ANALYSIS OF ALTERNATIVES

Legal name of applicant(s):	Roche Diagnostics International Ltd, Rotkreuz, Switzerland
Submitted by:	Roche Diagnostics International Ltd
Substances:	4-(1,1,3,3-Tetramethylbutyl)phenol, ethoxylated (covering well-defined substances and UVCB substances, polymers and homologues); (Octylphenolethoxylates, OPnEO).
Use titles:	Use of Octylphenolethoxylates in the Production of Sensors for Blood Gas and Electrolytes Analysis
Use number:	1

DECLARATION AND JUSTIFICATION OF CONFIDENTIALITY

We, Roche Diagnostics International Ltd, request that the information blacked out in this version of the Chemical Safety report is not disclosed to the public or any person requesting access to an official document. We hereby declare that, to the best of our knowledge, the blacked out fields comprise business or manufacturing secrets of our company ("Geschäfts- oder Fabrikationsgeheimnisse" according to section 7, para. 1, lit. g of the Federal Act on Freedom of Information in the Administration). Disclosure could potentially enable competitors to adapt their own business or manufacturing practices based on data normally not available to them.

Signature: Alexander Martius Date, Place: Rotkreuz, 27-Jul-2022

Alexander Martius, Head of Legal - Point of Care Customer Area

Signature: Dr. Jan Backmann Date, Place: Basel, 27-Jul-2022

Dr. Jan Backmann MSc PhD, Head of Chemical Legislation

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GLOSSARY

Term	Explanation
AA-EQS	Annual average environmental quality standard
ACS	American Chemical Society
AfA	Application for Authorisation
AoA	Analysis of Alternatives
BGE	Blood gas and electrolyte BGE is part of the Point of Care Roche business unit and the affected products in this portfolio are the b 123 and the b 221 systems. 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, Haematocrit, Na^+, K^+, Cl^-, Ca^{2+}, Glucose, Lactate, Urea/BUN. These critical parameters indicate for example whether oxygen is adequately delivered to tissues or help detecting jaundice in new-borns.
b 123 system	cobas® b 123 POC system
b 221 system	cobas® b 221 system
BUN	Blood Urea Nitrogen
CEC	Corporate Executive Committee
ChemO	Swiss Ordinance SR 813.11 on Protection against Dangerous Substances and Preparations (Chemicals Ordinance, ChemO) of 5 June 2015 (Status as of 5 May 2022).
CHF	Swiss Franc
CMC	Critical micelle concentration
cobas®	Trade name of Roche diagnostic system
Covid-19	Coronavirus disease of 2019
CSR	Chemical Safety Report
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
ECHA	European Chemicals Agency
ECS	Environmental Contributing Scenario

Term	Explanation
ED	Emergency Departments
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
EQS	Environment Quality Standard from the EU Water Frame Directive 2013/39/EU
ERC	Environmental Release Category
EU	European Union
FOEN	Federal Office for the Environment in Switzerland
FOPH	Federal Office of Public Health
GLU	Glucose
Hb	Haemoglobin
HDPE	High-density polyethylene
HLB	Hydrophilic-lipophilic balance
ICU	Intensive Care Units
ISE	Ion Selective Electrode
IVD	*In vitro* diagnostic medical devices. IVD products are regulated and defined by the Medical Devices Ordinance (MedDo) SR 812.213 of 1st of July of 2020 (Status as of 26 of May of 2021) as medical devices which are used as a reagent, reagent product, calibrator, control material, kit, instrument, apparatus, equipment or system in accordance with their specified purpose for the *in vitro* examination of specimens derived from the human body, including blood and tissue donations, and which are used solely or principally for the purpose of providing information: a. on physiological or pathological states; b. on congenital abnormalities; c. to determine safety and compatibility with potential recipients; d. to monitor therapeutic measures.

Term	Explanation
IVDR	EU Regulation concerning IVD medical devices Regulation (EU) 2017/746 of the European Parliament and of the Council of 5 April 2017 on *in vitro* diagnostic medical devices and repealing Directive 98/79/EC and Commission Decision 2010/227/EU (Status as of 28 January 2022
IW	Industrial Worker
LAC	Lactose
LEV	Local Exhaust Ventilation
MIO	Million
MSS	Metabolite Specific Sensor
NPT	Near Patient Testing
OCs	Operational Conditions
OP	Degradation product of OPnEO: 4-(1,1,3,3-tetramethylbutyl)phenol (4-tert-OP)
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]
ORRChem	Ordinance of the Swiss Federal Council on the Reduction of Risks relating to the Use of Certain Particularly Dangerous Substances, Preparations and Articles (Chemical Risk Reduction Ordinance, ORRChem) n° 814.81 of 18 May 2005.
OSH	Occupational Safety and Health
PEC	Predicted Environmental Concentration
PNEC	Predicted No Effect Concentration
PoC	Point of Care
PPE	Personal Protective Equipment
PROC	Process Category
Q1, Q2, etc.	Quartal 1, Quartal 2, etc.
QC	Quality Control
RAC	Committee for Risk Assessment

Term	Explanation
RDG	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).
RDI	Roche Diagnostics International Ltd (Rotkreuz, Switzerland)
REACH	Regulation on Registration Evaluation, Authorization and Restriction of Chemicals European Regulation (EC) No 1907/2006
RMMs	Risk Management Measures
SEA	Socio-economic Analysis
SECO	State Secretariat for Economic Affairs
spERC	Specific Environmental Release Category
SVHC	Substances of Very High Concern A SVHC is a chemical substance (or part of a group of chemical substances) which meets the criteria of art.57 REACH In fact, listing of a substance as an SVHC by the European Chemicals Agency (ECHA) is the first step in the procedure for limiting the use of a chemical (either with an authorization or a restriction)
sensor cartridge	Sensor Cartridges of the cobas® b 123
sensor cassette	Metabolite Specific Sensor (MSS) cassettes of the cobas® b 221 system: GLU/LAC/UREA (BUN) Cassette, GLU/LAC Cassette, GLU Cassette
UN SDGS	United Nations Sustainable Development Goals
UVCB	Substance of Unknown or Variable composition, Complex reaction products or Biological materials
WCS	Worker Contributing Scenario

1. SUMMARY

This Analysis of Alternatives (AoA) was developed to support this application for temporary exemption pursuant to Annex 1.17 number 2 paragraph 4 ORRChem of Roche Diagnostics International (RDI) to continue the use of Octylphenolethoxylates (OPnEO) after the end of the transitional period until complete substitution. The end of the transitional period referred to is defined in Annex 1.17 of the Swiss ORRChem, as the 2nd May 2024. OPnEO is listed as entry 42 in this Annex 1.17, paragraph 5.

OPnEO was included into Annex 1.17 ORRChem because of the endocrine disrupting properties of the degradation products for the environment. A Chemical Safety Report (CSR) has been submitted by the applicant as part of this application for temporary exemption and describes the use, the risk minimisation measures, the emissions and the mass balance of OPnEO in the manufacturing process of sensors for blood gas and electrolytes (BGE) analysis.

The assessment conducted in the Socio-Economic Analysis (SEA) of the EU Application for Authorisation (AfA) submitted by Roche Diagnostics GmbH (RDG) is also applicable in Switzerland. Therefore, it was agreed with the assessment authorities that no separate SEA will be developed for this application for temporary exemption. The SEA in the EU Dossier demonstrated that the **benefits of continued use of OPnEO outweigh the risks to the environment.**

The applicant RDI applies for a temporary exemption for the following use:

Use 1: Use of Octylphenolethoxylates in the Production of Sensors for Blood Gas and Electrolytes Analysis.

OPnEO is an important component of the [redacted] emulsion which is applied onto sensor components to form a [redacted] membrane. The membrane is a critical material for the resulting sensor performance. All components of the sensor, including the membrane, form an article according to the ChemO and the REACH Regulation. In accordance with ORRChem Annex 1.17, this application concerns the use of OPnEO in the production of the articles at the RDI site in Rotkreuz but does not concern the use of the OPnEO-containing articles.

The sensors are an integral part of two different devices called cartridge and cassette. Together with their respective measurement systems they form *in vitro* diagnostic (IVD) products used for BGE analysis and they enable the simultaneous measurement of several blood parameters in life-critical situations in Near Patient Testing (NPT). The sensors in scope of this application are integrated into:

- the cobas® b 123 sensor cartridge used with the cobas® b 123 POC system (referred to as sensor cartridge and b 123 system) and
- the Metabolite Specific Sensor (MSS) cassette used with the cobas® b 221 system (referred to as sensor cassette and b 221 system).

IVDs are highly regulated in countries worldwide. Due to those strict requirements, several steps which focus on performance of the IVD product must be completed to accomplish substitution. In general, the steps include feasibility assessment, development, verification, validation, regulatory approval / market authorisation and introduction to the market.

