, but this gain cannot be reliably estimated. As discussed above, this may imply a shift of turnover of the IVD business from EEA to non-EEA countries.

Additional impacts are likely to occur at RDG's suppliers through decreased need for raw materials at RDG. The information necessary for quantification of these impacts is not available, implying that the overall impacts are an underestimation.

In summary, **financial losses** as listed in Table 27 and compensation claims as listed in Table 28 and Table 25 are expected for the combined Use 2 & 3 and for Use 4 (for Roche IVD assays based on Use 4) depending on the scenario. Impacts for the CB Business are provided separately in Table 29 due to the different nature of the Business, i.e. sales of materials mainly to IVD manufacturers. Time when the impact is expected to occur, and maximum duration used for the calculations are indicated in the tables. Result of the calculations are provided in Sections 3.3.2 (financial losses) 3.3.3 (compensation claims from laboratories / hospitals) and 3.3.3.2 (compensation claims from CB customers).

See also Figure 51 for a qualitative, general illustration of the timelines in case all substitutions are delayed.

Table 27. 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	EEA: for 2 years after the sunset date Non-EEA: second year after the sunset date (for 2021 stocks are assumed to be available) • until customers have switched	EEA: 2 years Non-EEA: 1 year	Sales / EBITA from affected assays; based on predicted figures for 2021 (without growth in 2021 / 2022; or predictions for 2021 / 2022 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	EEA and non-EEA: 5 years	Sales / EBITA from affected portfolios; based on predicted figures from 2021 (i.e. without growth from 2021 or predictions for 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 Quantification of minimum values is the same as portfolios are affected even if substitutions are completed on time
Short- to medium-term loss of customers for the entire system incl. components that cannot be sold	BGE, AT, UA, RTD, RMD	EEA: from the sunset date Non-EEA: from second year after the sunset date (for 2021 stocks are assumed to be available)	EEA: 7 years Non-EEA: 6 years	Sales / EBITA from the systems that are not usable without the affected assay / component; based on predicted figures from 2021 (without growth; or predictions for 2021-2027 in case of a decline)*
Loss of new customers for the entire affected portfolios or systems if competitors are able to deliver the market with complete systems	All	Starting immediately after the sunset date	EEA and non-EEA: 7 years	Growth predictions for sales /EBITA for 2021-2027**
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	EEA: from the sunset date Non-EEA: from second year after the sunset date (for 2021 stocks are assumed to be available)	EEA: 7 years Non-EEA: 6 year	Sales / EBITA from affected assays based on predicted figures from 2021 (without growth from 2021 or predictions for 2021-2027 in case of a decline)*

Financial loss	Product group	Time when the impact is expected to occur	Maximum Duration	Quantification***
Medium-term loss of customers for the entire affected portfolios	CC, DM, HIV	No losses of customers expected as no alternative systems available		
Short- to medium-term loss of customers for the entire system incl. components that cannot be sold	BGE, AT, UA, RTD, RMD	EEA: from the sunset date Non-EEA: from second year after the sunset date (for 2021 stocks are assumed to be available)	EEA: 7 years Non-EEA: 6 years	Sales / EBITA from the systems that need the affected assay / component based on predicted figures from 2021 (without growth from 2021 or predictions for 2021-2027 in case of a decline)
Loss of new customers for the entire affected portfolios	CC, DM, HIV	No losses of new customers expected as the no complete systems assumed to be available on the market		
Loss of new customers for the entire affected systems as they are not usable	BGE, AT, UA, RTD, RMD	Starting immediately after the sunset date	7 years	Growth predictions for sales /EBITA for 2021-2027**

* 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 2021-2027 mean from beginning of the first until the end of the last year.

Additional cost is expected based on **customer claims due to breach of contracts**. The approach to estimate this for the two scenarios is summarised in Table 28. In this calculation, it is assumed that customers will claim all costs from Roche.

Table 28. Expected cost / compensation claims due to breach of contracts.

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				
Compensation of customers for affected operations and business lost or possibly compensation for increased testing efforts if samples can be sent to laboratories with competitors' systems	All Samples sent to competitors in limited cases for CC, DM, HIV, RTD	EEA: from the sunset date Non-EEA: from second year after the sunset date (for 2021 stocks are assumed to be available) ⇨ Until customers have switched	EEA: 2 years Non-EEA: 1 year	Cost based on affected assays not delivered Approximated by assay cost* (expected to be the minimum based on penalties in contracts, see Section 3.3.3)

Financial loss	Product group	Time when the impact is expected to occur	Maximum Duration	Quantification
		or contracts are terminated		
Compensation for costs connected to the switch from RDG's system to a competitor system	All	Customers are expected to switch mainly during the first two years after the sunset date	One-time payment Until contracts are terminated	Approximated by compensation for cost of new instruments (cost of instruments multiplied with installed base)** Cost not accounted for: e.g. rebuilding of infrastructure etc.
Additional penalties defined in contracts				not possible to quantify
Financial impacts for Scenario 2: Competitors cannot take over Roche's market share				
Compensation of customers for affected operations and business lost or possibly compensation for increased testing efforts if samples can be sent to laboratories with competitors' systems	All Samples sent to competitors in limited cases for CC, DM, HIV, RTD	EEA: from the sunset date Non-EEA: from second year after the sunset date (for 2021 stocks are assumed to be available) ⇨ Until contracts are terminated	EEA: 7 years Non-EEA: 6 years	Cost based on affected assays not delivered approximated by assay cost* (expected to be the minimum based on penalties in contracts, see Section 3.3.3)
Compensation for costs connected to the switch from RDG's system to a competitor system		Not applicable as no competitor systems available under this scenario		
Additional penalties defined in contracts				not possible to quantify

* For minimum duration (i.e. if substitutions are completed on time): Sales from affected assays or systems are not considered in the calculation of compensation claims 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.

In addition, the **losses and costs** given in Table 29 are expected for **Use 4** from the CB Business (proteins and MDx Enzymes).

Table 29. Expected cost / compensation claims for the CB Business

Financial loss	Product group	Time when the impact is expected to occur	Maximum Duration	Quantification***
Financial impacts for Scenario 1 and 2 (no difference between the scenarios for CB business)				
Loss based on the proteins and MDx Enzymes that cannot be sold	CB	EEA and non-EEA: second year after the sunset date (for 2021 stocks are assumed to be available)	EEA and non-EEA: 6 years	Sales / EBITA from affected materials based on predicted figures from 2021 (i.e. without growth from 2021)*
Loss of new customers for the materials that are not available	CB	Starting immediately after the sunset date	7 years	Growth predictions for sales /EBITA for 2021-2027**
Compensation of CB's customers (e.g. IVD manufacturers) for affected operations and business lost	CB	Claims are expected as soon as materials cannot be delivered ⇨ second year after the sunset date (for 2021 stocks are assumed to be available) ⇨ Until customers have found alternative solution	Possibly one-time payments or continuous claims as long as material is not delivered	Penalties are in principle unlimited Example calculated based on expected customer sales foregone
Additional penalties defined in contracts	CB			not possible to quantify

* For minimum duration (i.e. if substitutions are completed on time): Sales / EBITA from affected materials 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 affected materials that are planned to be replaced before the sunset date are not included in the calculation.
*** Range of years such as 2021-2027 mean from beginning of the first until the end of the last year.

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 EUR for Use 2&3 and [redacted] mio EUR (discounted to NPV) for Use 4 depending on whether substitutions are completed on time or not.
- ⇨ If **growth** occurred as predicted, an **additional EBITA** of [redacted] mio EUR (Use 2&3) and [redacted] mio EUR (Use 4) (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 EUR for Use 2&3 and [redacted] mio EUR (discounted to NPV) for Use 4 depending on whether substitutions are completed on time or not.
- ⇨ If **growth** occurred as predicted, an **additional EBITA** of [redacted] mio EUR (Use 2&3) and [redacted] mio EUR (Use 4) (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):

Estimated maximum **sales foregone** per product group and use for Scenario 1 is summarised in Table 30. Sales is used instead of EBITA to provide details on the level of the product group due to internal requirements for confidentiality. Maximum values are summarised in order to illustrate the relative importance of the different product groups. Detailed calculations including minimum values per product group are provided in the Supporting Document 2 to the SEA (File: SD2_SEA_Sales_RDG_Use2-4_CONFIDENTIAL). 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 in the EEA or non-EEA for a product group is given in brackets (this corresponds to the maximum duration for each impact given in Table 27). The maximum loss in sales (sales foregone) over these years is given for each product group. For example, for CC in the EEA a maximum of 2 years is assumed during which the affected assays cannot be sold (1 year for non-EEA due to potential stocks) and a maximum of 5 years during which all customers for the entire portfolio (including the affected assays) could be lost due to a switch to a competitor system after the first 2 years. The entire predicted growth will be lost as a maximum over the entire review period (7 years). Summed ranges of **sales foregone** per use group is given in Table 31. Maximum values correspond to the sum of values in Table 30. The aggregated ranges of **EBITA** (as an approximation of value added) foregone for Use 2&3 and Use 4 in Table 32 are based on the same assumptions as given for sales in Table 30[34]. The loss based on the non-EEA market is expected to be larger than for the EEA market (Table 32). In addition, if growth occurred as currently predicted, an aggregated

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

range of EBITA as given in Table 33 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 (UA, AT, RMD1, RTD). However, for some CC and DM assays as well as some proteins needed for CC assays, substitution in production is expected to be completed only after the sunset date. Similarly, HIV and BGE will not be replaced by different instruments before the sunset date. Therefore, for CC/DM and HIV, 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 and are expected to be permanent, i.e. customers are not expected to switch back to Roche when a complete portfolio is available again. As a consequence, minimum impacts are estimated in a similar way as maximum impacts, i.e. considering the loss of the entire portfolio until the end of the review period for product groups in which OPnEO / NPnEO will not be completely substituted by the sunset date. Those systems or product groups in which OPnEO / NPnEO is expected to be substituted before the sunset date (UA, AT, RMD1, RTD) are not considered and 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 27). Aggregated minimum values for sales foregone (Table 31) and EBITA foregone (Table 32) are close to maximum values. This is due to the fact that, for Scenario 1, impacts are dominated by the impacts on the portfolio level (see Table 30) which will occur if substitutions are completed on time or not, as described above.

Table 30. Scenario 1: Estimated maximum loss of sales over the review period from 2021 to the end of 2027, discounted to NPV at 4%. The number in brackets are the number of years during which the type of impact (loss of sales of affected assays or entire impacted portfolio) is expected as a maximum (financial figures are the sum over the given years). The sum between 'only affected assays' and 'affected portfolio' corresponds to the impacts over the review period of 7 years. Substitutions are assumed to be delayed so that impacts continue until the end of the review period.

Use group	**Product group**	**Max. loss in Sales over the review period (sales foregone in mio EUR)**					
		Only affected assays / products (existing customers)		**Impacted portfolio or system (existing customers)**		**Growth of impacted portfolio**	
		EEA	**non-EEA**	**EEA**	**non-EEA**	**EEA**	**non-EEA**
Use 2&3	CC	Use 2&3: [redacted] (2)	Use 2&3: [redacted] (1)	[redacted]	[redacted]	[redacted]	[redacted]
Use 4	DM	Use 4: [redacted] (1 / 2)	Use 4: [redacted] (1)	(5)	(5)	(7)	(7)

Use group	Product group	Max. loss in Sales over the review period (sales foregone in mio EUR)					
		Only affected assays / products (existing customers)		Impacted portfolio or system (existing customers)		Growth of impacted portfolio	
		EEA	non-EEA	EEA	non-EEA	EEA	non-EEA
Use 2&3	HIV	[redacted] (2)	[redacted] (1)	[redacted] (5)	[redacted] (5)	[redacted] (7)	[redacted] (7)
Use 3	BGE	Not applicable	Not applicable	[redacted](2)	Not applicable	Not applicable	Not applicable
Use 2&3 Use 4	AT	Not applicable	Not applicable	[redacted] (7)	[redacted] (6)	[redacted] (7)	[redacted] (7)
Use 2&3	UA	Not applicable	Not applicable	[redacted] (7)	[redacted] (6)	[redacted] (7)	[redacted] (7)
Use 3	RMD1	Not applicable	Not applicable	[redacted] (7)	Not applicable	[redacted] (7)	Not applicable
	RMD2	Not applicable	Not applicable	Not applicable	Not applicable	[redacted] (7)	Not applicable
Use 3	RTD	Not applicable	Not applicable	[redacted] (7)	Not applicable	[redacted] (7)	Not applicable
Use 4	TM	[redacted] (1)	[redacted] (1)	[redacted] (5)	[redacted] (5)	[redacted] (7)	[redacted] (7)
Use 4	CB (proteins)	[redacted] (6)	[redacted] (6)	Not applicable	Not applicable	[redacted] (7)	[redacted] (7)
Use 4	CB (MDx Enzymes)	[redacted] (6)	[redacted] (6)	Not applicable	Not applicable	[redacted] (7)	[redacted] (7)

Table 31. Scenario 1: Estimated range for sales foregone per use over the review period from 2021 until the end of 2027, discounted to 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.

