ANALYSIS OF ALTERNATIVES

and

SOCIO-ECONOMIC ANALYSIS

Public Version

28 October 2022

Legal name of applicant(s):	CSL Behring AG
Substance:	4-(1,1,3,3-tetramethylbutyl)phenol, ethoxylated – comprising well-defined substances and UVCB substances, polymers and homologues (4-tert-OPnEO) (Annex 1.17 of ORRChem, entry number: 42)
Use title:	Use of 4-(1,1,3,3-tetramethylbutyl) phenol, ethoxylated (as a detergent) for virus inactivation via S/D (Solvent/Detergent) treatment in the plasma-derived medicinal product Rhophylac
Use number:	1

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List of Abbreviations

AfA	Application for Authorisation
AoA	Analysis of Alternatives
CAPEX	Capital Expenditure
CAS	Chemical Abstracts Service
CHF	Swiss Franc
CLP	Classification, Labelling and Packaging
COVID	Coronavirus (COVID-19)
CSR	Chemical Safety Report
EAHP	European Association of Hospital Pharmacists
ECHA	European Chemicals Agency
EEA	European Economic Area
EHSS	Environment, Health, Safety and Sustainability
EU	European Union
FOPH	Federal Office of Public Health
FTEs	Full Time Equivalents
GDR	Global Depositary Receipt
GMP	Good Manufacturing Practice
HDN	Hemolytic Disease of the New-born
HLE	Health Life Expectancy
HvE	Human exposure Via the Environment
ID	Identification
IM	Intramuscular
ITP	Immune Thrombocytopenic Purpura
IV	Intravenous
JBPO	Japan Blood Products Organization
kg	Kilogram
LRF	Log Reduction Factor
NGOs	Non-Governmental Organisations
NUS	Non-use Scenario
OPEX	Operational Expenditure
PSURs	Periodic Safety Update Reports
R&D	Research & Development
RAADP	Routine antenatal anti-D prophylaxis
RBCs	Red Blood Cells
RCR	Risk Characterisation Ratios
REACH	Registration, Evaluation, Authorisation, and Restriction of Chemicals
Rh	Rhesus
RoW	Rest of World
S/D	Solvent/Detergent
SDG	Sustainable Development Goals
SEA	Socio-Economic Assessment

STOT SE	Specific Target Organ Toxicity Single Exposure
SVHC	Substances of Very High Concern
UN	United Nations
US	United States
UV	Ultraviolet
WHO	World Health Organisation

DECLARATION

We, CSL Behring AG, request that the information blacked out in this version of the Analysis of Alternatives and Socio-Economic Analysis 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.

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1. SUMMARY

1.1. Introduction

This Application for Authorisation (AfA) is being submitted by CSL Behring AG (hereafter referred to as CSL) for the substance Triton X-100. CSL use Triton X-100 as part of a solvent/detergent (S/D) virus inactivation treatment in the manufacturing process of the medicinal product Rhophylac®, intended for the suppression of rhesus isoimmunization in:

- Pregnancy and obstetric conditions in rhesus (D)-negative women with a rhesus-incompatible pregnancy;
- Incompatible transfusions in rhesus (D)-negative individuals transfused with blood components containing rhesus (D)-positive red blood cells.

Rhophylac® is additionally registered for the treatment of:

- Immune thrombocytopenic purpura (only in the US)

These products are commonly referred to as Rho(D) immune globulin products.

The annual consumption of Triton X-100 in Bern in 2021 was [redacted] kg (range 100-1,000 kg), and this is projected to decline each year of the requested review period. The estimated release of Triton X-100 to non-cleared wastewater in 2021 was [redacted] kg (range 30-300 kg). However, this is projected to decrease significantly starting in 2024 and decrease each year of the requested review period.

The reasons for the decline in use and reduced release are due to two reasons:

1. CSL has successfully identified an alternative which will be used to substitute Triton X-100. The alternative will be implemented as soon as practicable possible. Prior to implementing the alternative, CSL is required to generate the data package to be submitted to medicinal authorities who need to approve the manufacturing change.
2. Release of Triton X-100 will significantly reduce due to a risk reduction measure which will be installed at the Bern facility and this will reduce release of Triton X-100 by at least 88% during the requested review period.

In this Application for Authorisation, CSL is applying for an authorisation to cover the time period required to substitute Triton X-100 to the alternative as part of a 'bridging application'.

1.2. Availability and suitability of alternatives

CSL has identified a suitable alternative that fulfils technical and financial criteria. The alternative is available on the market in sufficient quantities to meet CSL's demands. Furthermore, CSL has tested the alternative at laboratory scale and on their manufacturing line in Bern. During initial testing CSL identified some process challenges associated with the alternative. CSL has resolved these challenges during continued testing and development of the process and issues are not expected to occur during the requested review period.