In this AoA, several options for substitution of OPnEO were initially considered from the applicant's perspective. As in the EU Dossier submitted by RDG, the direct substitution of OPnEO in the existing sensors would have been the preferred alternative. However, the applicant concluded that the only suitable option is **the development of a new generation product with entirely OPnEO-free**

sensors to replace the existing systems. This option is being pursued under the project [redacted]. The [redacted] project is currently in the [redacted] of the substitution process. It is expected that substitution of the OPnEO-containing systems b 123 and b 221 will be completed until [redacted].

The **temporary exemption** for the use of OPnEO for a **period** [redacted] after the end of the transitional period (2nd May 2024) is requested to complete the replacement of OPnEO in the production of the affected sensors. This period is needed due to **time-intensive development of a new generation technology,** as well as **due to the extensive regulatory requirements** demanded in the process to obtain **worldwide marketing authorisation** for the new IVD product.

2. INTRODUCTION

- ⇨ The applicant for this temporary exemption is **Roche Diagnostics International (RDI)**, which is an affiliate of **F. Hoffmann-La Roche Ltd**. (Roche)**.**
- ⇨ Roche is the world leader in ***in vitro*** **diagnostics** (IVD) and **tissue-based cancer diagnostics**, and one of the most well-known companies providing **clinically differentiated medicines and personalised healthcare**.
- ⇨ The current AoA was developed to support RDI's application for temporary exemption to **continue the use of OPnEO in production of sensors for BGE analysis after the end of the transitional period** until complete substitution.
- ⇨ **IVDs are highly regulated worldwide**. They can only be placed on the market with a **regulatory approval / market authorisation** by the respective health authorities.

Roche Diagnostics International Ltd (RDI, Rotkreuz, Switzerland), the applicant of this application for temporary exemption, is an affiliate of F. Hoffmann-La Roche Ltd. (collectively hereinafter referred to as "Roche"). As the world's largest biotech company, Roche develops innovative medicines, improving the standard of care across **oncology, immunology, infectious diseases, ophthalmology and neuroscience.** Roche is the world leader in ***in vitro*** **diagnostics and tissue-based cancer diagnostics, including the launch of several IVD tests during the Covid-19 pandemic** and one of the most well-known companies working on diabetes management. Roche's healthcare strategy aim is to provide medicines and diagnostics that enable significant improvements in the health, quality of life and survival of patients. Roche is a **leading provider of clinically differentiated medicines and personalised healthcare**[1], which is healthcare based on the separation of patients into different sub-groups according to biological differences such as genetic make-up or disease subtype. Using this information, physicians can treat patients more precisely.

RDI is part of the Roche Group and as such, RDI is publicly committed to substituting any Substances of Very High Concern (SVHC) from their processes and products[2,3].

In addition, another affiliate of the Roche Group, Roche Diagnostic GmbH (RDG), is the leading company in the IVD market worldwide and the EU importer of the BGE products in scope of this application. RDG is the applicant of the EU Dossier[4] referenced throughout this document concerning the authorisation for continued use of Octylphenolethoxylates (OPnEO) in IVD products.

The current AoA was developed to support this **application for a temporary exemption** pursuant to Annex 1.17 number 2 paragraph 4 ORRChem [1] **by RDI to continue the use of Octylphenolethoxylates (OPnEO) in the production of sensors in Rotkreuz until complete substitution by the end of 2033.** After the end of the **transitional period** on the **2nd of May 2024** it

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

[2] https://assets.cwp.roche.com/f/126832/x/7e699f3b90/compliance_2021_final.pdf

[3] Roche Website: 'Our SHE Goals and Performance', under 'environmental goals': https://www.roche.com/about/sustainability/environment/goals-performance#7c19f478-8579-431d-8f13-5fec7c4948b7

[4] The link to the complete EU Dossier is: https://echa.europa.eu/applications-for-authorisation-previous-consultations/-/substance-rev/45040/del/200/col/synonymDynamicField_1512/type/asc/pre/2/view

is **prohibited to use and place on the market for use in Switzerland the substance OPnEO** listed in Annex 1.17 of the ORRChem [1] with entry number 42.

The Federal Office for the Environment (FOEN) summarises the provisions of Annex 1.17 as follows[5]:
"…In line with the provisions of Annex XIV to REACH [2], the placing on the market and use of OPE [octylphenol and its ethoxylates] (…) is subject to general bans, which come into force in Switzerland on 2 May 2024. As in the EU, the substances listed in Annex 1.17 (ORRChem) are prohibited, though they may be declared exempt from the ban in certain circumstances: authorisations granted by the EU Commission are regarded in Switzerland as exemptions from the prohibition, provided the substances concerned are placed on the market and used in accordance with the terms of the EU authorisation. Furthermore, the provisions of Annex 1.17 ORRChem stipulate that the Chemicals Registration Authority, in consultation with the Federal Office for the Environment (FOEN), the Federal Office of Public Health (FOPH) and the State Secretariat for Economic Affairs (SECO), may grant additional temporary exemptions for placing prohibited substances on the market and using them in Switzerland if alternative substances or procedures are not yet available…".
For the application for a temporary exemption the information requirements and subsequent guidance documents are in accordance with Article 62, paragraph 4-6 of Regulation 1907/2006/EC (REACH)[6] [2]. Therefore, reference is made where applicable to EU requirements and guidance documents. Furthermore, the requirements for this application for temporary exemption were discussed and agreed upon during a meeting of the applicant RDI with the assessment authorities[7].

RDI currently engages OPnEO in different uses at the site of Rotkreuz. However, only one use by RDI is affected by Annex 1.17 number 2 paragraph 4 of the ORRChem [1] and is not included in the EU Dossier by RDG. This application for temporary exemption therefore only affects the following use:

Use 1: Use of Octylphenolethoxylates in the Production of Sensors for Blood Gas and Electrolytes Analysis

All components of the sensors in scope form an article according to the ChemO [3] and the REACH Regulation [2]. The use of articles containing OPnEO does not require application for temporary exemption according to ORRChem Annex 1.17, number 1. Therefore, **this application only concerns the use of OPnEO in the production** of the named sensors, but not the use of the sensors.

This AoA concerns two IVD products which include the above-mentioned sensors produced with OPnEO at RDI in Rotkreuz. The IVD products concerned are used in BGE analysis worldwide and enable the simultaneous measurement of several blood parameters in life-critical situations in Near Patient Testing (NPT).

IVDs are a category of medical devices, i.e. any apparatus, appliance, software, material or other article intended by the manufacturer to be used for human beings for the purpose of diagnosis, prevention, monitoring, etc. In contrast to other groups of medical devices, IVD do not come into direct contact with patients, but serve to derive information on the patient's state by analysis of

[5] https://www.bafu.admin.ch/bafu/en/home/topics/chemicals/info-specialists/chemicals--regulations-and-procedures/octylphenol--nonylphenol-and-their-ethoxylates.html

[6] This is found in Annex 1.17, number 2 paragraph 4 of the ORRChem [1]

[7] Minutes of the meeting between RDI and the assessment authorities on the 6th of December of 2021

specific parameters, e.g., in blood or tissue. This information can concern a physiological, pathological state, or a congenital abnormality, determine the safety and compatibility with potential recipients, or monitor therapeutic measures [4][5]. **IVDs are highly regulated** by IVD-specific regulations. The IVDs can only be placed on the market with a regulatory approval / market authorisation by the respective health authorities. A change in the specification of an IVD, depending on the extent of the change, can trigger a renewal of regulatory approval / authorisation or require adaptation of an IVD-regulatory approval / authorisation. Information requirements and timelines for the authorisation or registration process for IVDs can vary greatly between different countries.

In this AoA, the alternatives to replace OPnEO in the sensors are analysed. This includes whether an alternative substance can be used to replace OPnEO or if the sensors can be replaced by a new technology. Further, this AoA describes the steps required to complete the replacement, the uncertainties linked to this process, and the efforts already undertaken by RDI to realise substitution of OPnEO from the IVD products in scope.

3. ANALYSIS OF SUBSTANCE FUNCTION

- ⇨ **BGE products are IVDs which** function based on different principles. They all have in common that a target (health) marker in patient samples such as blood shall be qualitatively or quantitatively determined.
- ⇨ **Sensors** are used to provide **electrochemical signals related to the analyte content in the sample.** Measurements are performed by **dedicated, Roche-specific analyser systems.**
- ⇨ **OPnEO is used in the production of a [redacted] membrane placed onto the sensors** for BGE products. The surfactant allows membrane polymerisation which is **important for the sensor functionality**.
- ⇨ The sensors form an **article** together with the [redacted] membrane.

OPnEO is used in the production of the sensors at the RDI site in Rotkreuz. The sensors are an integral part of two different devices called cartridge and cassette, which contain several different sensors for Blood Gas and Electrolytes (BGE) analysis (see detailed information in Section 3.1). The RDI business unit concerned by this application is Point of Care (PoC) and in particular its product group BGE. Rotkreuz is the only Roche site worldwide at which the sensors in scope of this application are manufactured.