USE	Scenario 1: Range of sales foregone in mio EUR over the review period (mio EUR)*		
	EEA	non-EEA	Total
Use 2&3	[redacted]	[redacted]	[redacted]
Use 4	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]

* Minimum values: Substitutions are assumed to be implemented as planned. No economic losses for systems / assays 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.

Table 32. Scenario 1: Estimated range of loss of EBITA (as an approximation of value added foregone) per use over the review period from 2021 until the end of 2027, discounted to 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.

USE	Scenario 1: Range of EBITA foregone in mio EUR over the review period (mio EUR)*		
	EEA	non-EEA	Total
Use 2&3	[redacted]	[redacted]	[redacted]
Use 4	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]

* Minimum values: Substitutions are assumed to be implemented as planned. No economic losses for systems / assays 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.

Table 33. Scenario 1: Estimated range for sales foregone per use over the review period from 2021 to the end of 2027 due to predicted growth after 2021, discounted to NPV at 4%. Competitors are assumed to be able to take over Roche's market share.

USE	Scenario 1: Range of sales foregone over the review period due to growth after 2021 (mio EUR)*		
	EEA	non-EEA	Total
Use 2&3	[redacted]	[redacted]	[redacted]
Use 4	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]

* Minimum values: Substitutions are assumed to be implemented as planned. No economic losses from growth for systems / assays 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.

Table 34. Scenario 1: Estimated range of loss of EBITA (as an approximation of value added foregone) per use over the review period from 2021 until the end of 2027, due to predicted growth after 2021, discounted to NPV at 4%. Competitors are assumed to be able to take over Roche's market share.

USE	Scenario 1: Range of EBITA foregone over the review period due to growth after 2021 (mio EUR)*		
	EEA	non-EEA	Total
Use 2&3	[redacted]	[redacted]	[redacted]
Use 4	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]

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 51). Financial losses for this scenario are calculated based on sales of the affected assays or systems, taking into account that stocks are expected to be available for sales to non-EEA countries during the first year (i.e. losses for non-EEA markets are assumed to start from 2022). For **minimum losses**, planned substitution dates as given in the AoA for Use 2&3 and Use 4 are accounted for. **Maximum losses** are expected to occur until the end of the review period, i.e. are expected to occur over 7 years in the EEA) and 6 years in the non-EEA countries (with the exception of BGE). **Minimum and maximum values are therefore the same as in Scenario 1** for those product groups where the entire system is affected (BGE, AT, RMD; RTD). Sales / EBITA foregone are expected to be 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, HIV, TM). Minimum and maximum estimated sales (Table 31) and EBITA (Table 32) foregone for EEA and non-EEA combined for Use 2&3 and for Use 4 are therefore much smaller than under Scenario 1. Detailed calculations and values per product group are provided in the Supporting Document 2 to the SEA (File: SD2_SEA_Sales_RDG_Use2-4_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, HIV, TM). 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 (Table 37) and EBITA (Table 38) based on growth from systems that are affected in their entirety and growth of affected assays that are not available is still expected to occur.

Table 35. Scenario 2: Estimated range for sales foregone per use over the review period from 2021 to 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 2021 onwards.

USE	Scenario 2: Range of sales foregone over the review period (mio EUR)*		
	EEA	non-EEA	Total
Use 2&3	[redacted]	[redacted]	[redacted]
Use 4	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]

* Minimum values: Substitutions are assumed to be implemented as planned. No economic losses for systems / assays 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.

Table 36. Scenario 2: Estimated range of loss of EBITA (as an approximation of value added foregone) per use over the review period from 2021 till the end of 2027, discounted to 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.

USE	Scenario 2: Range of EBITA foregone over the review period (mio EUR)*		
	EEA	non-EEA	Total
Use 2&3	[redacted]	[redacted]	[redacted]
Use 4	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]

* Minimum values: Substitutions are assumed to be implemented as planned.
Maximum values: Substitutions are assumed to be delayed so that impacts continue until the end of the review period.

Table 37. Scenario 2: Estimated range for sales foregone per use over the review period from 2021 until the end of 2027 due to predicted growth after 2021, discounted to NPV at 4%. Competitors are assumed NOT to be able to take over Roche's market share.

USE	Scenario 2: Range of sales foregone over the review period due to growth after 2021 (mio EUR)*		
	EEA	non-EEA	Total
Use 2&3	[redacted]	[redacted]	[redacted]
Use 4	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]

* Minimum values: Substitutions are assumed to be implemented as planned. No economic losses from growth for systems / assays 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.

Table 38. Scenario 2: Estimated range of loss of EBITA (as an approximation of value added foregone) per use over the review period from 2021 until the end of 2027 due to predicted growth after 2021, discounted to NPV at 4%. Competitors are assumed NOT to be able to take over Roche's market share.

USE	Scenario 2: Range of EBITA foregone over the review period due to growth after 2021 (mio EUR)*		
	EEA	non-EEA	Total
Use 2&3	[redacted]	[redacted]	[redacted]
Use 4	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]

* Minimum values: Substitutions are assumed to be implemented as planned. No economic losses from growth for systems / assays 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.

3.3.3 Cost due to Customer Claims

3.3.3.1 Cost due to Customer Claims from Laboratories and Hospitals

- ⇨ Only a rough indication can be given for additional cost due to **customer claims**.
- ⇨ Under Scenario 1 and 2, **claims are expected due to assays not supplied**. As a minimum, these claims are estimated based on the sales price of the assays for 'substitution on time' (min) or 'all substitutions delayed' (max):
  - Scenario 1: [redacted] mio EUR.
  - Scenario 2: [redacted] mio EUR.
- ⇨ In Scenario 1, the cost for RDG's 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 EUR for the instruments alone **not including the far more important cost** for the tender process, installation, training etc. This cost is expected to be claimed from RDG by customers.
- ⇨ As compensation for further damages could be claimed from Roche and **compensation risk is generally unlimited, customer claims pose an inacceptable, potentially business-critical financial risk to Roche**.
- ⇨ Any occurring **cost that cannot be or is not claimed from Roche would have to be covered by the customers**, i.e. laboratories and hospitals themselves and thus ultimately by the healthcare system and patients.

Additional cost due to **customer claims** is difficult to estimate. Generally, it has to be noted that Roche will be held responsible for failure to deliver assays based on customer contracts.
Customer claims may be based on but are not limited to contractually defined penalties. Claims could be made for any incurred damages.

Definition of penalties in contracts varies greatly between customers. For example, for delays in delivery of assays the following types of penalties are defined for different customers within one single country:

- Percentage of value of goods to be paid for each 7-day period of delay of delivery (e.g. 1-5%) with a maximum percentage of the value of goods to be paid (e.g. 10-20%)
- Fixed penalty defined for the lack of one assay per 24-hour period started (e.g. EUR 1'500-3'000)

Some contracts also explicitly foresee that Roche may offer an alternative solution in case of prolonged delivery problems. This could include placement of equipment from another manufacturer. The measure would have to paid by Roche as long as the problem remains.

The following considerations therefore give an indication of the possible minimum amount expected to be claimed in both scenarios:

- Some contracts may have a maximum penalty defined as a percentage of the value of goods delivered. However, other contracts foresee penalties that could amount up to 1 mio EUR for one single assay that is needed 24/7 (24 hours, 7 days a week) missing over the course of 1

year alone. Therefore, the value of goods (i.e. IVD assays) not supplied is considered as a conservative estimate of the minimum that could be claimed on average from all customers.

- Sending out samples to other laboratories 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[35]. As sending out samples will only be possible to a limited extend such a factor is not applied to all customers but can give an indication of higher claims.

Further considerations for switching to a competitor system in Scenario 1 are discussed below. Due to the variety of provisions and as **compensation risk is generally unlimited**, only a **rough indication of possible customer claims** can be given for the two scenarios.

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

Customer claims for assays that cannot be supplied, and associated business lost are expected to be made where customers cannot switch to a different system quickly (all assays in centralised laboratories (CC, DM, HIV, RTD) and BGE)[36]. Compensation claims may also be made 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 Table 30) is used as a very conservative estimate for the minimum of customer claims (that could be based on contractual penalties or compensatory claims for damages) to be expected (see Table 39). The sales of the affected assays were considered for the first two years after the sunset date for EEA. For non-EEA only one year is considered due to expected stocks (see Table 19, values for 'only affected assays'). 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. Additional claims could be made based on assays already delivered that cannot be used anymore after the sunset date. These claims are not accounted for in both scenarios as expected stocks at customers are difficult to estimate.

Table 39: Scenario 1: Estimated compensation cost for assays not delivered during the first two years after the sunset date based on cost of the assays. Minimum and maximum are based on the assumption that substitutions are completed on time or that substitutions are delayed until the end of the review period.

USE	Scenario 1: Estimated claims for assays not delivered based on cost of the assays (mio EUR)		
	EEA	non-EEA	Total
Use 2&3	[redacted]	[redacted]	[redacted]
Use 4[1]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]

[35] 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.
[36] This is also the case for instrument-based UA. However, this is not included in the estimate as sales figures are not available separately for test strips / hand-held devices and instrument-based UA.

[1] Estimated claims for Use 4 only include RDG's IVD assays that are affected by Use 4. Possible claims based on the CB business are discussed in section 3.3.3.2.

For Scenario 1, i.e. in case customers can switch to a different supplier, these claims are expected to only occur up to 2 years after the sunset date. After that, customers are expected to have switched to a competitor. The cost for such a switch is equally expected to be claimed from Roche.

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 RDG'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_RDG_Use2-4_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 EUR. Divided by use (assignment of cost 50:50 for Use 2&3 and Use 4 in case the assays depend on both), this cost could amount to a maximum of [redacted] mio EUR for Use 2&3 and [redacted] mio EUR for Use 4. 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 compensation cost is expected to be much larger than [redacted] mio EUR. Customer claims due to switching to a different supplier are mainly expected within the first two years after a non-authorisation decision as customers are expected to switch during that period.

Table 40: Scenario 1: Estimated compensation cost for covering purchase of instrument caused by a switch to a different supplier by all customers (only instrument cost as a minimum indication). Minimum and maximum are based on the assumption that substitutions are completed on time (i.e. some instruments do not have to be replaced) or that substitutions are delayed until the end of the review period.

USE	Scenario 1: Minimum cost of a switch to a different supplier (only instrument cost) (mio EUR)		
	EEA	non-EEA	Total
Use 2&3	[redacted]	[redacted]	[redacted]
Use 4	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]

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**.

Therefore, **claims from customers** based on assays not supplied and business lost may last until the end of the review period, i.e. as long as assays are not available and contracts are in place. Therefore, customer claims were roughly estimated based on value of IVD assays not supplied as discussed above.

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. Additional claims could be made based on assays already delivered that cannot be used anymore after the sunset date. These claims are not accounted for in both scenarios as expected stocks at customers are difficult to estimate.

Table 41: Scenario 2: Estimated compensation cost for assays not delivered based on cost of the assays. Minimum and maximum are based on the assumption that substitutions are completed on time or that substitutions are delayed until the end of the review period.

USE	**Estimated penalties for assays not delivered based on cost of the assays (mio EUR)**		
	EEA	**non-EEA**	**Total**
Use 2&3	[redacted]	[redacted]	[redacted]
Use 4[1]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]

[1] Estimated claims for Use 4 only include RDG's IVD assays that are affected by Use 4. Possible claims based on the CB business are discussed in section 3.3.3.2.