The substitution of Triton X-100 with the identified alternative can only take place when medicinal product regulatory related criteria have been satisfied and variations to the relevant Marketing Authorisations of the impacted medicinal products have been granted. CSL has developed their substitution strategy and a substitution plan around the successfully implementation of the identified alternative in conjunction with market authorisations.

1.3. Requested review period

This AfA provides an overview of CSL's substitution plans of the alternative at their Bern site. The substitution plan covers the substitution of Triton X-100 as part of the S/D virus inactivation treatment to the alternative (S/D treatment is an important process in the manufacturing process for the inactivation of enveloped viruses in plasma-derived medicinal products). The substitution plan spans a five year review period (2024-2029) and it is designed taking the following requirements into account:

- **Regulatory requirements**: globally the regulatory processes of making a change to a medicinal product involve requirements in terms of data to be submitted in the dossier to obtain approval for the manufacturing variation. There are also variable durations for granting approval. In countries where higher data requirements and longer approval times apply, the variation may take as long as five years from the start of data generation, as compared to short durations (one to two years) expected in Switzerland and the EU, for example. Additionally, CSL's substitution plan requires that the relevant regulatory authorities promptly issue their approvals to variations and that there are no/only limited delays (which are known to occur).

1.4. Applied for Use and Non-use scenarios

In the applied for use scenario, CSL will continue to use Triton X-100 until the alternative is ready to be implemented for specific markets following respective market approval. In practice, consumption of Triton X-100 will decrease in a stepped manner as shown in the substitution plan. If ongoing pilot tests are successful, CSL is optimistic that a technical risk reduction measure can be installed in Bern. Initial testing has shown that the risk reduction measure will significantly reduce release of Triton X-100 during the requested time period.

Under the most likely non-use scenario (NUS), CSL will cease to manufacture Rhophylac® and the product will indefinitely disappear from the market. This non-use scenario is not acceptable from a public health perspective. Although the ceasing of Rhophylac® manufacturing operations will impact CSL, the Bern site will continue to operate.

1.5. Socio-economic benefits from continued use

From the public health perspective, there are significant socio-economic benefits from the continued use of Triton X-100 during the requested review period. Continued use will mean that patients and healthcare providers will be able to benefit from the ongoing availability of Rhophylac®. This is important as anti-D human immunoglobulin products such as Rhophylac® are potentially lifesaving and CSL is the market leader with Rhophylac® making up almost [redacted] (range 35-60%) of the global market. As part of continued use, manufacturing operations will not cease, jobs will be maintained, CSL will continue to make sales from Rhophylac® and their suppliers will not be impacted.

1.6. Impacts of a refused Authorisation

A refused authorisation will consist of the following impacts:

- **Impacts on patients and healthcare providers:** The single biggest impact is on patients and healthcare providers, the loss of Rhophylac® that is licensed globally in a total of 76 countries, will result in millions of patients (the main target population is pregnant women and their babies) being unable to access medical products resulting in significant impacts on a vulnerable population. The impacts range include mortality and different forms of morbidity.
- **Impacts on CSL sales**: a refused Authorisation will result in the ceasing of production and the net present value loss of sales in all countries, these are estimated as being CHF [redacted] million (range: 100-1,000 million) over the five year review period.
- **Social benefits linked to continued employment**: a refused Authorisation will also result in direct jobs loss at Bern and indirect and induced job losses are expected in the supply chain, these costs have not been monetised.

1.7. Residual risk to the environment of continued use

CSL is committed to minimising emissions of Triton X-100 to the environment and reduce emissions to the lowest level technically and practically possible. CSL is committed to piloting and installing a technical risk reduction measure which will reduce emissions by 88% from 2024 onwards. CSL's substitution plan also involves the alternative being implemented in a stepwise approach and this will see the consumption of Triton X-100 reduced every year of the review period.

1.8. Balance between benefits and risks

The main benefit of continued use is the continued availability of the medical treatment to patients. Over the five-year review period Rhophylac® will prevent [redacted] (range: 250,000-500,000) cases of haemolytic disease of the newborn (HDN). Over the same five-year review period CSL's substitution plan and risk reduction measure will mean a reduced amount of Triton X-100 ((ca. [redacted] kg (range 5-50 kg)) will be released.