An OPnEO-containing [redacted] emulsion is used in the production of the sensors in scope. It is applied onto sensor components to form a [redacted] membrane (see CSR Section 2.3.1 for a detailed description of the production process). All components of the sensor, including the membrane, form an article according to the ChemO [3] and the REACH Regulation [2]. In accordance with ORRChem Annex 1.17, this application concerns the use of OPnEO in the production of the articles (sensors) at the RDI site in Rotkreuz but does not concern the use of the OPnEO-containing articles.

In the following subsections, a general description of IVD- and BGE products as well as an overview of the BGE products in scope of this application are given. It is followed by a detailed description of the sensor function and the importance of OPnEO in sensor functionality.

3.1. General Description of the BGE products and sensors

According to the Medical Devices Ordinance (MedDo) SR 812.213 of 1st of July of 2020 (Status as of 26 of May of 2021), *in vitro* diagnostic medical devices (IVDs) are medical devices which are used as a reagent, reagent product, calibrator, control material, kit, instrument, apparatus, equipment or system in accordance with their specified purpose for the *in vitro* examination of specimens derived from the human body, including blood and tissue donations, and which are used solely or principally for the purpose of providing information [5]:

e. on physiological or pathological states;
f. on congenital abnormalities;
g. to determine safety and compatibility with potential recipients;
h. to monitor therapeutic measures.

IVDs function based on **different principles.** They all have in common that a **target (health) marker** in patient samples, such as blood and other fluids, shall be **qualitatively or quantitatively determined**. A reaction takes place between the marker in the sample and different reagents in the IVD to produce a signal that can be measured by different techniques, depending on the type of analyte measured. **Sensors** are used to provide **electrochemical signals related to the analyte content in the sample.** The signals are then translated into determined values by the measurement systems. The latter principle is specifically applied in BGE analysis.

BGE systems deliver fast and reliable results in situations critical to patients' health. These systems are used for **measuring several analytes in biological matrices**, such as in whole blood and other fluids. The measured parameters, as well as the matrix in which they are measured, are described below for each specific system and sensor (see Section 3.1.1 and 3.1.2). BGE systems enable the simultaneous measurement of several blood parameters in life-critical situations in Near Patient Testing (NPT). These critical parameters indicate, for example, whether oxygen is adequately delivered to tissues or help to detect jaundice in new-borns. BGE analysis is therefore used in critical care settings such as Intensive Care Units (ICU), Emergency Departments (ED) and Neonatology.

Parameter measurements in BGE systems are performed with **dedicated, Roche-specific analyser systems** (in the following referred to as 'systems') **and – for some parameters – specific sensors depending on the property to be measured.**

The systems and the respective sensors (articles) that are **in scope of this application** are:

- The cobas® b 123 sensor cartridge used with the cobas® b 123 POC system (hereafter referred to as **sensor cartridge** and **b 123 system**, respectively) and
- The Metabolite Specific Sensor (MSS) cassette used with the cobas® b 221 system (hereafter referred to as **sensor cassette** and **b 221 system**, respectively).

The systems and sensors are further described in the following sections and summarized in Table 1.

Both the sensor cartridge and the sensor cassette are "ready-to-use" articles that the user inserts into the corresponding system (see Figure 1 and Figure 3). Blood samples are pumped into the systems and positioned over the sensors for measurement. Several hundreds of samples may be measured with one sensor before it needs to be replaced.

3.1.1. Sensor cartridge of the b 123 system

The b 123 system is a fully automated, near-patient testing system for *in vitro* determination of up to 17 parameters in whole blood for aid in diagnosis and monitoring. 10 of these parameters are measured by the sensor cartridge in scope of this application. A description of the purpose of these parameters is shown below.

- **pH:**
  The pH value is used in the diagnosis and monitoring of the acid base status of the patient.
- **Blood gas (BG)**: O_2 and CO_2.
  pO_2 is the partial pressure of oxygen in blood. This value is used to assess the patient's oxygen status. pCO_2 is the partial pressure of carbon dioxide in blood and is used to assess the patient's adequate ventilation, gas exchange, and acid base status.

- **Electrolytes (ISE[8])**: Na^+, K^+, Cl^-, iCa^{2+} (ionized Ca^{2+}).
  The values are used to assess the concentration of the electrolytes in the sample.
- **Haematocrit (Hct)**:
  This value is used in the diagnosis and monitoring of physiological and pathological red blood cell volume status.
- **Metabolites:** Glucose (Glu) and Lactate (Lac).
  The parameters Glu and Lac are both used in diagnosis and monitoring of the physiological and pathological concentrations of these metabolites.

The sensor cartridge used in the b 123 system, and which is concerned by this application, is shown in Figure 1 and Figure 2. The cartridge is an article containing sensor spots that provide electrochemical signals related to the analyte content in the sample. The signals are then translated into determined values by the measurement system. As indicated above, the sensor cartridge is used to measure pH, BG, ISE, Hct and Glu/Lac (please refer to Section 3.2 for detailed information). Only two parameters, Glu and Lac, are measured with sensor spots containing OPnEO. Therefore, **only the use of OPnEO to specifically produce Glu/Lac sensor spots is in scope of this application**. Although there are sensor cartridges with different combinations of activated sensors (see Table 1), all sensor cartridges contain the Glu/Lac sensor spots, even if they are inactivated. Therefore, **OPnEO is needed to produce all types of sensor cartridges for the b 123 system**.

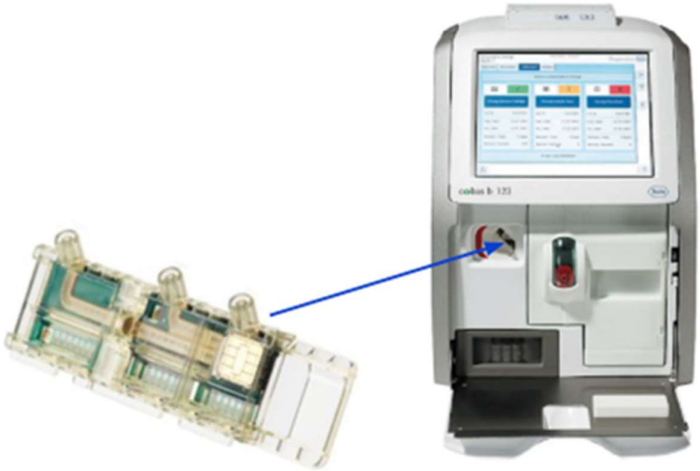

Figure 1. Sensor cartridge and b 123 system.

[8] An ion-selective electrode (ISE) is an example of an electrochemical sensor which is used to measure concentrations of free ions in aqueous solution.

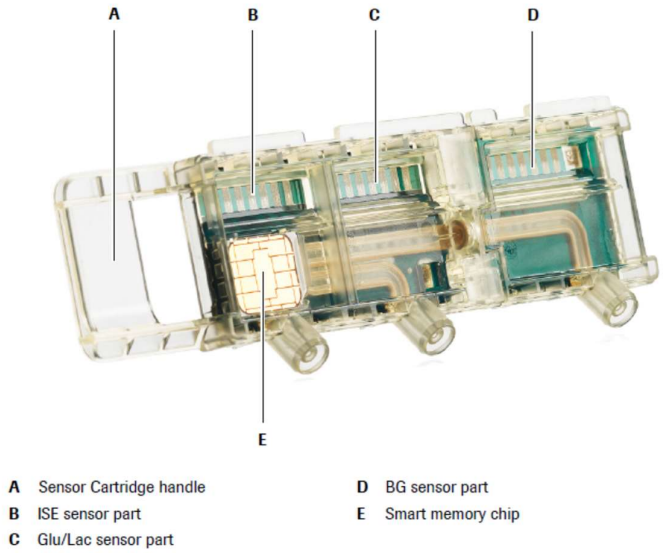

Figure 2. Detailed picture of the sensor cartridge which shows the different sensors contained in it.

3.1.2. Sensor cassette of the b 221 system

The b 221 system is a fully automated analyser system for high sample throughput for *in vitro* testing of the whole blood for the quantitative determination of up to 18 parameters. These parameters comprise the 17 parameters also measured by the b 123 system (see Section 3.1.1) and the additional parameter Urea/BUN[9].

Urea/BUN refers to the amount of urea nitrogen in the blood. The value is used in diagnosis and monitoring of physiological and pathological Urea- and Blood Urea nitrogen (BUN) levels.

Figure 3. Sensor cassette and b 221 system.

[9] BUN = Blood Urea Nitrogen

The sensor cassette (see Figure 3) used in the b 221 system is a **multi-parameter sensor which is used for measuring the 3 parameters Glu, Lac and Urea/BUN. OPnEO is required in all 3 sensors.** Therefore, the production of the sensor cassette is in scope of this application.