Based on information from country affiliates, customers would expect Roche to cover any cost incurred by a breach of delivery contracts. Therefore, it is likely that most of above discussed costs for both scenarios would be claimed from Roche. If this was not the case, the customers themselves - and thus ultimately insurance schemes and the healthcare system – would have to cover the additional cost, e.g. of switching to a different system.

3.3.3.2 Cost due to Customer Claims from CB Customers

- ⇨ Compensation is expected to be claimed from CB customers (e.g. IVD manufacturers) for lost business.
- ⇨ Claims for sales foregone for CB's customers of MDx Enzymes could amount to ca. [redacted] **mio EUR per year.**

Additional **claims for compensation could be made by affected CB customers**. These customers are producers of IVD assays or medicinal products. The impact on their business cannot easily be quantified, but losses are expected to be claimed from Roche. This poses an inacceptable, potentially business-critical financial risk to Roche, as **compensation risk is generally unlimited**.

For example, for the MDx Enzymes that are sold to IVD manufacturers in Molecular Diagnostics, claims for damages could indeed potentially be beyond control. Assuming that customers would only claim their sales foregone this could amount to ca. [redacted] mio EUR per year based on the expected sales for the affected MDx Enzymes of [redacted] mio EUR in 2021 and the assumption that the cost of MDx Enzymes would account for [redacted]-max. [redacted]% of the final assays. Such claims could occur if the substitutions projects for the MDx Enzymes are delayed.

3.3.3.3 Conclusion on Customer Claims

- ⇨ Possible compensation claims pose an **inacceptable, potentially business-critical risk** to Roche as compensation risk is generally unlimited.

Estimated compensation claims are in total in the range of [redacted] **(100-10'000) mio EUR** for all uses over the course of the review period depending on the scenario as discussed above. However, customer claims **could be much higher** than this due to the reasons given above. This estimate does not cover potential compensation claims from CB customers. Compensation risk is generally unlimited so that customer claims pose an **inacceptable, potentially business-critical financial risk** to Roche.

3.4. Social Impacts

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

The **social impacts of a non-authorisation** would be situated **on three levels:**

- **Social cost of unemployment due to market share losses of 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 RDG 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).
- **Increased social costs due to (temporary) unavailability of affected non-IVD products** (medicinal products) manufactured by downstream users of Roche based on its affected Custom Biotech products (not further discussed due to lack of information from the customers).

3.4.1 Social Cost of Unemployment

- ⇨ **Focus on job losses** as a result of the closure of production lines or below-capacity use of production lines resulting in job redundancy in production as well as in supporting functions.
- ⇨ **Several types of social costs related to job losses** can be identified.
- ⇨ Following ECHA guidance and taking into account a total of 414 Roche jobs (FTE) lost in the EEA (which is a very conservative estimate), the total social cost related to job losses has been calculated at **41.9 mio EUR**.

In order to establish the **social cost of unemployment** in case an authorisation would not be granted, the guidance provided by ECHA has been used (ref: Richard Dubourg, The Economics Interface Limited, September 2016). In this guidance, three sources of changes in employment have been identified to be associated with changes in the use of Annex XIV substances which might follow an authorisation decision (positive or negative):

1) **Job losses as a result of the closure of manufacturing plants and job gains associated with the establishment of new plants.**

2) **Job losses/gains due to changes in costs and market share of the applicant.**

3) **Job losses/gains due to possible impacts on competitors.**

In this application for authorisation, the focus is on job losses as a result of the closure of production lines or below-capacity use of production lines resulting in job redundancy in production as well as in supporting functions.

The following types of social costs, associated with job losses, have been identified in the ECHA guidance:

1) The value of output/wages lost during the period of unemployment;

2) The cost of searching for a new job, hiring and firing employees;

3) The impact of being made unemployed on future earnings and employment possibilities (the 'scarring' effect);

4) The value of leisure time during the period of unemployment;

5) The costs of health and other wellbeing effects of being unemployed on the unemployed individual;

6) The costs of health and other wellbeing effects of the individual being unemployed on others (e.g. the individual's children);

7) External costs of unemployment (e.g. health treatment costs paid for by taxpayers).

The impacts described above occur at different times over a number of years following the initial job loss in question. This has been addressed by the use of discounting, expressing money quantities accruing at different points in time in the values of a single year.

The **net present value of the social costs of one lost job has been estimated at 86'827 EUR** for the EU-28 (year 2014). This value was equivalent to 89'879 EUR in 2018 and using a discount rate of 4%, this value is equivalent to 101'102 EUR in 2021. As Roche factories in the EEA that are relevant for this dossier are based in Germany, the EU-28 value will probably be an underestimate. As only an indicative estimation was considered required, no attempts were made to set a value specifically for Germany.

As can be seen in Table 9, a total number of **712 jobs (FTE)** has been estimated by RDG to be dedicated to the Diagnostics businesses **affected directly** by this AfA. Except for UA, BGE, RMD and RTD, the number of jobs represent EEA values. RMD and RTD products are manufactured in the US and therefore the number of jobs given (i.e. 200 and 28 FTE, respectively) is situated for the largest part in the US. For BGE (i.e. 70 FTE), manufacture takes place in Switzerland. For UA, only a global number of employees has been made available (i.e. 60 FTE). However, UA products are manufactured in Germany and most of the jobs are in EEA Further, for CC + DM + HIV + TM + AT, the number of 54 FTEs (in the EEA) only represents employees working in production, which is an underestimation of the total number of potentially affected employees. Taking into account these uncertainties, it could be assumed that the number of Roche FTEs directly affected in the EEA in case all substitutions are delayed would be at least 414 (i.e. CC + DM + HIV + TM + AT (54) + UA (60) + CB (300)). An attempt was also made to estimate the number of indirectly affected employees at affiliates. However, no complete figures could be provided. Therefore, the indirectly affected jobs are not included in the calculation below. In conclusion, the number of 414 FTEs affected in the EEA in case all substitutions are delayed should be considered as a very conservative estimate of the total number of potentially affected jobs, as the estimates per product group do not include jobs at affiliates and only partially include employees in the sales organisation or further supporting functions. Further, it should be noted that the estimates per product group only consider jobs depending on the affected assays or systems, but not those depending on the entire portfolio (e.g. for CC, DM, HIV, TM). Therefore, it was **not possible to obtain an accurate estimate of the number of Roche jobs affected in Scenario 1** (competitors can take over Roche's market share). The figure of **414 Roche FTEs affected in the EEA** therefore **rather represents Scenario 2** (competitors cannot take over Roche's market share) than Roche job losses that could result from a switch of laboratories / hospitals to competitor systems (Scenario 1).

Taking the value of 101'102 EUR (2021 value) as a baseline for the social cost of unemployment (Dubourg, 2016), combined with an estimated number of 414 Roche job losses (FTE) in the case of non-authorisation, this results in **41'856'228 EUR as social cost of unemployment**. The total cost is spread over several years (8 in the general example for EU-28 as proposed by Dubourg, 2016). On average, unemployment takes about 1.6 years, during which the social cost of unemployment is the highest and driven by lost output and increased leisure time. In the years thereafter the social cost of unemployment is decreasing and driven by scarring costs.

As mentioned above, part of the **unemployment** would be in **non-EEA countries**. The related social costs in these countries is however **not quantified**. Further, it should also be noted that job losses may also occur outside of Roche, e.g. at the level of the suppliers or the customers, which are / could not be quantified either.

Concerning the two different scenarios distinguished in the economic impacts chapter (i.e., competitors can (Scenario 1) or cannot (Scenario 2) take over Roche's market share), both presenting two sub-scenarios depending on whether substitutions are delayed or completed as planned, the following **considerations** can be made **on the related social cost of unemployment**:

- The worst-case scenario would in theory be Scenario 1 with all substitutions delayed until the end of the review period. However, no accurate calculation could be made for this scenario as the estimated number of jobs per product group only considers jobs depending on the affected assays or systems, but not those depending on the entire portfolio (e.g. for CC, DM, HIV, TM). For this reason, but also because the jobs affected at affiliates could not be quantified, the social cost of unemployment related to this scenario can be expected to be substantially higher than the figure calculated above.

- The estimate presented above is considered relevant for Scenario 2 with all substitutions delayed until the end of the review period because the majority of jobs is expected to become redundant during the stop in production until (at least) the end of the review period, which is assumed to be 7 years. However, the estimate also represents a substantial underestimation because the jobs lost at affiliates are not taken into account.

- In case substitutions are completed as planned, both in Scenario 1 and 2, a lower number of Roche jobs may be lost because substitutions for UA, AT, RMD and RTD are planned to be completed before the sunset date. Additionally, some of the DM and CC assays are planned to be completed before the sunset date. For the EEA, the reduced job loss at Roche would however be minimal, as globally only 60 FTEs are assigned to the UA business, and the number of jobs assigned to AT, DM and CC is lower than the total of 54 FTEs given for CC + DM + HIV + TM + AT. Assuming that in total 50% of these jobs would not be lost (i.e. 57 FTE), this would only entail a reduction of ca. 14% to the social cost of unemployment calculated above. For Scenario 1 with substitutions completed as planned, the social cost of unemployment is nevertheless expected to be higher than the estimate presented above because of the same reasons as given for Scenario 1 with all substitutions delayed. However, the level of underestimation is expected to be lower. For Scenario 2 with substitutions completed as planned, the estimate presented above may also represent an underestimation because jobs lost at affiliates are not taken into account, but the level of underestimation may be the lowest of all scenarios.

Overall, when comparing the estimated social impacts **related to job losses** with the other impacts at the socio-economic side of the equation, it is clear that **these impacts are not dominant and contribute only marginally to the total estimated impacts**.

Finally, the qualification profile of affected employees (production, administrative support, sales) is largely different from that of employees that would be needed to address the crisis in the company (e.g. to speed up substitution, to address claims from customers or requests for assistance in finding solutions, etc.). Therefore, there would be also a certain distributional impact at the level of employment by Roche, which is described in the distributional impacts section.

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. 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 companion diagnostics – 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 doctors and patients on a huge range of conditions, yet IVDs cost remarkably little, with the total expenditure being ca. 21 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 approximately 66% of clinical decisions. These studies also confirm that the **relative spending of health care 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 approximately 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 approximately 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 health care 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 health care 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 health care 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 either directly (Uses 2&3) or indirectly (Use 4) (see Section 2.7.3 for detailed descriptions) in case an authorisation would not be granted, belong to Roche's portfolios of clinical chemistry, drug monitoring (covering both drugs used for treatment as well as drugs of abuse), immunoassays, urinalysis, blood gas and electrolyte monitoring, point of care monitoring of cardiometabolic parameters, molecular diagnostics and tissue diagnostics. A brief qualitative description of the general impacts expected on patients is given below and is summarised in Table 12:

- Concerning the **clinical chemistry** portfolio, a substantial number of assays would be affected (see Figure 26). 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 CREA, BILT3, ALB_BCG etc.) 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).

- **Blood gas and electrolyte** analysis comprises a critical care test set required in intensive care units (ICU), emergency departments (ED), neonatology departments, etc. The directly affected parameters are those for haemoglobin, haemoglobin derivatives and bilirubin. However, as all parameters (e.g. pO_2, pCO_2, pH, haematocrit, Na^+, K^+, Cl^-, Ca^{2+}, glucose, lactate, urea / BUN, total Hb, O_2 saturation, SO_2, O_2Hb, COHb, MetHb, HHb and bilirubin) are determined simultaneously to generate an array of information used in decision-taking. Results are typically required within 2 minutes to **enable fast clinical decision making** on the most acute patient conditions. It is clear that temporary missing parameters would potentially lead to **misdiagnosis**, **delayed treatment** and even **death** and therefore a substantial loss of QALYs and associated increased healthcare expenditure could reasonably be expected.

- 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.

- **Accutrend®**, the flexible point-of-care handheld device for the determination of important cardiometabolic parameters (i.e. cholesterol, triglyceride and glucose, as well as lactate), is intended for use in physicians' practices and clinics for the **monitoring of metabolic disorders and cardiovascular risk factors** in patients. A temporary unavailability could result in missing certain important changes and therefore delayed adjustment of treatment with potential loss of QALYs and associated increased healthcare expenditure.