2. AIMS AND SCOPE

2.1. Aims of the combined AoA and SEA

Triton® X-100 ($C_{14}H_{21}$-[C_2H_4O]$_n$-OH) (CAS Number 9036-19-5) (hereafter referred to as Triton X-100) is covered by the group of substances '*4-(1,1,3,3-tetramethylbutyl)phenol, ethoxylated – comprising well-defined substances and UVCB substances, polymers and homologues (4-tert-OPnEO)*' that are included in Annex XIV of the EU's REACH Regulation due to their endocrine activities on environmental organisms since 13 June 2017 (see Commission Regulation (EU) 2017/999[1]). Triton X-100 has been included as entry No. 42 in Annex 1.17 of the Swiss Chemical Risk Reduction Ordinance, ORRChem SR814.81) due to its endocrine disrupting properties in November 2021[2], with a sunset date on 2 May 2024 and a latest Application Date on 2 November 2022 (18 month before the sunset date).

CSL is a global biopharmaceutical company with an important research and development (R&D) and manufacturing facility based in Bern, Switzerland. Triton X-100 is used by CSL at its manufacturing plant in Bern. At the plant, purified Triton X-100 is used as a virus inactivation agent in the manufacturing process of the plasma derived protein therapeutics product Rhophylac®, intended[3] for the suppression of rhesus isoimmunization in:

- Pregnancy and obstetric conditions in rhesus (D)-negative women with an rhesus-incompatible pregnancy; and
- Incompatible transfusions in rhesus (D)-negative individuals transfused with blood components containing rhesus (D)-positive red blood cells

Additionally, Rhophylac® is also registered in the US for Immune Thrombocytopenic Purpura (ITP) treatment. ITP is a blood disorder characterized the immune system destroying platelets. A decreased number of platelets in the blood can cause easy bruising, bleeding gums, and internal bleeding.

These products are commonly referred to as Rho(D) immune globulin products.

Isoimmunization suppression is standard of care, and medical standards prescribe antepartum and postpartum prophylaxis. Isoimmunisation occurs when a pregnant woman's blood contains protein that is incompatible with the newborn's, prompting her immune system to respond and destroy the newborn's blood cells. The impact of this may cause several health problems for the unborn newborn, these range from mild to serve impacts that may complicate the mother's pregnancy. Rh hemolytic illness of the infant is a major cause of morbidity and mortality in many countries that lack prophylactic programmes.

In the manufacturing process Triton X-100 is used as part of a solvent/detergent (S/D) treatment. Triton X-100, the detergent, in conjunction with the solvent tri-n-butyl phosphate (TnBP), CAS#126-73-8, acts as a strong agent inactivating lipid enveloped

[1] http://eur-lex.europa.eu/legal-content/EN/TXT/?qid=1497426084925&uri=CELEX:32017R0999

[2] Chemikalien-Risikoreduktions-Verordnung, version of 1.November 2020; SR 814.81 - Verordnung vom 18. Mai 2005 zur Reduktion von Risiken beim Umgang mit bestimmten besonders gefährlichen Stoffen, Zubereitungen und Gegenständen (Chemikalien-Risikoreduktions-Verordnung, ChemRRV) (admin.ch) accessed 5 September 2022

[3] https://www.rhophylac.com/

viruses in the S/D treatment, a procedure accepted by authorities worldwide. [redacted] Triton X-100 fulfils several technical feasibility criteria for the manufacture of Rhophylac®.

CSL requests to use Triton X-100 beyond the aforementioned Sunset Date (2 May 2024). This combined AoA and SEA document discusses and demonstrates the following:

- The R&D that CSL has undertaken towards the identification of a feasible and suitable alternative for Triton X-100 and the time that would be required for switching to a technically feasible alternative
- CSL has identified a feasible alternative and substitution plans have been developed for the alternative to be implemented at Bern as rapidly as possible. These plans:
    - (a) respect the regulatory requirements that arise when the manufacturing process of authorised medicinal products changes and how variations to Marketing Authorisations must be applied for and granted to ensure patient safety; and
    - (b) ensure that no interruption of supply of Rhophylac® to patients would occur
- The socio-economic impacts that would arise for numerous patients and national health systems in Switzerland, the European Economic Area (EEA) and the rest of the world, if CSL was not granted an Authorisation for the continued use of Triton X-100 over the requested review period of five years. An overview of socio-economic impacts to CSL, its upstream and downstream supply chains is also provided; and
- The overall balance of benefits of the continued use of Triton X-100 as part of manufacturing Rhophylac® far outweigh the risks to the environment. Furthermore, CSL is committed to implementing additional risk management measures as soon as practicably possible at their Bern facility and these will lead to a risk reduction by significantly reducing emissions during the requested review period.

2.2. Substitution strategy context

Section 3.2 describes the successful R&D efforts by CSL towards the identification of a feasible alternative to Triton X-100. Previously performed R&D work on finding an alternative S/D treatment substance or technology started in 2017. In 2017, CSL identified [redacted] as possible alternative and has investigating the technical feasibility to substitute Triton X-100 with [redacted]. Several other possible alternatives were considered as part of CSL's R&D even before the Swiss Authorities announced, that 4-tert-OPnEO (Triton X-100) will be included in Annex 1.17 of the ORRChem with a sunset date on 2 May 2024.