All other parameters are measured by means of other electrodes and technologies that are not part of the cassette, do not require OPnEO and are therefore not in scope of this application.

3.2. Detailed description of the sensors and function of OPnEO

In this section a detailed description of the sensors in scope of this application is given regarding the types of samples and parameters measured, the principle of the measurements as well as the occurrence and function of OPnEO in the sensors. This information applies for both types of sensors and is therefore given combined in one section.

a) Function of the sensors
The sensors are used to provide electrochemical signals related to the specific analyte content in the sample. The measurement systems then translate these electrochemical signals into determined values.

b) Parameters measured
The sensors in scope of this application are used to measure some of the 18 parameters described in Section 3.1.1 and 3.1.2. The following table (Table 1) summarizes the parameters which are measured with the different types of sensor cartridges or sensor cassettes.

Table 1. Type of sensor cartridges and sensor cassettes in scope of this application and parameters measured by their active sensors. The X indicates that the sensor is activated, a bold **X** indicates active sensors relevant for this application.

Article (sales products)	**Parameters**										
	pH	**PCO_2**	**PO_2**	**Hct**	**Cl^-**	**Na^+**	**K^+**	**Ca^{2+}**	**Glu**	**Lac**	**Urea (BUN)**
b 123 system											
sensor cartridge BG*	X	X	X	X							
sensor cartridge BG/ISE*	X	X	X	X	X	X	X	X			
sensor cartridge BG/ISE/Glu	X	X	X	X	X	X	X	X	**X**		
sensor cartridge BG/ISE/Glu/Lac	X	X	X	X	X	X	X	X	**X**	**X**	
b 221 system											
Glu CASSETTE									**X**		
Glu/Lac CASSETTE									**X**	**X**	
Glu/Lac/Urea CASSETTE									**X**	**X**	**X**

*All sensor cartridges contain OPnEO as the Glu/Lac sensors are present on these cartridges even though they are inactivated.

c) Occurrence of OPnEO in the sensors
OPnEO is present in the sensors with the concentration shown below per type of sensor and type of system (see Table 2). The concentration shown applies to the smallest unit that can be separated as an article from the cartridge or cassette.

Table 2. Content of OPnEO in the sensors.

Article	OPnEO content
sensor used in the b 123 system	0.0006% w/w
sensor used in the b 221 system	0.0041% w/w

d) Principle of measurement of the sensors which contain OPnEO

The principle of measurement for the three parameters (Glu, Lac and Urea/BUN) that require OPnEO in the sensors is described below (for the function of OPnEO, please refer to point e):

1. Lactate (Lac)

Lactate oxidase enzyme present in the Lac sensor spot catalyses the reaction between lactate, water and oxygen present in the measured sample to produce H_2O_2. The H_2O_2 is determined amperometrically[10] using a [redacted] microelectrode. The resulting electrochemical signal is directly proportional to the lactate in the sample.

2. Glucose (Glu):

Glucose oxidase enzyme present in the Glu sensor spot catalyses the reaction between glucose, water and oxygen present in the measured sample to produce H_2O_2. The H_2O_2 is determined amperometrically[10] using a [redacted] microelectrode. The resulting electrochemical signal is directly proportional to the glucose in the sample.

3. Urea/BUN

Urea is broken down into ammonia and carbon dioxide by the urease enzyme in the Urea/BUN sensor spot. Ammonia and carbon dioxide react through hydrolysis to form ammonium- and bicarbonate ions. The ammonium ions are determined using a potentiometric ammonium ion-selective electrode[11].

e) Function of OPnEO in the sensors

During production of the Glu, Lac and Urea/BUN sensors, a [redacted] emulsion containing OPnEO is applied to the sensor electrode where it forms a [redacted] membrane (see CSR Section 2.3.1 for a detailed description of the production process).

The [redacted] emulsion contains a mixture of several surfactants of which OPnEO, a non-ionic surfactant, is the main emulsifier. The surfactant ensures the formation of micelles ([redacted]). [redacted]. The polymerized [redacted] is then mixed with the glucose and lactate oxidases and the ureases for immobilization of named enzymes. During sensor spot production, the [redacted] emulsion is then dispensed on top of the sensor electrode and dried in a carefully optimized process to form a [redacted] membrane including the enzymes on the sensor electrode. For a schematic cross-section through the Glu, Lac and Urea sensors of the b 123 and b 221 systems, please see Figure 4.

The properties of the [redacted] emulsion influence both the immobilization of the enzymes as well as the diffusion of the analyte within the enzyme spot and the cover membrane. Therefore,

[10] Amperometry in chemistry is the detection of ions in solutions based on electric current or changes in it.

[11] Potentiometric Ion-Selective Electrodes are a type of electrochemical sensors that convert the activity of a specific ion dissolved in a solution into an electrical potential.

the [redacted] emulsion is a critical material for the resulting sensor performance by influencing, e.g., signal height and in-use stability. Consequentially, it is influencing the quality of the measurement, i.e. how accurately the analyte content in the sample is determined. Insufficient measurement quality leads to the disposal of the impaired sensors. This decreases the overall production yield and therefore the numbers of sensors that can be sold to customers, because measurement quality needs to be guaranteed for sensors released to the market for measuring patient samples.

Figure 4. Schematic cross-section through Glucose, Lactate and Urea sensor spot in the b 123 and b 221 systems.

4. ANNUAL AMOUNT

The maximal annual amount of OPnEO which is expected to be used in 2026 at RDI is given in Table 3. Therefore, in this application, RDI applies for the use of a maximum annual amount of 119 g/a of OPnEO for the production of sensors. For more details on how this maximum was determined, please refer to Section 2.2.1.2 of the CSR of this application.

Table 3. Overview of annual amount of OPnEO used at the year of data acquisition as well as the maximum annual amount over the course of the period applied for, i.e. the amount expected in 2026 (amount applied for).

	Absolute amount in 2020	**Absolute amount in 2026**
Total amount of OPnEO	80 g/a	119 g/a

5. IDENTIFICATION OF POSSIBLE ALTERNATIVES

⇨ Several alternatives were analysed:

1) **Substitution** of OPnEO with alternative surfactants in the existing sensors.
2) **Use of alternative sensors** from Roche which are already on the market.
3) **Replacement of the sensors with those from competitors**, adapted to run on Roche instruments.
4) **Substitution** of the current system **with a new generation, OPnEO-free technology**.

⇨ The preferred Alternative 1 for **substitution of OPnEO in the existing sensors** with alternative surfactants was found to be **not possible without negatively impacting the performance claims** of the product.

⇨ Alternatives 2 and 3 are not feasible because **the existing technology only works with the currently used sensors** in scope of this application (sensor cartridge and -cassette).

⇨ **Re-development of the current systems are not feasible** in the context of the market situation due to **high technical risks** and **long timelines**.

⇨ The applicant concludes that **the development of a new technology is needed to phase out OPnEO** from the current BGE products (Alternative 4). This new generation technology is currently being developed in the [redacted] project.

Several options for the replacement of the OPnEO containing articles could be considered from the applicant's perspective, as it was done for previous applications for authorisation[12]:

1) **Substitution of OPnEO with alternative surfactants** in the existing sensors.
2) **Use of alternative sensors from Roche** which are already on the market.
3) **Replacement of the sensors with those from competitors**, adapted to run on Roche systems.
4) **Substitution** of the current system technology **with a new generation, OPnEO-free technology**.

Alternative 1: The first option is the replacement of OPnEO in the existing sensors. Extensive feasibility studies with the current sensor technology were performed and have demonstrated that the direct substitution of OPnEO is not possible without negatively impacting the performance claims of the product. Removal of OPnEO from the current sensors would require a re-development of the current systems, including software updates and re-validation and re-registration

[12] Link to the AoA in the EU Dossier: https://echa.europa.eu/documents/10162/b97edaf7-7405-5992-63b9-42798b3c2e3e

of the instruments concerned on the respective markets. More details on the assessment of Alternative 1 by the applicant can be found in Section 5.2

Alternative 2: This alternative consists of the replacement of the currently used sensors by other OPnEO-free existing sensors from Roche. This is not a suitable alternative as only the currently used sensor types are available for the systems in scope. Therefore, this alternative is not further discussed in this application for a temporary exemption.

Alternative 3: This alternative refers to the replacement of the affected sensors with those from competitors. This is also not a suitable alternative as the Roche systems only run with Roche products, including Roche sensors. Therefore, this alternative is not further discussed in this application for a temporary exemption.

Alternative 4: The last alternative is the development of new generation products with new and entirely OPnEO-free sensors with the aim to substitute the products currently on the market. After development and validation of the new technology, the new generation products must be registered as new IVDs with different health authorities before they can be placed on the market. Since the other alternatives considered (see above) are not feasible, **Alternative 4 is currently being pursued by the applicant** (see Section 5.3 for more details).