- Regarding **urinalysis** products, affected patient (i.e. manual reading) and point of care test strips are those containing the key PRO assay which screens for proteins in urine. Urine test strips are

key diagnostic tools that yield quick and reliable information on **pathological changes** in **urine** that could inform on e.g. urinary tract infection, kidney disease and diabetes. The PRO assay is central for informing on potential kidney dysfunction. Therefore, the temporary unavailability of the assay may result in **delayed diagnosis of kidney disease** with potential loss of QALYs and associated increased healthcare expenditure.

- Concerning the Roche **Molecular Diagnostics** portfolio, the affected assay under RMD1 is used for detection of **Influenza A and B**. Here as well, unavailability of this assay would result in **delayed diagnosis in patients**. It would furthermore result in less effective gathering of information for epidemiologists involved in establishing the composition of influenza vaccines and the follow-up of influenza epidemies and potential use of contaminated blood during blood transfusion. Since influenza is especially dangerous to people with reduced health condition, this may result in **poorer control of influenza epidemies.** In addition, it may result in an increase of influenza-related deaths or further reduced health condition in some patients as well, i.e. all resulting in a general loss of QALYs and increased healthcare expenditure.
  The affected assay under RMD2 represents a live cell molecular diagnostics assay that can **quickly identify multidrug-resistant organisms** (MDROs) and **assess antibiotic susceptibility**. Unavailability would lead to slower detection of MRDOs, delayed start-up of treatment and therefore a general increase in healthcare expenditure and poorer patient outcome (i.e. a general loss of QALYs).

- The affected Roche **Tissue Diagnostics** 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.

- The **tumour marker assay** is next to the HIV assay the second assay affected in the immunoassay portfolio. This assay is used in lung cancer panel, which is a series of different markers used to test the patient. Clearly, the unavailability of the assay may result in **delayed diagnosis** and therefore a **less ideal patient outcome** and consequently, a loss of QALYs and increased healthcare expenditure.

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

- ⇨ The overall **number of tests provided** by Roche performed worldwide per year ranges roughly between **2'000-3'000 mio tests**.
- ⇨ Assuming on average 10 tests per patient annually, this would result in **200-300 mio patients per year** that benefit from these tests.
- ⇨ 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 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 as well as a rough estimate of the number of patients who benefit from the performed tests is presented in Table 11. The overall **number of tests** provided by Roche performed **in the EEA** roughly ranges **between 1'000 and 1'500 mio / year**. A **similar** number of tests provided by Roche is performed yearly **outside the EEA**. Altogether, roughly **2'000-3'000 mio tests** are performed yearly **worldwide** (again, directly affected assays only), the majority (ca. 80%) 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 **200-300 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 RDG 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 UA, AT, RMD, 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 worldwide) 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). For the calculations below, 12 months of temporary unavailability was assumed as a worst-case. The **economic impacts to RDG in terms of EBITA foregone** have been calculated to range roughly **between** [redacted] **and** [redacted] **mio EUR** over the different scenarios (see Table 31 and Table 32 for further details). The scenario with the highest economic impact to RDG 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 – 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 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 chapter.

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 ca. 1'338'000 and 71'000 EUR, respectively (recalculated to 2018 value). Taking into account a discount rate of 4%, the value in 2021 (i.e. the year of the sunset date) is calculated to be ca. 1'510'000 and 80'000 EUR, respectively. 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[37]. Using this general **VOLY** value, one could roughly calculate that only ca. [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 in terms of EBITA foregone estimated to result from non-authorisation (i.e. [redacted] (700-7'000) mio EUR). Taking into account the fact that roughly [redacted] mio tests per year are currently performed (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. 20'000 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 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 in terms of EBITA foregone resulting from non-authorisation (i.e. [redacted] mio EUR). 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. 380'000 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).

Another indicative calculation, using the **cancer related VSL and VSCC**[38], demonstrated that only ca. [redacted] fatal cancer cases or ca. [redacted] cancer cases in general (through very-early-stage detection)

[38] Concerning cancer these values are even higher, with a VSL reported of 5'260'000 EUR (recalculated to 2018 value). Also, the willingness to pay to avoid a cancer case in general (regardless of fatality), i.e. the VSCC (Value of a Statistical Cancer Case) was determined to be 416'000 EUR (in 2018 value) [11]. Taking into account a discount rate of 4%, the value in 2021 (i.e. the year of the sunset date) is calculated to be ca. 5'900'000 and 470'000 EUR, respectively, for the VSL and the VSCC.

should be avoided under normal conditions of availability of the affected assays, to equal the economic impacts to Roche in terms of EBITA foregone. Even if only the TM assay, used in lung cancer panel, would be considered, of which currently [redacted] mio tests are performed per year ([redacted] mio in the EEA), this would mean that **only 1 on ca. 52'000 TM tests would have to result in a prevented fatality**.

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 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 and substitutions are completed as planned) and using the maximum economic impacts to Roche 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 chapter (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 chapter 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 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 WHO, the **number of newly diagnosed HIV infections in 2017** was 159'420 in the WHO European region (i.e. 20 per 100'000) [http://www.euro.who.int/en/health-topics/communicable-diseases/hivaids/data-and-statistics/infographic-newly-diagnosed-hiv-infections-in-the-who-european-region,-2016] and 1.8 million globally (i.e. 24 per 100'000) [https://www.who.int/hiv/data/2017_hiv-incidence-2000-2030.png?ua=1].

Considering the **market share of Roche in HIV IVDs**, one could then by approximation calculate for how many diagnoses of new HIV infections per year Roche's HIV assays are responsible. The current market share of Roche in HIV IVDs is [redacted] and [redacted]% inside and outside the EEA, respectively. Considering these values, **Roche's HIV IVDs** can be assumed to be **responsible for**

the diagnosis of [redacted] new HIV infections per year in the EEA and of [redacted] new HIV infections per year outside the EEA.

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 2021 and then progressively to [redacted] and [redacted] in 2022, 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 chapter:

- Scenario 1 – Competitors can take over Roche's market share – i.e. unavailability until the switch to competitor systems is complete:
    - 2 years in the EEA.
    - 1 year outside the EEA starting in 2022 (because assays can still be used after the sunset date until stocks are used up and until the end of shelf life is reached).

- Scenario 2 – Competitors cannot take over Roche's market share – i.e. unavailability until substitutions by Roche are completed:
    - 7 years in the EEA.
    - 6 years outside the EEA starting in 2022 (same justification as under Scenario 1).

Consequently, the **HIV combiPT assay** can be calculated to be **responsible for the following number of newly diagnosed HIV infections** inside and outside the EEA under the different scenarios:

- Scenario 1:
    - [redacted] diagnoses inside the EEA.
    - [redacted] diagnoses outside the EEA.

- Scenario 2:
    - [redacted] diagnoses inside the EEA.
    - [redacted] diagnoses outside the EEA.

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 40'000-50'000 EUR 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] to [redacted] mio EUR inside the EEA.
  - [redacted] to [redacted] mio EUR outside the EEA.

- **Scenario 2:**
  - [redacted] to [redacted] mio EUR inside the EEA.
  - [redacted] to [redacted] mio EUR outside the EEA.

These estimates should be considered as **substantial underestimations** of the social impacts in terms of increased healthcare spending 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 many 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 can be assumed to be a dominant factor at the socio-economic side of the equation.

3.4.3 Social Impacts due to (Temporary) Unavailability of Non-IVD Products

⇨ Additional impacts on healthcare are expected due to expected unavailability of medicinal products depending on CB raw materials.

The only non-IVD use affected by non-authorisation is the **downstream use of raw material supplied by Roche's Custom Biotech** department for cell cultures in the manufacturing of pharmaceuticals. Because RDG has **limited information** on downstream user products due to confidentiality reasons, **no further evaluation** of the potential social impacts of non-authorisation is performed here. However, given the fact that the downstream products are medicinal products that likely cannot be produced any more in case of non-authorisation, **additional impacts on the healthcare system** and thus on patients are expected.

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 **>> 2-44mio EUR / kg (Use 2&3)** and **>> 900-9000 mio EUR / kg (Use 4)**
- ⇨ 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 2& 3 and Use 4 **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 2&3 (Table 42) and for Use 4 (Table 43) 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 chapters (see Figure 50 and Figure 51):

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

Table 42. Use 2&3: Overview of the impacts over the 7 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: Release to surface water: $OP_{equiv.}$: 108-618 kg $NP_{equiv.}$: 5.8-19 kg Release to soil (Use 3): $OP_{equiv.}$: 90-515 kg $NP_{equiv.}$: 16-55 kg PEC < EQS / PNEC values	No releases of OP or $NP_{equiv.}$ from RDG's activities in Penzberg and Mannheim covered in Use 2 or customers activities based on RDG's assays covered in Use 3

Type of impact	Stakeholders impacted	Applied for use scenario*	Non-use scenario*
Economic impacts	RDG	Roche will be able to continue their current IVD assay business with existing customers	Estimated loss of EBITA due to the interruption of IVD sales (existing assays and existing customers) **Scenario 1:** [redacted] mio EUR **Scenario 2:** [redacted] mio EUR
	RDG	Roche is expected to be able to grow their IVD assay business 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 EUR **Scenario 2:** [redacted] mio EUR
	RDG / customers	Roche will be able to keep their contractual obligations and Roche's customers will be able to continue their business providing laboratory services to the healthcare system	Due to non-supply by Roche, 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). Roche will face claims from customers: **Rough minimum estimates:** **Scenario 1:** Compensation for assays not supplied: [redacted] mio EUR Compensations for switching to a competitor system (based on instrument cost only): [redacted] mio EUR **Total Scenario 1:** [redacted] mio EUR **Scenario 2:** Compensation for assays not supplied: [redacted] mio EUR **Maximum claims cannot be quantified but pose a potentially business-critical financial risk to Roche**

Type of impact	Stakeholders impacted	Applied for use scenario*	Non-use scenario*
	RDG / customers	Roche as well as their customers will be able to keep or expand their position on the IVD market	Loss of trust in Roche as IVD supplier Loss of trust in laboratories, risk of loss of accreditation for reimbursement by health insurances
Social impacts	Patients	Millions of patients will continue to benefit from health services based on RDG's IVD assays including diagnosis, monitoring etc.	**Patients will face a lack of healthcare services** over a minimum of 1 (Scenario 1) to a maximum of 7 years (Scenario 2): Estimated cost to society in terms of increased healthcare costs: >> [redacted] (500-5'000) mio EUR**
	Workers	RDG as well as Roche affiliates in many countries will continue to be an important employer (for RDG: in Germany)	Impact on employment: 41.9 mio EUR in all scenarios for both uses [Note that only jobs affected at RDG itself have been included, i.e. no jobs affected at affiliates]

* 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 cost will be higher than the maximum total estimate for EBITA foregone for Use 2&3 and Use 4 combined. To assign this value to the two use groups, the values for maximum EBITA foregone per use group were employed.