Through screening investigations, which included laboratory testing and testing on the Rhophylac® manufacturing line, technical feasibility of the OPE-free alternative, [redacted], was confirmed in the summer of 2022.

This allowed CSL to progress the development of their substitution plan. The substitution plan spans the requested five-year review period from May 2024 to May 2029. CSL's substitution plan includes ongoing actions and a commitment to pilot and implement a technical risk reduction measure and both these activities will continue following submission of the application for authorisation. The alternative, [redacted], will be

implemented for markets once CSL has successfully obtained variations to the Marketing Authorisations of Rhophylac® in each market.

The following key points are explained in this document:

- CSL's efforts to minimise disruption to manufacturing operations during the implementation of the alternative; and
- Rhophylac is a licensed medicinal product in 76 countries. The time required for obtaining variations to Marketing Authorisations varies by country.

2.3. Temporal scope

The temporal boundaries of the analysis consider the following:

- When impacts would be triggered;
- When impacts would be realised; and
- For how long CSL as a minimum would require the continued use of Triton X-100.

The impact assessment periods used in this analysis and the key years are presented in **Table 2-1**.

Table 2-1: Temporal boundaries of impact assessment			
Present value basis (year)		2021	
Start of discounting basis (year)		2022	
Impact baseline (year)		2024	
Scenario	**Impact type**	**Impact temporal boundary**	**Notes**
"Applied for Use"	Adverse impacts on the aquatic environment	5 years	Based on the length of requested review period
"Non-use"	Removal of Rhophylac® from the market/ patient impact	Up to 5 years	Based on length of review period and CSL substitution plan
	Loss of sales for CSL plant	5 years	Based on the length of requested review period
	Loss of employment	13.8 months / 1.15 years	Average period of unemployment in Switzerland respectively[4]

2.4. Geographic scope

CSL uses Triton X-100 at Bern in Switzerland. Releases of Triton X-100 are discussed in more detail in the CSR and section 4.2.2 Impacts on environmental compartments.

2.5. Relevant supply chains

2.5.1. Supply chain upstream of CSL

CSL's existing supplier of Triton X-100 is [redacted]

[4] https://ec.europa.eu/eurostat/databrowser/view/LFSQ_UGAD__custom_3360656/default/table?lang=en

[5] Verabschiedete Gutachten und bisherige Konsultationen zu Zulassungsanträgen - ECHA (europa.eu)

The main use of purified Triton X-100 is by the pharmaceutical industry for virus inactivation in biopharmaceutical production.

Suppliers of materials and consumables to the CSL plant include several companies, some of which are based within Switzerland and the EEA, the impacts of the non-use scenario has not be calculated for these suppliers.

2.5.2. Impacts on CSL

Ceasing the production of Rhophylac® would have economic impacts on the manufacturing plant, but it is unlikely to impact other operations at the Bern site. However, some directly employed workers at the Bern site and administration and marketing staff may be made redundant by the ceasing of production.

CSL has identified the current production figures for Rhophylac® and has broken down the volumes of sales between Switzerland, EEA and non-EEA destinations, these are presented in section 3.1.2 and **Table 3-2**. The volume of all global sales come from the Bern site alone. As such, only the Bern plant would be impacted under the non-use Scenario.

Production of Rhophylac® is expected to increase, the reason for this is due to growing awareness of isoimmunisation and the growing global population. The finished Rhophylac® product is shown in **Figure 2-1**.

Figure 2-1: Images of Rhophylac® products
Source: CSL

2.5.3. Healthcare providers and patients

Key characteristics of the users of the relevant Rhophylac® product manufactured by CSL are summarised in **Table 2-2**.

Table 2-2: Healthcare providers and patients using Rhophylac®	
Relevant patients and distribution channels	**Number of patients**
Suppression of isoimmunisation is standard of care and medical guidelines recommend ante and postpartal prophylaxis. Isoimmunisation is a condition in a pregnant woman's blood where protein is incompatible with the newborn's blood causing her immune system to react and destroy the newborn's blood cells. Distribution: Mainly individual hospitals and private medical practices. Governments/national health authorities distribute the products in a few markets.	In Europe around [redacted] patients use Rho(D) immune globulin products. In Switzerland and Europe around [redacted] patients per year use Rhophylac®.
Source: CSL	

Table 3-2 presents the number of patients that might require treatment with Rhophylac® in Switzerland, the EEA and RoW. These numbers aligned with the Periodic Safety Update Reports (PSURs) that CSL generates each year for Rhophylac®. The variations to Marketing Authorisations in Switzerland, the EEA and RoW will not be completed before the Sunset Date, however, approval within Switzerland and the EEA may be granted one year after the Sunset Date. As such, patients may be affected in- and outside Switzerland and the EEA.