In summary, the applicant concluded that the only suitable option is Alternative 4: development of a new generation product with entirely OPnEO-free sensors. This option is currently being pursued under the project [redacted]

5.1. General steps required for substitution

A substitution process consists of several general steps. These steps are basically identical regardless of whether the substitution concerns the phase out of a specific Substance of Very High Concern (SVHC) (see Alternative 1 in Section 5.2) or if it concerns the whole technology (see Alternative 4 in Section 5.3). However, the magnitude of effort is manifold increased for the development of a new SVHC-free sensor and system technology compared to substitution of the SVHC only within the existing sensors. The substitution steps include feasibility assessment, development, verification, validation, regulatory approval/market authorisation from health authorities (where relevant) and introduction to the market. They are summarised in Table 4 and discussed in detail in the following Sections 5.1.1 to 5.1.6.

Table 4. General steps required for substitution.

Step	Details
Feasibility assessment	● Identification and availability assessment of alternative substance(s) or identification of new sensor technology ● Qualify supplier and raw material of the alternative substance(s) and/or technology constituents ● Production of first laboratory lots of adapted sensors or new generation technology sensors ● Performance testing of the adapted or new generation sensors to test the most critical product specifications

Step	Details
Development & design transfer to production	● Development of adapted or new generation sensor cartridge or cassette for the adapted or new generation sensor ● Development of calibration and control reagents and, if relevant, of the associated systems (instrument and software), including design and production documentation ● Transfer of the adapted or new generation sensor and -system design to production (including creation or update of manufacturing instructions for sensors and their systems) and production scale-up
Verification of analytical performance and validation of production process	● Production of pilot lots of modified or new generation sensors and their systems for detailed performance verification ● Validation of production process for sensors and systems ● Verification of shelf-life and on-board stability of the adapted or new generation sensors and any new raw materials included in their system ● Verification of analytical performance of the sensors and measurement systems regarding accuracy, precision, linearity and correctness of the measurement values (see Section 5.1.3 for details)
Validation of system performance	● Validation of sensor and system performance in external studies at hospitals, if required
Regulatory approval / market authorisation worldwide	● Notification to the authorities of the changes in the sensors (minor or major change) or ● Application for new market authorisation for new generation sensors and systems or re-registration of adapted sensors
Introduction to the market	● Phase-out of sensors with OPnEO based on shelf life and: o Replacement with adapted, OPnEO-free sensors or o Introduction of the new generation system including newly developed OPnEO-free sensors to the market

5.1.1. Feasibility assessment

In the feasibility assessment step, alternative surfactants or new generation technologies are assessed to replace OPnEO in the IVDs currently on the market. This includes an availability assessment of alternative surfactants and other new raw materials which need to be available in constant quality and with a reliable supply chain. For this purpose, available suppliers have to be assessed and qualified. For the qualification of a supplier, the supplier has to fulfil certain criteria defined by Roche procurement. For the qualification of a critical raw material, at least 3 independent lots of material have to be evaluated during the feasibility assessment. Furthermore, laboratory lots of solutions (used for, e.g., dispensing and printing of sensors) need to be produced, in order to test the performance of the adapted or new generation sensors.

Performance testing of the sensors is the basis to ensure that the adapted or new generation technology works before modification of other parts of the system (e.g. software, measurement system, calibration and control fluids) are started. Examples of parameters tested in this step include:

- Precision and specificity of the electrochemical sensor response for the analytes measured,
- Sufficient linearity of the response when measured as a function of analyte concentration, and
- Temperature stress of the involved materials and of the manufactured sub-components of the sensor.

At this step it is decided whether sensors containing alternative surfactants (as proposed in Alternative 1) fulfil the system specifications and can be used to replace OPnEO. As described in detail in Section 5.2, the feasibility assessment of the possible alternative surfactants identified by the applicant failed and therefore, Alternative 1 is not a suitable option to phase out OPnEO.

5.1.2. Development & design transfer to production

Both adaptation of the sensor by surfactant substitution (Alternative 1) and introduction of a new generation technology sensor (Alternative 4) require (re-)development of further associated components of the system. In case of an adapted sensor, development may only concern calibration, control fluids and instrument control software changes of an existing system. However, for a new generation technology, the development further extents to the measurement system as a whole, including the instrument as well as the measurement electronics, firmware and calculation software providing the measurement results. In any case, an initial or updated version of the manufacturing instructions (including process control- and quality control release procedures) will be created after development and during the design transfer to production.

Consequentially, the requirement for the development of a new generation technology adds significantly more cost and effort to the substitution process because it affects not only the sensors, but the measurement system as a whole. Nevertheless, due to the failure of the feasibility assessment for direct substitution of OPnEO with an alternative surfactant (see also Section 5.2.2), the development of a new, OPnEO-free system (as proposed in Alternative 4) is the only feasible option to phase out OPnEO from the sensors. More information on Alternative 4 is given in Section 5.3 of this AoA.

5.1.3. Verification of analytical performance and validation of production process

In the verification step, **pilot lots of the sensors** with the selected alternative surfactant or of the new generation sensors **and their systems** are produced by the respective production facilities. The production process of the pilot lots of the sensors and their systems is validated during their manufacturing phase. To this end, the manufacturing instructions (including process control and quality control release procedures), which were developed during the development and design transfer to production-step (see Section 5.1.2), need to be updated and approved. The testing of the shelf-life and on-board stability as well as verification of the assay performance are executed in the Research and Development department.

During analytical performance verification, the system as a whole is assessed by measuring real samples. This assessment is performed in Roche laboratories before the systems are released for use in clinical studies in hospitals. The verification is typically done using sensors, calibration fluids and instruments which are produced by the production facilities. On one hand, the verification extends the evaluations done during the feasibility step, on the other hand the verification step also includes

evaluations which are required by norms and guidelines. Examples of parameters tested during the verification step include

- precision and accuracy,
- influence of chemical interference which may be present in the patient sample,
- linearity as a function of analyte concentration,
- comparability to competitor systems and reference methods, and
- limits of detection.

It has to be kept in mind that in case a new generation technology has been developed (Alternative 4), the step to verify analytical performance is significantly extended compared to a pure substance change in the sensor. This is because verification has to be performed not only for sensors, but also for their associated systems (instrument, software and calibration/control fluids).

5.1.4. Validation of system performance

After the manufacturing process of the sensors (including calibrators and instruments, if affected) has been approved and their analytical performance has been verified, the performance of the whole system can be validated in clinical studies at hospitals. Once all required aspects of the validation are successfully completed, the products are ready for market authorisation.

5.1.5. Worldwide regulatory approval/market authorisation

IVDs are highly regulated in countries worldwide. Usually, a country specific market authorisation by the health authorities is required. Changing an ingredient in the product (e.g., by substitution of a surfactant as proposed in Alternative 1) often has an impact on the current authorisation, requiring notification of the change(s) to the corresponding health authorities or even requiring application for a new authorisation. The development of a new generation sensor and system, however, requires a new authorisation in every country where the system shall be placed on the market. Furthermore, efforts for market authorisations are increased if they need to be extended to instrument, software and calibration/control fluids, as it is the case for newly developed systems (Alternative 4). The new IVD Regulation [4]further increased the technical information- and data requirements demanded for the application, and therefore also the efforts and the time required for completion of market authorisation for an IVD product.

5.1.6. Introduction to the market

Once the approval of the change applied for or for the new authorisation has been received from all relevant health authorities, the production can be switched to the modified sensors or new generation technology, and they can be introduced to the market to replace the OPnEO-containing b 123 and b 221 systems.

5.2. Efforts made to replace OPnEO with an alternative surfactant (Alternative 1)

As described earlier, the replacement of OPnEO with an alternative surfactant would have been the preferred alternative, but it is not considered technically feasible. The detailed evaluation of the alternatives and of the efforts made to replace OPnEO with a substitution candidate are explained in the following sections.

In Section 5.2.1, the specifications for selecting an alternative surfactant and the selected substances are described.
In Section 5.2.2, the assessment of technical feasibility of the alternative surfactants is explained.

5.2.1. Selection of alternative surfactants for feasibility testing

Alternative surfactants were pre-selected as substitution candidates in compliance with regulatory requirements, chemical legislations, commercial availability and secure supply of the substances. Besides these compliance requirements, the substitution candidates had to possess the following chemical properties required for a stable [redacted] emulsion and a reliable [redacted] membrane formation on the electrode surface:

- Non-ionic type of surfactant,
- Hydrophilic-lipophilic balance (HLB)[13] comparable to that of OPnEO (17.3),
- Critical micelle concentration (CMC)[14] comparable to the standard formulation with OPnEO (approx. 1916 mg/L), and
- Similar molecular weight and chemical structure.