Table 43. Use 4: Overview of the impacts over the 7 years of the review period in the non-usescenario 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	Total over the review period: Release to surface water: $OP_{equiv.}$: 0.11-1.65 kg $NP_{equiv.}$: 0 kg PEC (surface water) < EQS values	No releases of OP or $NP_{equiv.}$ from RDG sites based on production processes

Type of impact	Stakeholders impacted	Applied for use scenario*	Non-use scenario*
Economic impacts	RDG	• Roche will be able to continue their current IVD assay and Custom Biotech business with existing customers	Estimated loss of EBITA due to the interruption of IVD sales and sales of proteins and MDx Enzymes through Custom Biotech (existing assays and existing customers) **Scenario 1:** [redacted] mio EUR **Scenario 2:** [redacted] mio EUR
	RDG	• Roche is expected to be able to grow their IVD assay and Custom Biotech business by winning new customers	Loss of EBITA from growth of the IVD and Custom Biotech business due to the inability to provide a complete portfolio or from growth of assays or materials that cannot be provided **Scenario 1:** [redacted] mio EUR **Scenario 2:** [redacted] mio EUR
	RDG / customers	• Roche will be able to keep their contractual obligations • Roche's customers (laboratories / hospitals) will be able to continue their business providing laboratory services to the healthcare system • Roche's Custom Biotech customers (IVD manufacturers, manufacturers of medicinal products) will be able to continue their business providing IVD assays and medicinal products to their customers and thus to the healthcare system	Due to non-supply by Roche, 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). Roche will face claims from customers: **Rough minimum estimates:** **Scenario 1:** Compensation for assays not supplied: [redacted] mio EUR Compensations for switching to a competitor system (based on instrument cost only): [redacted] mio EUR **Total Scenario 1**: [redacted] mio EUR **Scenario 2:** Compensation for assays not supplied: [redacted] mio EUR **Scenario 1 and 2**: Compensation for materials not delivered to CB customers (e.g. other IVD manufacturers): Rough estimate from MDx Enzymes: [redacted] mio EUR per year

Type of impact	Stakeholders impacted	Applied for use scenario*	Non-use scenario*
			Maximum claims cannot be quantified but pose a potentially business-critical financial risk to Roche
	RDG / customers	• Roche as well as their customers will be able to keep or expand their position on the IVD and Custom Biotech market	Loss of trust in Roche as IVD supplier and supplier of raw materials Loss of trust in Custom Biotech's customers as suppliers of IVD assays and medicinal products Loss of trust in laboratories, risk of loss of accreditation for reimbursement by health insurances
Social impacts	Patients	• Millions of patients will continue to benefit from health services based on RDG's IVD assays as well as IVD assays produced by RDG's Custom Biotech customers (e.g. health benefits resulting from diagnosis, monitoring etc.) • Patients will also continue to benefit from pharmaceutical products of RDG's Custom Biotech customers.	**Patients will face a lack of healthcare services** over a minimum of 1 (Scenario 1) to a maximum of 7 years (Scenario 2): Estimated cost to society based on QALY lost: >> [redacted] (200-2'000) mio EUR**
	Workers	• RDG as well as Roche affiliates in many countries will continue to be an important employer (for RDG: in Germany)	Impact on employment: 41.9 mio EUR in all scenarios for all uses [Note that only jobs affected at RDG itself have been included, i.e. no jobs affected at affiliates or Custom Biotech customers of RDG]

*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 as given in the timelines in the AoA).
**In the social impact assessment, it was estimated that increased healthcare cost will be higher than the maximum total estimate for EBITA foregone for Use 2&3 and Use 4 combined. To assign this value to the two use groups, the values for maximum EBITA foregone per use group were employed.

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**. A lot of these projects are currently on track and are expected to be completed on time with a high likelihood (e.g. RTD and some CC assays). Furthermore, as shown in the AoAs, 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** these **assays and processes 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. In addition, for some assays, technical difficulties have been encountered (e.g. some DM and some CC assays) and a delay in the range of 0.5-2 years is currently expected. 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. Especially **with regard to used amounts and emissions**, the **likely impact** (in terms of OP / $NP_{equiv.}$ released) will be **closer to the minimum**. This is due to the fact that protein processes using larger amounts are substituted first (Use 4). For Use 3, this is due to the fact that the assays using the largest amounts are either expected to be completed on time (RTD, emissions likely to be eliminated at the sunset date or shortly after) or with a limited delay (CC3, emissions likely to be eliminated 2-2.5 years after the sunset date).

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 costs) **are likely to be a dominant factor in determining the outcome of the socio-economic analysis**. Increased healthcare costs due to temporary unavailability of the affected assays would inevitably put stress on the EEA 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 costs in the minimum scenario (for Use 2 & 3 and Use 4 together in Scenario 1 with all substitutions on time) are expected to be several orders of magnitude higher than the maximum economic impact to Roche in terms of EBITA foregone (for Use 2 & 3 and Use 4 together in Scenario 1 with all substitutions delayed). Consequently, social impacts in terms of increased healthcare costs are expected to be higher than maximum EBITA foregone independent of the scenario.

For comparison with emissions, the minimum value calculated for the social impacts (in terms of increased healthcare costs) was assigned to the two use groups (Use 2&3 in Table 42 and Use 4 in Table 43) based on estimated maximum EBITA foregone calculated for the separate uses. This minimum value for social impacts per group of uses ([redacted] (500-5'000) mio EUR for Use 2&3 and [redacted] (200-2'000) mio EUR for Use 4) 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 for each group of uses (see Table 44). As discussed in the social impact analysis, the minimum social impacts in terms of increased healthcare 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 44. Minimal societal cost of non-use (in terms of increased healthcare 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	
	Use 2&3	**Use 4**
Total cost (mio EUR per year)*	[redacted] >>500-5'000	[redacted] >>200-2'000
Total releases (kg OP / $NP_{equiv.}$ if substitutions are completed as planned)**	114-220***	0.11
Ratio (mio EUR/kg)	[redacted] >> 2-44	[redacted] >>900-9'000

* Cost is based on minimum social impacts due to temporary unavailability of assays ([redacted] (700 -7'000) mio EUR) assigned to the two use groups separately.
**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 lower value represents the release to surface water, the upper value the sum of the releases to surface water and soil assuming that 100% of sludge from Use 3 is applied to agricultural soil. The likely value will be in-between as on average 45% of sludge is applied to soil in EEA.

Further impacts

Depending on the scenario, Roche will face **substantial loss of EBITA** from [redacted] (100-7'000) mio EUR over the course of the review period. As, depending on the scenario, these impacts may be distributional (see Section 4.2) and 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. It should be noted though, that **in case (partly) non-EEA companies would take over Roche's market share**, this would imply an **additional loss to the economy of the EEA**.

Expected claims from customers to Roche 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. In addition, an estimation of sales foregone of a CB customer for the example of MDx Enzymes was given. However, potential compensation claims from other CB customers are not included. Estimated compensation claims are in total in the range of [redacted] (100-10'000) mio EUR for all uses. However, customer claims could be much higher than this. Compensation risk is generally unlimited so that **customer claims pose an inacceptable, potentially business-critical financial risk to Roche**. Therefore, impacts based on customer claims could be **far more important than impacts based on EBITA foregone**. These impacts represent a **net loss to the EEA economy** as Roche would lose resources to these claims that could otherwise be used for future investments (see Section 4.2). However, as reliable values cannot

be estimated, it was not possible to include these impacts in the above calculation of cost of non-use per kg of OP / NP_{equiv}. emitted. In addition to financial claims, **loss of trust from customers** is expected to have an **important impact** on Roche's business **which can** also **not be quantified**.

Further impacts, such as **impacts on employment** are currently estimated to be **of less importance**. However, they could reach substantial values in case Roche should lose entire portfolios and / or Roche's business should be threatened by high compensation claims.

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 **may** also **have financial implications** (if not all costs ran into can be claimed from Roche) which would ultimately have to be borne by the healthcare system and / or patients. 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 2& 3 and Use 4 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** 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 non-EEA manufacturers are involved this may however result in an overall net loss to the EEA economy.
- ⇨ The **economic impact to Roche in terms of claims by / compensations to be paid to its customers are not distributional** and would result in a net loss to the EEA economy.
- ⇨ The **social impacts related to unemployment are distributional** but may lead to an overall net loss to the EEA economy in case non-EEA manufacturers are involved in taking over Roche's market share.
- ⇨ The **social impacts in terms of increased healthcare costs** related to the temporary unavailability of Roche's affected products are **not distributional** and will put additional stress on the EEA economy. As these impacts are not limited to the EEA, the economy of non-EEA countries/regions would be affected as well.
- ⇨ **Environmental impacts may shift both within EEA countries and towards non-EEA countries** in case of non-authorisation, depending on which competitors take over Roche's market share and whether or not these competitors are still using NPnEO / OPnEO in the manufacture of the products under consideration. 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 chapters can be considered distributional. **Distributional impacts** may relate to **shifts of impacts between economic operators** (applicant, competitors, suppliers of alternatives, customers, general public), potentially including **geographical shifts**, and / or **shifts of impacts** within the applicant's business itself. An overview is given in Table 45.

Table 45. 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). The quantified economic impact to Roche in terms of claims by/compensations to be paid to its	

Affected group	Economic impact	Health and environmental impact
	customers cannot be considered distributional. This impact is not only an impact to Roche but also needs to be considered as a net impact on the EEA economy. The reason is that resources will be lost that cannot be used anymore for other investments, such as research and development and further innovation. Customer claims could pose a potentially business-critical financial risk to Roche.	
Suppliers of NPnEO and OPnEO	The economic impact to suppliers of NPnEO and OPnEO is not quantified in the SEA because it is considered very limited (considering the low yearly amounts used by Roche). Nevertheless, a small economic impact could be expected, which is to be considered distributional, since the loss to the suppliers of NPnEO and OPnEO will result in a gain of similar magnitude to suppliers of alternatives. Note that multiple alternatives are (expected to be) involved in the replacement of NPnEO / OPnEO and that consequently multiple suppliers may be involved as well.	
Suppliers of alternatives in or outside the EEA	The economic benefit to suppliers of alternatives in or outside the EEA are not quantified in the SEA but can be expected to be of a similar magnitude as the economic impact to the suppliers of NPnEO/OPnEO (see above).	
Competitors in or outside the EEA	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 EBITA foregone. Note that multiple competitors may be involved, and that the competitor(s) taking over are not necessarily companies in the EEA, hence a geographical shift may occur to non-EEA	

Affected group	Economic impact	Health and environmental impact
	companies, resulting in a net loss to the EEA economy.	
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 is expected to be claimed back from Roche. Costs not covered by such claims may be distributional as well and may eventually shift to patients and insurance companies.	As there is a lot of financial pressure on the healthcare system, hospitals running into additional costs that cannot be claimed back from Roche 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.
Downstream users of CB products	These downstream users are manufacturers of IVDs themselves and / or of medicinal products. The economic impact on these downstream users could not be quantified but is expected to be claimed at least partly to be compensated for by Roche. Costs not covered by such claims may be distributional as well and may eventually shift to patients and insurance companies.	
Patients in and outside the EEA	As Roche represents a substantial market share both in and outside the EEA 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 increase healthcare costs. These increased costs are expected to represent a net loss to both EEA and non-EEA economy.	Reduced patient outcome (e.g. expressed as an overall reduction of QALYs) is to be expected both inside and outside the EEA due to a temporary unavailability of Roche's affected IVD assays, i.e. lack of healthcare services.

Affected group	Economic impact	Health and environmental impact
Geographical scope*		
Germany	The dominant part of the social cost of unemployment in case of a non-authorisation is assumed to occur in Germany. However, in case (a) competitor(s) can take over Roche's market share, additional jobs would be generated in the countries/regions where the competing companies are vested. It should be noted that part of or even all jobs lost in Germany may be shifted to another EEA country or even to a non-EEA region depending on which competitor(s) take over. This could result in an additional net loss to the EEA economy. Note that the loss of jobs at affiliates of Roche, at suppliers, and at downstream users, has not been quantified. A certain amount of these job losses may occur in Germany as well and may be shifted in a similar way as explained above.	Part of the environmental impacts in case an authorisation would be granted can be expected to occur in Germany due to the release of NP(nEO) / OP(nEO) to surface water at the production sites of Mannheim and Penzberg and the release to surface water and / or soil at downstream users situated in Germany. Potential landfill of waste in Germany may result in (additional) releases to German surface waters through discharge of drainage water. As the receiving surface waters are rivers, the related impacts are expected to be at least partly distributed to other (mostly EEA) countries as well. In case of non-authorisation, the environmental impacts related to the affected Roche products will be reduced to zero (in terms of releases to the environment). However, in case (a) non-EEA manufacturer(s) take(s) over Roche's market share and also use(s) NPnEO / OPnEO in the manufacture of the affected products, a (partial) geographical shift of the environmental impacts outside the EEA would occur. In case (an) EEA manufacturer(s) take(s) over, releases would only be zero in case the manufacturer(s) do(es) not use NPnEO / OPnEO. A (partial) geographical shift of impacts may occur in case the manufacturer(s) use(s) NPnEO / OPnEO as well but received an authorisation while Roche did not.