2.5.4. Competition

Rhophylac® is a market leading product that has been available for over 25 years. In several countries it is the only available registered product and no generics are available.

Within Switzerland and Europe, Rhophylac® has large market shares. Market shares in other regions of the world are also significant and an important contribution to overall global sales and the manufacturing operations at Bern. These market shares are provided in **Table 2-3** below and they align with the information presented in **Table 3-1**.

Table 2-3: CSL's market share of Rho(D) immune globulin products in different regions	
Region	**Rhophylac® market share (%)**
Switzerland	[redacted]
Europe	
Africa	
Latin	
Middle east	
Asia & Pacific	
North America	
Source: Marketing Research Bureau, 2018 and CSL	

The loss of Rhophylac® in markets where it is the main product or in those countries where it is the only available product, would be highly significant as in the vast majority of situations the patients (pregnant women and their unborn babies) would not have access to an alternative medical product to prevent haemolytic disease of the newborn. It is highly unlikely that competitors will be able to fill the gap in the market left by a refused authorisation. [redacted].

The impacts on patients are discussed in section 4. CSL's Rhophylac® product compliments several Swiss Policies and development goals along with United Nations Development goals.

Rhophylac® is also licensed for Intravenous (IV), and intramuscular (IM) administration. This is an advantage compared to other alternative products, when large doses are required (used for incompatible transfusions) or when injection into the muscle cannot be ensured, for example in obese patients where injection into fatty tissue can reduce the bioavailability.

As previously noted, the needed variations to Marketing Authorisations will not be complete prior to the Sunset Date, therefore the SEA focus will be on the Swiss, EEA and non-EEA markets which could be impacted if CSL was not granted an Authorisation for the continued use of Triton X-100.

3. ANALYSIS OF ALTERNATIVES

3.1. SVHC use applied for

3.1.1. Description of the function(s) of the Annex 1.17 substance and performance requirements of associated products

CSL uses Triton X-100 in the production of the plasma-derived protein therapy product, Rhophylac®. As part of the manufacturing process Triton X-100 is used as a virus-inactivation agent. Triton X-100, in conjunction with tri-n-butyl phosphate (TnBP), CAS#126-73-8, is utilised in the production process as part of a S/D treatment. The S/D treatment is a dedicated inactivation step for enveloped viruses and is a procedure generally accepted by authorities worldwide. [redacted]. Triton X-100 meets a number of technical feasibility criteria (see section 3.3.1.2) for the production of Rhophylac®.

The S/D treatment is used in the manufacturing process and trace quantities are present in the final product (the medicine). Every manufactured lot is tested and the average concentration in the final product [redacted]

A description of the use of Triton X-100 and the wastewater systems in Bern are described in the CSR.

3.1.2. Market analysis of products manufactured with the Annex 1.17 substance

Rhophylac®, produced by CSL, is the only product of its type that is available on the Swiss market. Therefore within Switzerland there are no competitor products and CSL has 100% of the Swiss market. In Switzerland, Rhophylac® is also listed as being an essential medicine, see Appendix 1 of SR 531.215.32, ATC J06BB01 (Swiss Federal Council, 2015).

In total, Rhophylac® has marketing approval in 76 countries.

CSL has a global market share of [redacted] (range 35-60%) and [redacted] share within the EEA and [redacted] of the RoW Rho(D) immune globulin

market. This market share is reported in the Worldwide Plasma Proteins Market 2018 market report (Marketing Research Bureau, 2018). **Table 3-1** describes the companies that produce similar products and the different relative market share and sales in different regions.

Table 3-1: Global Rho(D) Immune Globulin sales (US Dollars)

Company	Africa	Latin America	Middle East	Asia & Pacific	Europe#	North America	World Total	Global market share
	Sales $(MM)							Percent
[redacted]								

Source: Marketing Research Bureau, 2018
*Non-profits include Sanquin and Hemoderivados
#Europe is different to the EEA, in this report Europe refers to Albania, Austria, Baltic States, Belarus, Belgium, Bosnia Herzegovina, Bulgaria, Croatia, Czech Republic, Denmark, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Kosovo, Macedonia, Montenegro, Netherlands, Norway, Poland, Portugal, Romania, Russia, Serbia, Slovakia, Slovenia, Spain, Sweden, Switzerland, Ukraine, and the United Kingdom

The market share of Rhophylac® plays a significantly important role in aiding global health and contribute to the profitability of the manufacturing operations in Bern. An overview of the volume of sales as a percentage of total production is provided in **Table 3-2**.