The final selection of the substitution candidates was then based on ecotoxicological assessments of the substances, substance supplier evaluations and economic feasibility.

Based on the compiled shortlist, the substitution candidates were **tested for technical feasibility of substitution** in order to identify the appropriate surfactant for further verification and validation in a next step (see Section 5.2.2).

Table 5. List of pre-selected substitution candidates.

ID	CAS-No.	Description	HLB[13]	CMC[14] (25 °C, mg/L)
Reference	**-**	**Octylphenol ethoxylated**	**17.3**	**1916**
1	64366-70-7	Oxirane, 2-methyl-, polymer with oxirane, mono(2-ethylhexyl) ether	18	8454
2	9005-64-5	Sorbitan, mono-dodecanoate, poly(oxy-1,2-ethanediyl) derivatives	16.7	60

[13] The hydrophile-lipophile balance (HLB) number is used as a measure of the ratio of hydrophilic and lipophilic groups in a surfactant. Values ranging 0.60 define the affinity of the surfactant for water or oil. Non-ionic surfactants with HLB > 10 have affinity for water (hydrophilic) and with < 10 have an affinity of oil (lipophilic).

[14] CMC is defined as the concentration of surfactants above which micelles form and all additional surfactants added to the system will form micelles. Low values indicate that the surfactant is a neutral surfactant, while increasing values indicate cationic or even anionic surfactant.

ID	CAS-No.	Description	HLB[13]	CMC[14] (25 °C, mg/L)
3	9005-67-8	Polyethylene glycol sorbitan monostearate, Polyoxyethylene sorbitan monostearate	14.9	27
4	68131-40-8	secondary alcohol ethoxylate, nonionic surfactant used in multiple applications including emulsion polymerization	17.4	558
5	9004-95-9	Polyethylene glycol hexadecyl ether, Polyoxyethylene (20) cetyl ether	15.7	90
6	9005-00-9	Polyoxyethylene (100) stearyl ether	18	94
7	9003-11-6	Poly(ethylene glycol)-block-poly(propylene glycol)-block-poly(ethylene glycol), PEG-PPG-PEG	19	n.a.

5.2.2. Technical feasibility of the substitution of OPnEO by alternative surfactants

In a first step, substitute candidates were selected according to the chemical properties as described in Section 5.2.1. The second step focused on the assessment of the compatibility of the substitution candidates to fulfil the following criteria:

- The surfactant must not produce enzyme denaturation[15].
- The surfactant must guarantee the functionality of the [redacted] emulsion. It must allow reproducible synthesis of the [redacted] emulsion and must not reduce the storage stability of this emulsion.
- The surfactants must be compatible with the chemical composition of the cover membrane of the sensors, i.e. by not producing excessive amounts of holes and/or defects in the cover membrane.
- The surfactant must not negatively affect the adhesion of the sensor spots to the cartridge/cassette surface.

[15] Enzyme denaturation is a process in the enzyme lose its original structure and therefore part of its properties. Denaturation can occur by application of some external stress or by reaction with another substance.

Once the basic criteria above were fulfilled, actual test lots of the sensors were produced using the [redacted] emulsion containing the alternative surfactant. Then the sensor lots were tested for electrochemical performance requirements. These requirements include that the surfactant must not alter the basic electrochemical signal properties beyond specifications set by the Research and Development department. As an example, it must not change the sensor response to blood matrix effects, which is the influence of normal constituents of blood other than the analyte, e.g. blood proteins.

Table 6 summarizes the technical risks evaluated during this feasibility assessment and the outcome of the evaluation for the 7 candidate substances listed in Table 5.

Table 6. Evaluated technical risks and outcomes for the test [redacted] emulsions containing the candidate substances (substance ID given according to Table 5).

Technical risk evaluated	Evaluation outcome per test emulsion*
Fulfilment of synthesis process specifications	failed: 1, 6, 7 pass: 2, 3, 4, 5
Fulfilment of material specifications of the final [redacted] emulsion	failed: 4 pass: 2, 3, 5
Compliance with the limit value of the electrochemical signal for fresh [redacted]/freshly printed sensors	failed: 3, 5 pass: 2
Passing calibration and quality control tests after sensor production with fresh [redacted]/on freshly printed sensors	failed: - pass: 2
Fulfilment of preliminary performance criteria for in-use stability	failed: 2 → **not feasible within the performance claim of the product** pass: -
Compatibility with batch dispensing process	Not tested**
Acceptable sensor yield (3 lots process validation, 10 lots yield verification)	Not tested**
Stability of [redacted] emulsion during storage	Not tested**
Performance after software adaptation	Not tested**
Fulfilment of performance criteria for in-use stability after defined storage period and transport stress (3 lots)	Not tested**
Validation in external studies	Not tested**

* Numbers indicate the candidate substance IDs as listed in Table 5.
** Not assessed because no candidate substance passed all previous evaluated risk criteria.

In summary, the feasibility studies for the replacement of OPnEO failed since none of the seven test emulsions passed the preliminary performance criteria for in-use stability. Therefore, the subsequent

assessment steps listed in Table 6 were not performed. **The substitution of OPnEO in the [redacted] emulsion with one of the identified substitution candidates is not feasible within the performance criteria of the existing system.**

Therefore, to phase out of OPnEO in the existing systems the introduction of a new sensor technology without OPnEO would be needed. This would require a re-development of the systems (including measuring technology and software) followed by the corresponding verification and validation of the modified systems. This would further lead to worldwide registration requirements of the modified b 123 and b 221 systems.

Consequently, the technical risks in the re-development of the current systems are high and long timelines as well as large efforts are expected. Therefore, re-development of the existing systems is not feasible in the context of the market situation. **As a result, OPnEO will not be replaced by an alternative surfactant, but the sensor technology, as a whole, will be newly developed together with a new generation system.**

5.3. Efforts made to replace OPnEO with an alternative technology (Alternative 4)

As Alternative 1 is not feasible, the development of a new system technology is needed to phase out OPnEO from the sensors. This is already addressed in the [redacted] project, which aims to develop a new generation BGE product using new sensor cartridges to replace the b 123 and b 221 systems.

As noted in chapter 5.2.2, the technologies of the current systems and of the new [redacted] sensors are not backward-compatible, meaning that the new [redacted] sensor technology does not work with the currently used b 123 and b 221 systems. Therefore, a completely new system is currently being developed with entirely new OPnEO-free sensors and new equipment. The steps required for this development and the current status of the project are described in Section 6.

6. SUBSTITUTION PROGRAM

- ⇨ Substitution is currently pursued by the [redacted] project to replace the sensors with a new technology (Alternative 4).
- ⇨ The [redacted] **project** is currently at the [redacted] of the substitution timeline. Substitution of the current technology is expected to be completed by [redacted] as shown in Figure 5.
- ⇨ Due to the high time efforts required for the development of a new technology and market authorisation requirements worldwide, **the applicant applies for a period of [redacted] for continued use of OPnEO in the production of sensors for BGE analysis** after the end of the transitional period (2nd May 2024).
- ⇨ The estimated cost of the [redacted] project for the BGE product group at Roche is [redacted] CHF.

In this section, the timeline for Alternative 4 'Substitution of the current system technology with a new generation, OPnEO-free technology' is described.

An introduction of an OPnEO-free sensor technology requires the steps as mentioned in Table 4, Section 5.1, but with larger efforts than for the substitution of the SVHC only (Alternative 1), since more comprehensive specifications have to be fulfilled. The new generation [redacted] system will replace both b 123 and b 221 systems.

The replacement plan with the likely duration of each step is shown in Table 7 and displayed in Figure 5. For detailed description of the general steps, please refer to Table 4.

Table 7. Substitution plan for the [redacted] project.

Step	Likely Duration*
Feasibility assessment	[redacted]
Development & design transfer to production	[redacted]
Verification of analytical performance and validation of production process	[redacted]
Validation of system performance	[redacted]
Regulatory approval / market authorisation worldwide	[redacted]

Introduction to the market / phase out of old systems	Introduction to the market of [redacted]: by [redacted] Phase out of old systems: by [redacted]

* Q indicates the quarters of the year: Q1 January to March, Q2 April – June, Q3 July – September, Q4 October - December. A duration from e.g. Q1 2023-Q3 2023 means a duration of 9 months, starting at the beginning of Q1 until the end of Q3. This terminology will also appear in the text.

Figure 5. Replacement timelines to phase out OPnEO in b 123 and b 221 systems and development timeline of the [redacted] system.