Affected group	Economic impact	Health and environmental impact
		The impact on human health due to temporary unavailability of Roche's affected products would partly occur in Germany (note that the geographic distribution of the impact due to temporary unavailability of IVD/medicinal products of Roche's CB downstream users is unknown).
Other EEA countries	A certain (unquantified) social cost of unemployment would occur in EEA countries other than Germany due to potential job losses at suppliers, affiliates of Roche, and downstream users. As explained above, jobs can be shifted to other EEA countries or even to non-EEA countries or regions, in the latter case resulting in a net loss to the EEA economy.	Part of the environmental impacts in case an authorisation would be granted are expected to occur in EEA countries other than Germany mainly because of the release of NPnEO / OPnEO at downstream users of the affected IVD assays, which are situated all over the EEA. Potential landfill of waste in EEA countries other than Germany may result in (additional) releases to non-German surface waters through discharge of drainage water. As the receiving surface waters are rivers, the related impacts are expected to be at least partly distributed to other (mostly EEA) countries as well, including Germany. In the situation where no authorisation would be granted, a similar potential shift of environmental impacts may occur as described above. The impact on human health due to temporary unavailability of Roche's affected products is assumed to be spread over most EEA countries, as Roche is well represented on the IVD market in the EEA (note that the geographic distribution of the impact due to temporary unavailability of

Affected group	Economic impact	Health and environmental impact
		IVD/medicinal products of Roche's CB downstream users is unknown).
Non-EEA countries	Another part of the social cost of unemployment (not quantified in this SEA) in case of a non-authorisation would occur in countries such as Switzerland and the US due to the fact that part of the affected Roche products on the EEA market are being produced in these countries. Another unquantified social cost of unemployment could occur in non-EEA countries due to potential job losses at suppliers, affiliates of Roche, and downstream users. In case (a) competitor(s) can take over Roche's market share, the lost jobs in non-EEA countries can be shifted to other non-EEA countries or regions, but also to EEA countries, in the latter case resulting in a net gain to the EEA economy.	Similarly, as explained above for EEA countries, part of the environmental impacts would also occur in non-EEA countries, as part of the affected Roche products on the EEA market are being produced in non-EEA countries (e.g., Switzerland, the US) and most of the affected products are used by downstream users outside the EEA as well. In the situation where no authorisation would be granted, shifts of environmental impacts between the EEA and non-EEA countries/regions may occur as described above. The impact on human health due to temporary unavailability of Roche's affected products is assumed to be spread over several non-EEA countries and regions, as Roche is well represented on the global IVD market (note that the geographic distribution of the impact due to temporary unavailability of IVD/medicinal products of Roche's CB downstream users is unknown).
Applicant's business		
Employees	Unemployment is expected as a result of closure or below capacity-use of production lines and associated redundancy of directly and indirectly involved jobs. Although the social cost of unemployment is considered both temporary and distributional, in Scenario 1 it will most likely not be the same group of employees that would fill the new jobs created at competing companies taking over Roche's market share. In Scenario 2,	

Affected group	Economic impact	Health and environmental impact
	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		
Socio-economic groups based on skills (A/B/C)	Job losses are expected to occur predominantly in group C (manual, non-skilled) due to interruption of production lines. Some job losses are also expected in group B (skilled, semi-skilled) due to job losses in administrative/supporting/sales functions that would become redundant due to interruption of production lines. The lost jobs in group C and B may be generated elsewhere 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 (see above). The smallest loss could be expected in group C (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 claims or requests from customers to find solutions, lawyers supporting the company, etc.). This impact is nevertheless considered to be limited	

Affected group	Economic impact	Health and environmental impact
	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 socio-economic analysis are distributional can be summarised as follows:

- The **economic impact** to Roche 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 non-EEA manufacturers are involved this may however result in an overall net loss to the EEA economy.

- The **economic impact** to Roche in terms of **claims by / compensations** to be paid to its customers are not distributional and would result in a net loss to the EEA economy.

- The **social impacts** related to **unemployment are** distributional but may lead to an overall net loss to the EEA economy in case non-EEA manufacturers are involved in taking over Roche's market share.

- The **social impacts** in terms of **increased healthcare costs** related to the temporary unavailability of Roche's affected products are not distributional and will put additional stress on the EEA economy. As these impacts are not limited to the EEA, the economy of non-EEA countries/regions would be affected as well.

- **Environmental impacts** may shift both within EEA countries and towards non-EEA countries in case of non-authorisation, depending on which competitors take over Roche's market share and whether or not these competitors are still using NPnEO / OPnEO in the manufacture of the products under consideration. Consequently, a non-authorisation for Roche does not necessarily result in an equivalent reduction of releases of NPnEO / OPnEO to the environment.

4.3. Uncertainty Analysis

- ⇨ The **uncertainty concerning** whether or not **competitors** can take over Roche'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 Roche's market share.
- Scenario 2: Competitors cannot take over Roche'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 46.

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

An **accurate quantification of the social impacts** under the different scenarios and sub-scenarios **in terms of increased healthcare 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 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 or a specific type of assay would have to be in terms of gained QALYs / avoiding mortality resulting from potentially fatal health conditions / avoiding mortality related to cancer / avoiding cancer cases in general (through very-early-stage-detection) to equal the economic impacts to Roche in terms of EBITA foregone. This calculation was done using the total number of missing tests under Scenario 1 (competitors can take over Roche'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 Roche'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 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 46.

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 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 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 46 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 – there could be large differences due to the large geographical differences in prevalence of undetected HIV infections and the fact that no account is taken of the geographical factor in the use of the combiPT assay.

- The assumption that the 2017 figures of new HIV infections detected would still be relevant at and after the sunset date.

- 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 extrapolation to 2021 value.

- 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** Roche's market share.

- In Scenario 2, it is assumed that **competitors cannot take over** Roche'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 7-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 46 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 chapter, 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 however considered **more likely that the majority of the substitutions will either be completed on time or with limited delay**, rather than that a majority of the substitutions will run into significant delays and would require until the end of the review period in order to be completed. Consequently, **within each Scenario (1 and 2), the actual impact is expected to be closer to the lower boundary** than to the higher boundary of the calculated range.

The estimates of the economic impacts to Roche 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 46.

Altogether, it can be concluded that **the estimated range for the economic impacts on Roche 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 Roche 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 Roche in terms of **customer claims** is also assessed qualitatively in Table 46.

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 46 (and discussed in the economic and combined impacts assessment chapters) that maximum claims cannot be quantified and may lead to a potentially business-critical financial risk for Roche. Finally, it should also be noted that the estimates of economic impacts to

Roche in terms of compensations to be paid to its customers are the highest in Scenario 1, where competitors can take over Roche's market share and where the temporary unavailability of assays/proteins and consequently the social impacts in terms of increased healthcare costs are expected to be the lowest.

Uncertainty related to the social cost of unemployment

Only one quantitative estimate was made for the social cost of unemployment. The reason for not performing separate calculations for each scenario and sub-scenario as described under the economic impact assessment is that the differences between the different scenarios and sub-scenarios are not expected to be important enough to be quantified in detail, taking into account the fact that the social cost of unemployment is not a dominant factor in determining the outcome of the SEA. The differences between the scenarios are discussed qualitatively in the social impacts chapter.

The main uncertainties that were encountered during the assessment of the social cost of unemployment are summarised in Table 46. Taking all these uncertainties together, it can be safely **concluded that the calculated cost of unemployment represents a substantial underestimation of the actual social cost related to job losses for all scenarios**.

The main reasons for this are that the number of jobs were only available at the level of the affected assays (i.e. not at the level of the entire portfolio) and that they only partially include employees in the sales organisation or further supporting functions. In addition, job losses at affiliates are not taken into account due to the absence of reliable estimates for each affected portfolio.

It is further concluded that the **level of underestimation** of the actual cost of unemployment is as follows for the different scenarios:

Scenario 1, substitutions delayed > Scenario 1, substitutions on time > Scenario 2, substitutions delayed > Scenario 2, substitutions on time > estimate provided in the social impacts chapter

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 46. 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 46. 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, or [redacted] mio tests/year for the TM assay (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 very accurate. 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.
Contribution of affected assays to the gain of QALYs / prevention of fatalities (cancer-related or not) / avoidance of cancer cases in general (through very-early-stage-detection)	It was assumed that all assays contribute to this (only for TM a separate calculation was done for avoiding cancer-related mortality and avoidance of cancer cases in general)	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 chapter.	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 20'000 tests should result in the gain of 1 QALY, only 1 on 380'000 tests should*

Source of uncertainty	Description of assumption	Justification	Influence on the outcome of the assessment
			prevent a fatal health condition, only 1 on 52'000 TM tests should prevent fatality related to cancer
Monetary values used for VOSL, VSL, cancer-specific VSL, and VSCC	VOSL: 55'800 EUR (2003) VSL: 1'052'000 EUR (2003) Cancer-specific VSL: 5'000'000 (2012) VSCC: 396'000 (2012)	Values used were taken from the ECHA guidance on socio-economic analysis under authorisation (VOSL, VSL) [10] and reports of studies commissioned by ECHA (cancer-specific VSL, VSCC) [11].	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, cancer-specific VSL and VSCC to 2021	From the date the value was derived for until 2018: actual inflation figures were applied From 2018 to 2021: 4%	A 4% discount rate is recommended in the ECHA guidance on socio-economic analysis under authorisation [10].	If the actual inflation over the period 2018-2021 would be (much) lower than 4%, a directly proportional increase of the minimum efficiency of the affected assays would be calculated (in order for the social impacts to equal the maximum EBITA foregone). This would however not change the overall outcome of the assessment.
Type of social benefit of affected assays	The social benefits of the affected assays were narrowed (in view of the indicative calculations) to gain of QALYs / prevention of fatalities / avoidance of cancer-related fatalities / avoidance of cancer cases in general (through very-early-stage-detection)	The social benefit of the affected assays/portfolios is much broader than what is considered in this 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	Not taking into account the wider social benefits of the affected assays/portfolios further adds to the underestimation of the social impacts resulting from a temporary unavailability of affected assays.

Source of uncertainty	Description of assumption	Justification	Influence on the outcome of the assessment
		reduction in healthcare costs (e.g. see Table 12).	
Social benefits of downstream uses of CB products	The social benefits of the downstream uses of CB products were not taken into account in the indicative calculation	An important part of the downstream uses of Roche's CB products result in IVD products as well. However, since no detailed information could be obtained from the customers, the social impacts in case of a temporary unavailability of CB raw materials could not be included in the calculation. The same holds for the single non-IVD use identified, which is the use of CB products as raw material for cell cultures in the manufacture of pharmaceuticals.	Provided that a temporary unavailability of CB products to downstream users would also result in a temporary unavailability of the products manufactured by these downstream users (i.e. IVD assays and pharmaceuticals), a further increase of the social impacts is expected, which has not been accounted for in the indicative calculations.
Economic impacts – EBITA foregone			
Time frame during which financial losses would occur because affected assays/proteins cannot be sold anymore after the sunset date	See Table 27– Depending on the scenario, until switch to another supplier is completed or until substitution is completed	This assumption is depending on two other assumptions: i.e. the time needed for a customer to switch to a competitor system, and the assumption that the impact starts later when there is a possibility to use available stocks.	Impact on the outcome of the assessment is considered to be limited. Reference can be made to the next two assumptions.
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, installation phase, need for	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 → would increase the estimate of EBITA

Source of uncertainty	Description of assumption	Justification	Influence on the outcome of the assessment
		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.	foregone. The opposite is true when a longer time would be needed for switching. Only a marginal effect is expected on the overall outcome.
Use of available stocks	Where relevant (non-EEA use or EEA use of end products only affected by Use 4 (processes)), it is assumed that assays/proteins from stocks can still be used until the end of shelf life and that 1 year could be bridged using stocks available at customers	The assumption is considered acceptable although practical issues (e.g. logistics) could result in shorter periods than 1 year of continued use. Further, the maximum availability of stocks is limited by the actual shelf life of the products.	In case less than 1 year could be covered due to stock building and use until end of shelf life, a higher loss of EBITA due to the non-ability of selling affected assays/proteins would be the result. The opposite is true when stocks would be available to bridge more than one year. 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 5 years of the review period after completed switch of customers to competitor systems (CC, DM, HIV, TM)	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 (or 1 year later in case use of available stocks is possible) until the end of the	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. Reference can be made to the assumption on use of available stocks.