Table 3-2: Rhophylac® sales figures

Volume of Swiss sales	Volume of EEA sales	Volume of other region sales	Total volume of sales
[redacted]			

Source: CSL

Before medicinal products can be used routinely, they require a Marketing Authorisation. Where there is a change to the manufacturing process of a medicinal product, this change has to be approved by the relevant authority before the product can/can continue to be marketed. Although there are similarities to the Marketing Authorisation criteria around the world, there are some differences in the requirements. Therefore applicants need to spend considerable time and effort to meet criteria, submit adapted applications and pay

relevant fees. The differences in criteria often entail authorities requiring additional data (mainly medicinal product stability data) which may take more time to generate, and some authorities may take more time than others to reach their decision.

3.1.3. Annual volume of the SVHC used

Past and projected consumption of Triton X-100

Table 3-3 summaries data for the consumption of Triton X-100 used in Bern, in the past (2012-2020) and present (2021) consumption.

Table 3-3: Levels of past and present consumption of Triton X-100 in Bern	
Consumption	**Bern**
Past consumption of Triton X-100 (2012-2020)	[redacted] kg (average: [redacted] kg/y maximum: [redacted] kg/y)
Current consumption of Triton X-100 (2021)	[redacted] kg

The annual tonnage band of Triton X-100 used at Bern is in the 0.1-1.0 t/y range.

Estimated future consumptions volumes may be higher than current volumes due to possible production volume increases. However, a step wise reduction in the use of Triton X-100 is expected as the alternative will be phased in upon regulatory approvals for the changed manufacturing process. Consumption of Triton X-100 is directly related to the number of batches that take place annually. [redacted]

Projected Triton X-100 phase out

If CSL's substitution plan adheres to the envisaged substitution plan, consumption of Triton X-100 will start decreasing from Q3/2024 and from this point in time consumption will be lower than what is described above. The substitution plan is discussed in more detail in section 4.1.2. **Figure 4-1** shows the expected phase out of Triton X-100 over the review period according to the substitution plan.

3.2. Efforts made to identify alternatives

Triton X-100 has been used at Bern since the initial manufacturing of Rhophylac®, and it has not replaced another viral inactivation reagent or method. Triton X-100 is commonly used for virus inactivation in pharmaceutical products (e.g. Dichtelmüller *et al.*, 2009; Farcet *et al.*, 2019), and several applications for authorisation have been submitted to ECHA[6] covering the use of Triton X-100 for pharmaceutical products, some covering uses other than virus inactivation.

CSL started to investigate Triton X-100 alternatives in 2017. Initially CSL identified 12 possible alternatives and following an initial assessment, CSL initiated testing of the five most promising alternatives. The screening criteria used included the following considerations:

[6] https://echa.europa.eu/applications-for-authorisation-previous-consultations

1. Established SD-agent for virus inactivation
2. Health, safety and environment performance
[redacted]

The five alternatives (identified in section 3.2.3) were tested on a laboratory scale. One of the alternatives was identified as being the most promising. This most feasible alternative still presented technical challenges and during 2022 CSL undertook full scale testing of the alternative and resolved the associated challenges. The substitution plan is discussed in more detail in section 4.1.2.

3.2.1. Research and development

The starting point of CSL's R&D was the identification of alternative virus inactivation substances. These were based on CSL's experience and knowledge of the sector, alternatives described in literature and discussions with CSL's current supplier of Triton X-100.

3.2.2. Consultations with customers and suppliers of alternatives

As previously described, [redacted]

3.2.3. Identification of alternatives

The list of potential alternatives identified and assessed by CSL between 2017 and 2021 appear below.

The most promising alternatives were investigated in lab-studies:

[redacted]

Other alternatives were only theoretically assessed:

[redacted]

7 [redacted]

3.2.4. Shortlist of alternatives

The most promising alternatives are shortlisted in **Table 3-4** below. These alternatives were shortlisted based on CSL's knowledge of its processes and alternatives that are typically known to medical regulatory authorities and are therefore more likely to be accepted by authorities.

Table 3-4: Shortlisted alternatives

Number	Alternative name	CAS Number	Description of alternative
1	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]
3	[redacted]	[redacted]	[redacted]
4	[redacted]	[redacted]	[redacted]
5	[redacted]	[redacted]	[redacted]

3.3. Assessment of shortlisted alternatives

3.3.1. General requirements of the alternative

Triton X-100 fulfils several technical feasibility criteria for the manufacture of Rhophylac® and the alternative would ideally be as compatible as possible with CSL's existing manufacturing processes.

3.3.1.1. Availability of the alternatives

CSL has assessed that all of the main alternatives are available on the market (although the market availability of [redacted]).