Specific information on the general steps which are performed in the [redacted] system development project can be summarised as follows:

- **Feasibility assessment** of the new and improved sensor technology for increased performance of all patient blood measurements. This includes feasibility assessment of the OPnEO-free sensor technology for measurement of Glucose, Lactate and Urea which previously contained OPnEO, but also feasibility of all other sensor technologies integrated in the sensor cartridge which do not contain OPnEO. This assessment also includes the feasibility of the new and improved components enabling the use of the new sensor cartridge in the system. This comprises the calibration and control fluids, a system for transport of samples and waste fluids, sensitive measuring electronics, mechanical hardware and software control.
- **Development** of the integrated system comprising sensor cartridge, calibration and control reagents, instrument and software and further **design transfer to production** with final production scale-up.
- **Verification of analytical performance** of system and component performance, comprising analytical performance, usability, system reliability, and **validation of the production process**.
- **Validation of system performance** in clinical studies.
- **Regulatory approval / market authorisation** worldwide, and
- **Introduction to the market** in various countries.

6.1. Technical Feasibility Status and Replacement Schedule

As discussed previously, the **development of a new generation technology is needed to phase out OPnEO**. Therefore, a successor system is developed using a OPnEO-free sensor technology. The

planned timeline for the introduction of the new generation technology into the market is shown in Figure 5.

The [redacted] project is currently in the [redacted] stage [redacted]. The currently used systems can only be replaced by the new generation [redacted] systems once the newly launched [redacted] system is registered in the various countries where it will be introduced. The registration timelines are difficult to forecast due to the following reasons:

- Increased efforts for market authorisation application and validation because they need to be extended to instrument, software and calibration/control fluids for newly developed systems,
- High number of countries in which authorisation(s) must be applied for,
- Changing national requirements for authorisation processes, including the new EU IVD Regulation [4] which further increases the efforts and therefore also the time required for authorisation approval.

It is expected that the launch of the new system on the markets will take place by [redacted] after the authorisations with the health authorities have been obtained. At this timepoint, the replacement of the installed b 123 and b 221 equipment ([redacted]) will be started. The production output of [redacted] systems and contractual obligations with existing customers (i.e. specifications on minimal supply times of products to customers) will limit the pace at which the replacement can be performed. Therefore, it is expected that the current systems will be phased out by the [redacted]. For the b 221 system, there is a possibility that it will not be compliant with the IVDR amendment [6]. If so, it will have to be taken off the market earlier. However, even in this case, the system will need to be kept in operation at Roche internally until end of 2033 because it is part of the quality control release procedures for the calibration and control fluids, sensor cartridges and associated instruments of the b 123 system.

Consequentially, the use of OPnEO in the production of sensors for the current BGE products will have to be continued until approx. [redacted] for both b 123 and b 221 systems. Due to the short shelf-lives of 5 months (for sensor cartridge of the b 123 system) and 15 weeks (for sensor cassette of the b 221 system), stock-building of the sensors to cease the use of OPnEO in sensor production at an earlier timepoint is not a feasible option.

As a conclusion, based on the information given in this section, substitution of the current systems is expected to be completed by the [redacted]. Due to the **extensive development phase** and the **long timelines for regulatory approval** which are **difficult to foresee**, RDI applies for temporary exemption from prohibition to continue the use of OPnEO in production of sensors for BGE analysis **for a period of** [redacted] starting from the date of the transitional period (2nd May 2024).

6.2. Costs of the Substitution

Roche's Research and Development department is currently working on the complete substitution of OPnEO in the affected BGE products. As described in this AoA, this is being performed by developing a new technology under the [redacted] project. Roche is and will be investing a large number of financial and human resources into this project. The estimated cost is given in Table 8.

Table 8. Substitution: investment costs including cost for required personnel.

Use	Product group	Cost (mio CHF)
		estimated cost [redacted] project
Use 1	BGE	[redacted]

7. FURTHER EFFORTS REGARDING SUBSTITUTION

- ⇨ Since 2015, Roche is publicly committed **to substitute any Substances of Very High Concern** from their processes and products. OPnEO has already been substituted in a number of products and processes.
- ⇨ Roche is an active member of the American Chemical Society **Green Chemistry** Institute Pharmaceutical Roundtable.
- ⇨ Roche supports the **United Nations Sustainable Development Goals**.
- ⇨ Roche has been recognised as one of the **most sustainable healthcare companies** in the Pharmaceuticals index of the Dow Jones Sustainability Indices for the **thirteenth year running**.

Since 2015, Roche has a public company-wide commitment[16] which has been approved by the Corporate Executive Committee (CEC) to substitute any SVHCs used in their products and processes. This public commitment states that the company will **stop the use of SVHCs** after they are put on the EU Candidate List - where technically possible, within 10 years of listing.

This goal is supported by an internal document [7] where it is already recommended **to avoid Candidate List-substances in the development of new products and processes.** Roche engages to avoid regrettable substitutions by close collaboration of product and process development with regulatory experts and toxicologists as well as ecotoxicologists. Following this commitment, Roche has **successfully replaced OPnEO in a number of products / processes.** The replacement of OPnEO in the remaining products has already been planned and started as described in the AoA of additional AfAs submitted by RDG and RDL in the EU[17] and in the UK[18]. However, a temporary exemption is required to allow sufficient time to switch to the alternatives, taking into account uncertainties in the timelines. As part of these efforts, OPnEO has already been replaced in the Hb Calibrator, a calibration solution that is needed for the determination of haemoglobins and bilirubin in the b 221 system. OPnEO is needed in other reagent solutions for the b 123 and b 221 systems which are not affected by Annex 1.17 number 2 paragraph 4 of the ORRChem [1]. These reagents will also be replaced when changing these systems with the described new technology.

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

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[16] Roche Website: 'Our SHE Goals and Performance', under 'environmental goals' https://assets.cwp.roche.com/f/126832/x/70206811f5/20200331-she-goals-2020-2025-communication.pdf

[17] The link to the complete EU Dossier is: https://echa.europa.eu/applications-for-authorisation-previous-consultations/-/substance-rev/45040/del/200/col/synonymDynamicField_1512/type/asc/pre/2/view

[18] The UK Dossier is not yet publicly available; therefore no link can be provided.

As a global healthcare company, Roche is committed to support the United Nations Sustainable Development Goals (UN SDGs) in line with the business strategy; in particular SDG3, which aims at ensuring healthy lives and promoting wellbeing for all[19].

In 2021[20], for the thirteenth year running, **Roche has been recognised as one of the most sustainable companies in the Pharmaceuticals index** of the Dow Jones Sustainability Indices (DJSI). This is based on an analysis of economic, social and environmental performance of the company.

[19] Roche Website: 'Sustainable development goals': https://www.roche.com/sustainability/un-sdgs.htm

[20] Roche Website: https://www.roche.ch/com/investors/updates/inv-update-2022-03-15.htm

8. SOCIO-ECONOMIC ANALYSIS

- ⇨ The applicant has agreed with the assessment authorities that **a separate SEA is not required for this application** for temporary exemption. Instead, the SEA submitted with the EU Dossier by RDG can be referenced.
- ⇨ For the use applied for, there are **no environmental impacts from the continued use of OPnEO** because there are no OPnEO emissions from the sensor production and the use of the sensors.
- ⇨ A refusal of the temporary exemption will result in the **worldwide unavailability of critical BGE products in Intensive Care Units and Emergency Rooms** as those sensors are only produced at Rotkreuz.
- ⇨ In conclusion, the **socio-economic benefits outweigh the risks for the continued use of OPnEO** in the production of sensors at Rotkreuz.

As agreed with the assessment authorities[21], a separate socio-economic analysis (SEA) was not developed for this application since a detailed analysis was already performed as part of the EU Dossier submitted by RDG[22]. This analysis is also valid for the current application since the scope of both dossiers is very similar. For example, the EU Dossier covers the formulation and the use of different IVDs including the Hb Calibrator, which is a calibration solution that used to contain OPnEO and is needed in the b 221 system (see also Section 7). The benefits of the b 221 system, which is also in scope of this application for temporary exemption (see Section 3.1.2), have therefore already been assessed in the SEA submitted with the EU Dossier by RDG.

The applicant of the EU Dossier, RDG, demonstrates in the SEA that the **benefits of continued use of OPnEO in the concerned IVDs outweighs the risks to the environment**. Detailed information can be found in the original SEA (referred to as the EU SEA in the following). This analysis is based on the core elements listed in the following sections, which are also applicable to the current application for Switzerland. The key results of this analysis as well as the most important differences when compared to the use for the sensor production in this application are summarized below.

8.1. Non-use scenario (see EU SEA Section 2.9)

The analysis of the non-use scenario shows that the IVDs' production and supply covered in the EU Dossier would have to be interrupted if the authorisation was not granted. The same is true for the sensor production and therefore the supply of the sensors. The following specific aspects for the sensors in the b 123 and b 221 systems should be considered in addition to the discussion in the EU SEA:

- **Stock building**: stock building of sensors is not possible due their short shelf life (see Section 6.1).