Source of uncertainty	Description of assumption	Justification	Influence on the outcome of the assessment
	review period or until substitution is completed (BGE, AT, UA, RMD, RTD)		
Loss of predicted growth	All predicted growth lost over the entire review period	The assumption is justified since it can reasonable 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. 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.

Source of uncertainty	Description of assumption	Justification	Influence on the outcome of the assessment
Economic impacts – Claims			
Magnitude of customers claims for assays / materials not supplied	Assumed to be equal to the value of goods delivered (i.e. sales of affected assays or affected materials)	Contractual penalties differ from contract to contract and compensation risk is generally unlimited. The value of goods delivered was used as a very conservative estimate for the minimum of customer claims (that could be based on contractual penalties or compensatory claims for damages) to be expected for the inability to supply the affected assays/materials over a certain period of time (Scenario 1: until switch to competitor system completed; Scenario 2: until substitution completed). Concerning time needed to switch to a competitor system, available stocks, and use of tests after the sunset date, the same assumptions as described above are taken.	Only a rough indication of possible customer claims can be given. Likely results in an underestimation of actual customer claims.
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.	This could lead to an overestimation of customer claims (based on value of goods delivered) mainly under Scenario 2 (competitors cannot take over Roche's market share) with all substitutions delayed until the end of the review period. However, value of goods delivered is considered as a minimum estimate for actual customer claims. Therefore, the underestimation based on value

Source of uncertainty	Description of assumption	Justification	Influence on the outcome of the assessment
			of goods delivered is expected to be more important than an overestimation due to not taking into account duration of contracts.
Additional claims to compensate for assays already supplied which cannot be used anymore after the sunset date	Not taken into account	Not feasible to estimate without making too many assumptions – Omission in view of a conservative estimation was preferred.	Leads to underestimation of the impacts.
Compensations 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 compensation cost is expected to be much larger than the estimated minimum cost.
Percentage of customers claiming compensations for switching to competitor systems (Scenario 1)	100%	This is considered a reasonable assumption, as there is a lot of financial pressure on healthcare services and therefore it is assumed that hospitals/laboratories would do what is needed to recover costs incurred.	No substantial impact on the outcome for Scenario 1 expected. The other extreme (no switching of customers to competitor systems and therefore no claims for such a switch) is covered by Scenario 2.
Claims from CB customers	An overall quantification is not possible – only one indicative example given	Claims from Roche's CB customers (i.e. producers of IVD assays or medicinal products)	Non-inclusion of potential claims from Roche's CB customers further adds to the general level of underestimation of the

Source of uncertainty	Description of assumption	Justification	Influence on the outcome of the assessment
		cannot easily be quantified because compensation risk is generally unlimited. Data for an indicative estimate were only available for one process group.	economic impacts to Roche in terms of customer claims. This could represent an important underestimation as compensation risk is generally unlimited and poses an inacceptable, potentially business-critical financial risk to 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 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 Roche production sites in the EEA	See Table 9.	Estimates are made at the level of the affected processes/assays, whereas no numbers are available for entire portfolios. Further, some estimates relate to jobs in production and not or only partly include jobs in other functions (e.g. sales or other supporting functions).	The absence of estimates of potentially affected jobs for entire portfolios results in an important underestimation of the social cost of unemployment in Scenario 1. The fact that some estimates do not or only partly include jobs in supporting functions results in an underestimation of the social cost of unemployment in all scenarios.
Estimation of number of affected jobs at Roche's affiliates	See Table 9 – only available for BGE (affected system only) and not for the other portfolios – therefore not included in the assessment	It was preferred not to include an estimate for the number of affected jobs at Roche's affiliates because no accurate job numbers are available for all affected portfolios/systems and therefore the inclusion would only further add to the uncertainty related to the assessment.	The omission of affected jobs at Roche's affiliates results in a substantial underestimation of the social cost of unemployment in all scenarios but most of all in Scenario 1.

Source of uncertainty	Description of assumption	Justification	Influence on the outcome of the assessment
Distinction between the number of EEA and non-EEA employees	See Table 9 – in certain cases only global numbers of employees were given	For the estimation of the total number of jobs lost in the EEA, only assumptions needed to be made for UA (produced in Germany, but only a global number of employees provided). The total number of employees (60 FTE) was included in the assessment. This was considered justified because most of the jobs will be lost in EEA (due to production in Germany) and the estimate of the total number of jobs lost in the EEA represented an underestimation anyhow (see above).	Only a limited effect expected on the outcome of the assessment (levels out a small part of the substantial underestimation of the total numbers of jobs lost in the EEA).
Estimation of number of jobs affected outside Roche (suppliers, customers, etc.)	Not included in the assessment.	No accurate estimates could be made, and therefore omission was preferred in view of a conservative estimation instead of further adding to the uncertainty around the prediction.	Leads to an underestimation of the actual cost of unemployment. Nevertheless, the contribution of jobs lost outside Roche is expected to be very limited compared to those lost at Roche and Roche's affiliates.
Social cost of unemployment of one job (FTE) lost	Figure provided by Dubourg (2016) for EU-28 (86'827 EUR, 2014 value)	The study by Dubourg (2016) was commissioned by ECHA and recommended for use in socio-economic analyses under REACH. Although the social cost of unemployment would probably be higher for Germany, no geographical correction was made for the EU-28 figure.	Best available average figure for EU-28. Because the actual value for Germany could reasonably be expected to be higher than the average for EU-28, the use of the average value leads to an underestimation of the actual cost of unemployment.

Source of uncertainty	Description of assumption	Justification	Influence on the outcome of the assessment
Extrapolation of the EU-28 value provided by Dubourg (2016) from 2014 to 2021	From 2014 to 2018: actual inflation figures were applied From 2018 to 2021: 4%	A 4% discount rate is recommended in the ECHA guidelines on socio-economic analysis under authorisation.	If the actual inflation over the period 2018-2021 would be (much) lower than 4%, a directly proportional decrease of the social cost of unemployment would be calculated. This would however not change the overall outcome of the assessment.
Environmental impacts*			
Estimate of release to wastewater for the production sites (Use 2 and 4)	Based on site-specific data	Site-specific data instead of standard release factors was used to account for RMMs implemented by the submission date.	Estimates of releases may be associated with some error but influence on the overall outcome of the assessment is expected to be small.
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 known and fractions going to waste were estimated per assay and instrument. Removal of OPnEO / NPnEO through treatment of liquid waste in some countries is uncertain.	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 in some countries, 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	Sum of releases from the sunset date until the end of the	Both the indicative calculations of the social impacts resulting from	Although the same scenario was used, for the social impacts only a minimum value could

Source of uncertainty	Description of assumption	Justification	Influence on the outcome of the assessment
social impacts as given in Table 44.	review period in case all substitutions are completed on time.	temporary unavailability of IVDs and the calculation of releases were based the scenario in which all substitutions are completed on time.	be determined. As a consequence, the ratios presented in Table 44 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.
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 EEA, on average 45% of total sewage sludge are used in agriculture [5]. Therefore, releases to soil represent a maximum and are very likely overestimated. This is accounted for by providing a range in the comparison with social impacts (Table 44).
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 the production sites (Use 2 and 4) (i.e. which releases from different activities at one site can occur within one day)	It is assumed that the release from one process or formulation batch occurs within one day It is assumed that one batch from each formulation activity could be produced on the same day	The assumptions are worst-case: the protein production processes are usually conducted over several days. Further, batches from all formulation activities are not produced on the same day.	Due to worst-case assumptions, releases per day and therefore actual PECs are expected to be lower than the calculated PECs under normal operating conditions. For verification see also ‘sum of modelling parameters’.

Source of uncertainty	Description of assumption	Justification	Influence on the outcome of the assessment
Distribution over time of release to wastewater from downstream uses (Use 3)	Number of operating days between 260 (assays rather used in centralised laboratories) and 365 (assays rather used at points of care or 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 EEA (Use 3) for calculation of local release and thus local PEC	REACH standard parameters for wide-dispersive use in the EEA: Fraction of total tonnage used in the region: 0.1 Fraction of regional tonnage used at local scale: 0.0005	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. 30% lower for OPnEO and ca. 100% higher for NPnEO than actual release from an average laboratory. Maximum predicted releases and PECs were estimated based on actual data for large laboratories.	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.
Point in time used for calculation of PECs	PECs are calculated based on releases at the sunset date in case all substitutions are delayed	Worst -case scenario: all substitution projects that are planned to be completed before the sunset date were assumed to be delayed until after the sunset date, although this is not likely.	Maximum PECs will be lower if at least some substitution projects that were planned to be completed before the sunset date are completed as planned. It should be noted that PECs are expected to further decrease over the course of the review period due to completion of substitution projects. If all substitutions were delayed and growth occurred as predicted, total releases could be higher (see 'sum of releases over review period'), but PECs are expected to remain

Source of uncertainty	Description of assumption	Justification	Influence on the outcome of the assessment
			similar in most cases as growth would mainly occur through additional customers (i.e. additional sites of release). For emissions per day from the production sites, worst-case assumptions were already applied (see separate line). Therefore, release per day is not expected to increase significantly.
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'.
Modelling parameters: efficiency of activated carbon treatment	Activated carbon (Mannheim): OP: 85%	Mannheim: Efficiency towards OP and NP removal was measured in	The modelling outcome was found to be very conservative.

Source of uncertainty	Description of assumption	Justification	Influence on the outcome of the assessment
(Mannheim) or microfiltration (Penzberg)	OPnEO and further degradation products: 0% NP: 25% NPnEO and further degradation products: 0% Membrane filtration (Penzberg): Removal rate of 70% of the sorbed OPnEO / NPnEO compounds	Mannheim. Due to lack of data for ethoxylates or carboxylates, removal was set to 0 as a conservative approach. Penzberg: Removal rate of 70% is the lower value reported for nano-filtration. Removal rate is only applied to compounds adsorbed to sludge which will be retained by the membrane filtration.	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 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 Uses 2& 3 and Use 4 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] **(700-7'000) mio EUR in total for all uses**.
- ⇨ For Roche, claims from its customers based on breach of contracts could amount as a minimum to [redacted] (100-10'000) mio EUR. Maximum claims pose a **potentially business-critical financial risk** to Roche.
- ⇨ 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 RDG over the course of the review period is estimated to range between [redacted] and [redacted] (100-7'000) mio EUR
- ⇨ 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 2&3 and Use 4 **outweigh the remaining risks** to the environment.
- ⇨ Due to **quality and regulatory requirements** for IVD assays, any review period shorter than **7 years** would not be sufficiently long for completing the substitution of OPnEO and NPnEO in all processes and 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 Roche Diagnostics GmbH (RDG), the leading company in the *in vitro* diagnostic market in Europe and worldwide. The current SEA was developed to support RDG's AfA to continue the use of two groups of substances OPnEO / NPnEO after the sunset date until complete substitution. OPnEO and NPnEO were included in Annex XIV (entries 42 and 43) of the Registration on Evaluation, Authorisation and Restriction of Chemicals (REACH) by the European Chemical Agency (ECHA) because of the endocrine disrupting properties for the environment of their degradation products with a sunset date of 4th of January 2021.

In the '**non-use' scenario**, **RDG will not be able to continue the formulation and filling of the affected IVD assays** (i.e. the products containing OPnEO / NPnEO; Use 2) **as well as to produce and supply proteins** (including MDx Enzymes which are specific types of proteins) **and to conjugate latex beads**. The proteins and latex beads are needed to formulate certain IVD assays at RDG and at other IVD manufacturers that are RDG's customers (Use 4). In addition, laboratories and hospitals will not be able to use certain IVD assays (Use 3) and will thus **not be able to provide complete healthcare services to patients**. RDG's formulation of IVD assays as well as the production processes will need to be interrupted until the necessary steps to switch to an alternative surfactant or, in some cases, alternative products are completed, including - where required - 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**.

Expected impacts based on the described 'non-use' scenario will occur throughout the entire EEA. In addition, worldwide impacts are also considered as RDG produces in Penzberg and Mannheim for the global market and RDG's products are sold worldwide.

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] (700-7'000) mio EUR** in total for all uses. Several hundred million of patients worldwide are expected to face a temporary lack of healthcare services over at least 1 year up to 7 years after the sunset date.