3.3.1.2. Technical feasibility of the alternatives

Technical feasibility criteria for alternatives for Triton X-100

A detailed look at the functionality of Triton X-100 and the most relevant feasibility criteria for potential alternatives was undertaken. The feasibility considered several criteria including the log reduction factor (LRF) of virus inactivation via S/D treatment, [redacted], processing time, temperature, yields, the comparability with existing process sequences, the comparability of final product (including impurities), the stability of Rhophylac®, residual concentrations of the detergent, site environment, health, safety and sustainability (EHSS) acceptability, the cost of the alternative, freedom to operate and regulatory acceptability.

[redacted] was found to be the most feasible option to replace Triton X-100. [redacted] and excellent virus inactivation properties. The replacement of Triton X-100 with [redacted] does not require any major reconstruction of CSL's existing facility. During scaling up tests, challenges were identified. Several actions aimed at resolving them were undertaken and each challenge was overcome.

The outcome of the parameter and process optimization was successful and [redacted] was identified as being the

alternative substance of choice to substitute Triton X-100. CSL's final process setpoint definition is scheduled for the next coming months (estimated conclusion end of 2022/early 2023). Confirmation runs on full scale will then be performed before entering formal process performance qualification later in 2023 followed by generation of data packages needed for health authority regulatory submissions and approvals.

3.3.1.3. Safety considerations related to using the alternative

One of the technical feasibility criteria was that the alternative had to meet plant environment, health, safety and sustainability (EHSS) acceptability. CSL was committed to identifying a substance with a less hazardous profile and a substance that is unlikely to be a regrettable substitution. **Table 3-5** presents the harmonised classification of Triton X-100, [redacted].

Table 3-5: Hazard classification of key components of Triton X-100, [redacted]

Substance	CAS Number	CLP hazard classification
Triton X-100	9036-19-5	**No harmonised classification – Most common classification (1528 notifiers):** Acute Tox. 4 H302 Eye Dam. 1 H318 Aquatic Acute 3 H412
[redacted]		

Source: ECHA website (accessed September 2022)

The information in the table does not raise immediate concerns with regard to any of the suggested alternatives, in particular [redacted]. However, some notifiers have classified [redacted]. Although some notifiers have suggested [redacted] is not an SVHC or subject to REACH Authorisation. Therefore its use will lead to an overall risk reduction.

3.3.1.4. Economic feasibility of the alternatives

Economic factors were considered at the shortlist and testing stage, when the merits of [redacted] were investigated. The profitability of manufacturing the product would be recalculated if the detergent costs exceed [redacted]. In terms of economic feasibility, CSL reached the following conclusions.

Table 3-6: Comparison of the economic feasibility of the alternatives		
Substance	**Economic impacts**	**Conclusion**
[redacted]	Raw material costs are comparable to Triton X-100 and manufacturing costs will essentially stay the same when research into improving performance is complete	Economically feasible
[redacted]	Raw material costs are comparable to Triton X-100 and manufacturing costs would be expected to stay the same	Economically feasible
[redacted]	There is a significant risk that manufacturing costs would be much higher on a commercial scale due to raw material and intellectual property rights. Manufacturing costs estimated to be around [redacted]	Product profitability calculation required - costs exceed [redacted] criteria (considered to be economically infeasible)
[redacted]	Raw material costs are comparable to Triton X-100 and manufacturing costs would be expected to stay the same	Economically feasible
[redacted]	Raw materials costs are higher than Triton X-100, ca. [redacted] and this excludes the additional manufacturing costs which would increase significantly. [redacted]	Economically infeasible
Source: CSL		

CSL will have to cover the cost of preparing and submitting applications for variations to medicinal product Marketing Authorisations. The overall time, cost and effort of generating the data, preparing the documenting, submitting the documentation and paying the relevant fees is not insignificant. However, all these costs will only arise under the applied for use scenario, in the non-use scenario, CSL will most likely cease to manufacture Rhophylac®. Therefore, the costs are not considered relevant in assessing the economic feasibility of the alternative under the non-use scenario and these have not been calculated.

Beyond the cost of implementing [redacted] as part of manufacturing operations at Bern, CSL is also committed to reducing the existing emissions of Triton X-100 that will take place during the requested review period. The measures investigated to date are discussed in section 4.2.2 Impacts on environmental compartments.

3.4. Conclusion on shortlisted alternatives

[redacted] has been identified by CSL as being the alternative to replace Triton X-100.

There are still several steps that require completion before CSL can switch to using [redacted] as the alternative. CSL is submitting this AfA to allow CSL to perform remaining development and confirmation work, and generate information needed for health authority regulatory submissions and approvals. It is for this reason CSL is seeking a five-year review period.