[21] Minutes of the meeting between RDI and the assessment authorities on the 6th of December of 2021

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

- **Relocation outside of Switzerland:** in principle the sensors could be produced outside of Switzerland and the EEA as the final sensors are not subject to ORRChem Annex 1.17. However, as discussed in the EU SEA, this would not be economically and technically feasible and it is also not possible within a short timeframe (e.g., because the new production site would also require a validation phase and a market authorisation).
- **Replacement by another Roche product**: in the EU SEA, it is discussed that it may be possible to a limited extent to replace the b 221 system with the b 123 system. However, the replacement was not considered as a feasible alternative, e.g., due to the cost and the difference in customer segments in which the two systems are applied. Since both systems are part of this application for temporary exemption, such a replacement is not an alternative at all for termination of the use of OPnEO in the sensor production.

8.2. Information on the length of the review period (see EU SEA Section 2.10)

Please note that the situation for the b 221 system has changed since the submission of the EU Dossier (May 2019). The length of the review period requested in this application is explained in detail in this AoA, Section 6.1. Note that the term ‘review period’ as used under EU REACH [2] is equivalent to the term ‘period applied for’ in this application for temporary exemption.

8.3. Environmental impacts (see EU SEA Section 3.1)

As discussed in the CSR of this application and in contrast to the EU Dossier, there are no OPnEO emissions from the sensor production and the use of the sensors. Consequentially, there are no environmental impacts related to such emissions from the continued use of OPnEO in the sensor production.

8.4. Economic impacts (see EU SEA Section 3.2 and 3.3)

The considerations regarding competitors and timelines for replacement of instruments as well as the type of economic impacts described in the EU SEA are also applicable to this application. However, the numbers regarding economic impacts cannot be directly translated, since the assessment was done:

- across all products covered in the EU Dossier,
- only on the b 221 system (see Section 7) but not on the b 123 system (because the b 123 system is not in scope of the EU Dossier as the Hb Calibrator is not used for this system), and
- only for sales in the EEA.

Furthermore, the review period assessed in the EU SEA was only 7 years, as this review period was defined to allow the substitution of the products and processes covered in the EU Dossier. The use of the sensors produced in Switzerland is not subject to authorisation under REACH [2] and is therefore not covered in the EU Dossier.

8.5. Social impacts (see EU SEA Section 3.4)

As in the EU SEA, the social cost of unemployment is expected not to play a major role in the analysis.

The benefits for patients of the b 221 system are discussed as part of the impact analysis in the EU SEA (see e.g Table 12 in Section 2.8.4 and Section 3.4.2 of the EU SEA). These benefits are also valid for the b 123 system as it is very similar to the b 221 system. In addition, the overall analysis of

the value of IVDs for healthcare and the impact of the lack of IVDs on patients and healthcare cost is valid for the b 123 and b 221 systems and consequently also for this application.

From a health benefit point of view, as described in the EU SEA, **BGE analysis is considered one of the most important tools for diagnosis in critically ill patients**. Millions of patients worldwide depend on the accurate, reproducible and reliable results of these BGE products. The analysers deliver rapid and reliable results. They are easy to handle and require little maintenance. A refusal of the temporary exemption will result in the **unavailability of critical BGE products in Intensive Care Units and Emergency Rooms worldwide as the sensors are only produced in Switzerland.**

8.6. Combined assessment of impacts (see EU SEA Section 4)

RDG as the applicant of the EU Dossier came to the conclusion that the **socio-economic benefits of continued use of OPnEO outweigh the risks to the environment due to the lack of services for patients and high impact on health care costs** (much higher than possible economic losses of the applicant). This conclusion is also valid for this application for temporary exemption. As outlined above the type of social impacts in the case of the non-use scenario are similar. Also, the impacts would be worldwide as the production of sensors only takes place in Switzerland. On the other hand, there are actually **no environmental impacts** and therefore no remaining risks to the environment. Therefore, socio-economic benefits outweigh the risks for the continued use of OPnEO in the production of sensors.

9. CONCLUSION

The current AoA was developed to support RDI's application for a **temporary exemption to continue the use of Octylphenolethoxylates** (OPnEO) after the end of the transitional period (2nd May 2024) in the production of sensors for blood gas and electrolytes (BGE) analysis in Rotkreuz.

Several options for the replacement of the OPnEO containing articles were initially considered from the applicant's perspective. As in the EU Dossier submitted by RDG[23], **direct replacement** of OPnEO in the existing sensors would have been the preferred alternative. Efforts were made to replace OPnEO with an alternative surfactant. Seven substitution candidates were identified based on surfactant requirements, regulatory compliance and chemical properties. Then, these candidates were tested for technical feasibility of substitution within the current sensor technology. However, the extensive feasibility studies performed demonstrated that the direct substitution of OPnEO is not possible. None of the alternative surfactants achieved an acceptable performance when compared to the currently used products. Therefore, the removal of OPnEO from the current sensors would require a re-development of the current systems, including software updates, re-validation, and re-registration of the instruments concerned on the respective markets. The technical risks in the re-development of the current BGE products and the expected timelines and efforts for such a re-development are high and not feasible in the context of the market situation. As a result, the **replacement of OPnEO by an alternative surfactant or the elimination of OPnEO in the current sensor technology were not feasible options.**

Therefore, the applicant concluded that **the only feasible option is the development of a new generation product with entirely OPnEO-free sensors** to replace the current b 123 and b 221 systems (Alternative 4 within this AoA). This option is currently being pursued under the project [redacted].

The steps of the substitution process applied on Alternative 4 are basically identical to the steps required to substitute OPnEO with an alternative surfactant (Alternative 1). However, the effort in the development of a new generation technology sensor and system is significantly larger. Furthermore, a new generation BGE product requires new market authorisations worldwide, which further extends the timeline for complete substitution of the current BGE products with the new technology.

In general, a substitution program includes the steps feasibility assessment, development, verification, validation, regulatory approval / market authorisation and introduction to the market. The [redacted] project is currently at the [redacted], and complete replacement of the currently used systems by the new [redacted] system is expected to be completed [redacted]. The short shelf-lives of 5 months (for the sensor cartridge of b 123 system) and 15 weeks (for the sensor cassette of b 221 system) do not allow stock-building of these articles to cease their production at an earlier timepoint.

The BGE systems containing the sensors enable the simultaneous measurement of several blood parameters in life-critical situations in Near Patient Testing (NPT). Without a temporary exemption, RDI would need to stop the production of the sensors in scope in Rotkreuz for years. Because Rotkreuz is the only manufacturing site for the sensors used in these BGE products, this interruption of supply of the sensors would **not only affect patients in Switzerland, but worldwide**. The socio-

[23] Link to the EU Dossier: https://echa.europa.eu/de/applications-for-authorisation-previous-consultations/-/substance-rev/45044/del/200/col/synonymDynamicField_1512/type/asc/pre/2/view

economic analysis of the EU Dossier showed that these **important benefits outweigh any remaining risks to the environment**. This conclusion is further confirmed by the fact that there **are no environmental impacts** from the continued use of OPnEO. As shown in the CSR of this application, there are **no OPnEO emissions** from the sensor production and from the use of the sensors.

RDI applies for **a temporary exemption** to continue the use of OPnEO in the production of sensors for Blood Gas and Electrolyte Analysis **for a period of** [redacted] after the date of the transitional period (2nd of May 2024). This period is required due to the **complexity of the substitution project**, including development a new generation BGE product and extensive validation thereof, as well as applications for **new market authorisations worldwide**.

10. REFERENCES

[1] The Swiss Federal Council, Ordinance on the Reduction of Risks relating to the Use of Certain Particularly Dangerous Substances, Preparations and Articles (Chemical Risk Reduction Ordinance, ORRChem), May 2005, status as of 1 May 2022

[2] Regulation (EC) No 1907/2006 of the European Parliament and of the Council of 18 December 2006 concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH), establishing a European Chemicals Agency, amending Directive 1999/45/EC and repealing Council Regulation (EEC) No 793/93 and Commission Regulation (EC) No 1488/94 as well as Council Directive 76/769/EEC and Commission Directives 91/155/EEC, 93/67/EEC, 93/105/EC and 2000/21/EC.

[3] Swiss Ordinance SR 813.11 on Protection against Dangerous Substances and Preparations (Chemicals Ordinance, ChemO) of 5 June 2015 (Status as of 5 May 2022).

[4] Regulation (EU) 2017/746 of the European Parliament and of the Council of 5 April 2017 on *in vitro* diagnostic medical devices and repealing Directive 98/79/EC and Commission Decision 2010/227/EU (Status as of 28 January 2022)

[5] Medical Devices Ordinance (MedDo) SR 812.213 of 1st of July of 2020 (Status as of 26 of May of 2021

[6] Proposal for a Regulation of the European Parliament and of the Council amending Regulation (EU) 2017/746 as regards transitional provisions for certain in vitro diagnostic medical devices and deferred application of requirements for in-house devices, COM(2021)627, dated 14.10.2021

[7] 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.