For Roche, claims from its customers (i.e. laboratories and hospitals as well as other IVD manufacturers) based on breach of contracts could amount as a minimum to [redacted] (100-10'000) mio EUR. Maximum **claims** cannot be quantified but **pose a potentially business-critical financial risk to Roche**. 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 RDG over the course of the review period is estimated to range between [redacted] and [redacted] (100-7'000) mio EUR.

As shown in the Chemical Safety Reports (CSR) for the three uses, usage of OPnEO / NPnEO is substantially reduced before the sunset date based on substitutions already completed. Furthermore, additional risk management measures at the production sites and additional instructions for disposal for laboratories and hospitals **have reduced or will reduce emissions to wastewater** until the sunset date **by 29% OPnEO and 13% NPnEO compared to 2016-2017 for the uses covered by this application (Uses 2, 3 and 4).** Emissions will be further 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. 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 108-620 kg $OP_{equiv.}$ and 5.8-19 kg $NP_{equiv.}$ for surface water and 90-515 kg $OP_{equiv.}$ and 16-55 kg $NP_{equiv.}$ as a maximum for soil over the 7 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 risk management measures are not technically and practically feasible. Releases at the production sites are already reduced to low levels. Effectiveness of RMMs implemented by the submission date will be verified by a monitoring campaign for OPnEO in Mannheim and Penzberg. The required reconstructions to additional collect rinsing waters would be associated with high cost and a major part of the substitutions will likely be finalised before such reconstructions would be completed. At laboratories and hospitals additional risk management measures are not feasible within a reasonable time frame to effectively reduce emissions. The majority of emissions is likely to be already eliminated within 1 to 3 years after the sunset date.

Based on the combined impacts assessment, **the ratio of minimal societal cost** (in terms of increased healthcare costs) per kg OP or $NP_{equiv.}$ emitted are expected to be **much larger than 2-44 mio EUR / kg for Use 2&3 and much larger than 900-9'000 mio EUR / kg for Use 4**.

Consequently, it can be concluded with high certainty that the socio-economic benefits of continued use of OPnEO / NPnEO associated with Use 2& 3and Use 4 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 **7-year review period** will allow RDG to complete the evaluation of alternatives, validate and assure performance of the affected products, and if necessary, submit change notifications as a regulatory requirement for *in vitro* diagnostic assays. Millions of patients worldwide depend on the accurate, reproducible and reliable results of these assays. RDG is committed to **substitute OPnEO / NPnEO as fast as possible for each individual product and process**. However, RDG has concluded **that any review period shorter than 7 years** would not be sufficiently long for completing the substitution of OPnEO and NPnEO in all processes and products.

In summary, RDG is applying for an authorisation to continue the use of OPnEO and NPnEO in accordance with article 60(2) of REACH for the following reasons:

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

2) RDG IVD assays depending on the use of OPnEO / NPnEO in the assays (Use 2&3) or in the production of proteins and latex beads (Use 4) have an **unquestionable social value** and

3) **7 years** are needed for replacement of OPnEO / NPnEO in all products and processes due to high quality and regulatory requirements for IVD assays.

6. REFERENCES

[1] Backmann J. Factsheet and Q&A Roche Group-wide Goal to Phase out Substances of Very High Concern, Group SHE Chemical Legislation Unit (LSOL), Last update: February 2018.

[2] ECHA (2011) Guidance on the preparation of an application for authorisation, Version 1, January 2011

[3] BIVDA (British In Vitro Diagnostics Association). The Value of IVDs. The contribution of the in vitro diagnostics industry to patients, the NHS and the UK economy. Available: https://www.bivda.org.uk/Portals/0/The%20Value%20of%20IVDs%208pp%20web.pdfhttps://www.bivda.org.uk/Portals/0/The%20Value%20of%20IVDs%208pp%20web.pdf

[4] Brown, Robert B., and Julie Audet. 'Current techniques for single-cell lysis'. Journal of the Royal Society Interface 5.Suppl 2 (2008): S131-S138.

[5] EUROPEAN COMMISSION (2017). REPORT FROM THE COMMISSION TO THE EUROPEAN PARLIAMENT, THE COUNCIL, THE EUROPEAN ECONOMIC AND SOCIAL COMMITTEE AND THE COMMITTEE OF THE REGIONS on the implementation of EU waste legislation for the period 2010-2012; Implementation of Directive 2008/98/EC on waste, Directive 86/278/EEC on sewage sludge, Directive 1999/31/EC on the landfill of waste, Directive 94/62/EC on packaging and packaging waste, Directive 2002/96/EC on waste electrical and electronic equipment (WEEE), and Directive 2006/66/EC on batteries and accumulators. Brussels, 27.2.2017, COM(2017) 88 final

[6] Véronique Stark-Rogel, Roger Borner, and Jan Backmann (2016). Mitt Umweltchem Ökotox, 22. Jahrg. 2016/ Nr. 2, p. 44-50: In-depth chemical analysis and assessment of a broad range of liquid waste from in-vitro diagnostic instruments.

[7] Cressman S, Lam S, Tammemagi MC, Evans WK, Leighl NB, Regier DA, et al. (2014). Resource utilization and costs during the initial years of lung cancer screening with computed tomography in Canada. Journal of Thoracic Oncology 9, 1449-1458.

[8] Directive 2013/39/EU of The European Parliament and of the Council of 12 August 2013 amending Directives 2000/60/EC and 2008/105/EC as regards priority substances in the field of water policy

[9] Donaldson C, Baker R, Mason H, Jones-Lee M, Lancsar E, Wildman J, Bateman I, Loomes G, Robinson A, Sugden R, Pinto Prades JL, Ryan M, Shackley P, Smith R (2011). The social value of a QALY: raising the bar or barring the raise? BMC Health Services Research 11, 8.

[10] ECHA (2011). ECHA Guidance Document on Socio-Economic Analysis in Authorisation. Available: https://echa.europa.eu/documents/10162/23036412/sea_authorisation_en.pdf/aadf96ec-fbfa-4bc7-9740-a3f6ceb68e6e

[11] ECHA (2016). Valuing selected health impacts of chemicals – Summary of the results and critical review of the ECHA study. Available: https://echa.europa.eu/documents/10162/13630/echa_review_wtp_en.pdf

[12] EDMA (2011). EDMA Market Statistics Report.

[13] EFPIA (2012). The Pharmaceutical Industry in Figures: Key Data 2012. European Federation of Pharmaceutical Associations and Industries.

[14] Fang C, Otero HJ, Greenberg D, Neumann PJ (2011). Cost-utility analyses of diagnostic laboratory tests: a systematic review. Value in Health 14, 1010-1018.

[15] Gifford Lum, 'Urine Drug Testing: Approaches to Screening and Confirmation Testing', laboratory medicine, 6, no.35 (2004), pp.368-373

[16] Arle J, Mohaupt V, Kirst I (2016) Monitoring of Surface Waters in Germany under the Water Framework Directive — A Review of Approaches, Methods and Results. Federal Environmental Agency (Umweltbundesamt).

[17] Lewin Group, Inc. (2005). The value of diagnostics innovation, adoption and diffusion into health care. Available: https://dx.advamed.org/sites/dx.advamed.org/files/resource/Lewin%20Value%20of%20Diagnostics%20Report.pdf

[18] Mignogna MD, Fedele S, Lo Russo L, Ruoppo E, Lo Muzio L (2002). Costs and effectiveness in the care of patients with oral and pharyngeal cancer: analysis of a paradox. European Journal of Cancer Prevention 11, 205-208.
[19] National Institute of Health and Care Excellence (NICE) (2010): Measuring effectiveness and cost effectiveness: the QALY.
[20] NewExt (2003). New Elements for the Assessment of External Costs from Energy Technologies. Available: http://www.ier.uni-stuttgart.de/forschung/projektwebsites/newext/newext_final.pdf.
[21] Rohr U-P, Binder C, Dieterle T, Giusti F, Messina CGM, Toerien E, Moch H, Schäfer HH (2016). The value of in vitro diagnostic testing in medical practice: a status report. PLoS ONE 11(3): e0149856. doi:10.1371/journal.pone.0149856
[22] RPA (2015). Quantification and valuation of the human health impacts of chemicals based on quality and disability-adjusted life-years. ECHA Service Request SR 19. Available: https://echa.europa.eu/documents/10162/13639/report_qualy_daly_en.pdf/f8c20060-8e7d-4b87-9e0c-64ba2999e63d
[23] Ryen L, Svensson M (2014). The Willingness to Pay for a Quality Adjusted Life Year: A Review of the Empirical Literature. Health Economics.
[24] Baggaley RF, Irvine MA, Leber W, Cambiano V, Figueroa J, McMullen H, Anderson J, Santos AC, Terris-Prestholt F, Miners A, Hollingsworth TD, Griffiths CJ (2017). Cost-effectiveness of screening for HIV in primary care: a health economics modelling analysis. Lancet HIV 4, e465-e474.
[25] Bert F, Gualano MR, Biancone P, Brescia V, Camussi E, Martorana M, Secinaro S, Siliquini R (2018). Cost-effectiveness of HIV screening in high-income countries: a systematic review. Health Policy 122, 533-547.
[26] Sanders GD, Bayoumi AM, Sundaram V, Bilir SP, Neukermans K, Rydzak CE, Douglass LR, Lazzeroni L, Holodniy M, Owens DK (2005). Cost-effectiveness of screening for HIV in the era of highly active antiretroviral therapy. New England Journal of Medicine 352, 570-585.
[27] Walensky RP, Weinstein MC, Kimmel AD, Seage GR 3rd, Losina E, Sax PE, Zhang H, Smith HE, Freedberg KA, Paltiel AD (2005). Routine human immunodeficiency virus testing: an economic evaluation of current guidelines. Am J Med 118, 292-300.
[28] Walensky RP, Wood R, Fofana MO, Martinson NA, Losina E, April MD, Bassett IV, Morris BL, Freedberg KA, Paltiel AD (2011). The clinical impact and cost-effectiveness of routine, voluntary HIV screening in South Africa. J Acquir Immune Defic Syndr 56, 26-35.
[29] Yazdanpanah Y, Sloan CE, Charlois-Ou C, Le Vu S, Semaille C, Costagliola D, Pillonel J, Poullié A-I, Scemama O, Deuffic-Burban S, Losina E, Walensky RP, Freedberg KA, Paltiel AD (2010). Routine HIV screening in France: clinical impact and cost-effectiveness. PLoS One 5, e13132.

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 health care 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 health care 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 approximately 66% of clinical decisions. A report by the Lewin Group [17] 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 **health care 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 approximately 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 GBP annually on IVD products, which is less than 1% of the total NHS budget [3]. The review of Rohr et al. [21] revealed that approximately 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.

[1] Roche website, Personalised healthcare:
https://www.roche.com/about/priorities/personalised_healthcare/phc_mission.htm

Cost-utility analysis and monetisation of health benefits / impacts

The relative efficiency of investments in health care 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 health care 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 health care 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 5'0000 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 GBP 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. 50'461 EUR in 2018-20'000-30'000 GBP in 2010 is ca. 28'391-42'587 EUR in 2018).

- The Social Value of a QALY project, performed by Donaldson et al. [9], was reported to yield values of 10'000-70'000 GBP per QALY (ca. 13'493-94'454 EUR in 2018). Most methods of

aggregating the data resulted in values of 18'000-40'000 GBP per QALY (ca. 24'288-53'974 EUR in 2018).

- 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. 131'617 and 26'831 EUR in 2018, respectively). Around 80% of all estimates were below 75'000 EUR (in 2010, i.e. < 83'064 EUR in 2018). 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 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). 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 105'2000 and 55'800 EUR, respectively (in 2003, i.e. ca. 1'338'000 and 71'000 EUR in 2018). For sensitivity analysis, the median values of 2258000 and 125200 EUR, respectively, should be considered (i.e. 2'870'000 and 159'000 EUR in 2018).

- 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 socio-economic analysis 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. 5'260'000 and 3'682'000 EUR in 2018), and the VSCC was 396'000 EUR based on the original results and 350'000 EUR after a robustness check (i.e. 417'000 and 368'000 EUR in 2018). 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. 431'000 EUR in 2018).