4. SOCIO-ECONOMIC ANALYSIS

4.1. Continued use scenario

4.1.1. Summary of substitution activities

The substitution of Triton X-100 with an alternative consists of four main stages:

1. Identify a suitable alternative for Triton X-100;
2. Develop the manufacturing process with the identified alternative and generate formal data-package to support filing of manufacturing process change with relevant health authorities;
3. Obtaining the relevant approvals for the changed manufacturing process from health authorities in each of the markets; and
4. Once health authority approval is granted, implementing the changed manufacturing process at Bern

The first phase has been completed, [redacted] has been identified as being a suitable alternative. CSL will progress with final process setpoint definition in the coming months (end 2022/early 2023). Confirmation runs on full scale will then be performed before entering formal process performance qualification later in 2023. This will be followed by generation of data packages needed for health authority regulatory submissions and approvals of the changed manufacturing process.

A five-year review period is requested to complete remaining work, to submit and have the numerous applications for variations to Marketing Authorisations approved. The requested review period allows for some contingency in case there are any delays in the approval process. This review period is critical to prevent any interruptions in the supply of Rhophylac® to patients worldwide. This is particularly important, as CSL's Rhophylac® product is the market leader, and in several countries, it is the only product of this type that is available.

4.1.2. Substitution plan

CSL has successfully identified an alternative and the sections below describe the plan to implement the alternative.

4.1.2.1. Factors affecting substitution

The efforts by CSL to successfully identify an alternative substance are described in section 3 and this led to [redacted] being identified as the alternative of choice. After identifying the alternative, CSL has developed a substitution plan for the substitution of Triton X-100 at Bern. The plan is presented in **Figure 4-1** below. The plan spans the period May 2024 to May 2029 and involves the substitution of Triton X-100 following successfully obtaining approvals of variations to the Marketing Authorisations of Rhophylac®.

There are significant differences in the data requirements and evaluation timelines for the various global regulatory authorities. As such the substitution will be impacted by the following factors:

- Shelf-life period to be covered by stability data within variation data package varies between 6 months and 36 months (i.e. full shelf-life of Rhophylac®) depending on authorisation jurisdiction. This stability data requirement defines the earliest

possible submission date for each individual market around the world. Submission roll-out will start around the Sunset Date and will for most countries happen post-Sunset Date.

- Authority application assessment time before granting approval varies between approximately 4 months to 24 months. This variable review time combined with the earliest possible submission date defines the earliest expected approval time for each individual market around the world.
- There are inherent uncertainties to the submission/approval timelines. Therefore, some contingency time is required for any unexpected delays in receiving market authorisations.

Based on these factors, CSL estimates that for the entirety of variations to be approved by health authorities around the world, a period of up to five years from the Sunset Date (i.e. May 2024) until May 2029 is necessary.

If an Authorisation was not granted (or one was granted, but with a shorter than required review period), then relevant manufacturing operations would likely cease at Bern or there would be a period, during which the Bern plant would not be allowed to supply certain markets, i.e. for those markets, for which the use of [redacted] would not yet have been approved by corresponding health authorities. This would cause non-acceptable impact on public health of the affected markets.

4.1.2.2. List of actions and timetable with milestones

CSL have devised an optimal substitution plan, the orange line in **Figure 4-1**, that presents the relative market volume with approved new manufacturing process. It assumes a best-case regulatory approval scenario. In this scenario, [redacted]. Remaining markets are expected to be approved by February 2028. There are some uncertainties inherent to the submission/approval timelines. Therefore, contingency time is required for any unexpected delays, and this is built into the substitution plan.

Implementation of the new process at CSL is planned according to regulatory approvals, as well as internal implementation strategy, which ensures a manageable global supply plan. During the implementation phase, manufacturing will be run in campaigns, i.e. manufacturing using the Triton X-100 process will be performed alternating to manufacturing using the new process. Hence, CSL's implementation strategy (considering some contingency) foresees [redacted] of the lots being manufactured using the new process in the 1st, 2nd, 3rd, 4th and 5th year, respectively. The used Triton X-100 amount is correspondingly reduced from an assumed maximum amount of [redacted] kg Triton X-100 in the 1st year of the requested review period to [redacted] kg Triton X-100 in the 5th year of the extension, see blue bars in **Figure 4-1**.

4.1.2.1. Monitoring of the implementation of the substitution plan

CSL will continue to monitor the status of the Marketing Authorisations and their substitution performance throughout the review period. CSL is committed to achieve the substitution of Triton X-100 as outlined. CSL will monitor whether circumstances may allow the substitution to progress faster than anticipated.

4.1.2.2. Conclusions

CSL is committed to substituting Triton X-100 and require a five year bridging period including some contingency time to allow CSL to fully implement the alternative for all markets. The time is mainly defined by country specific medicinal product regulation requirements. Without a review period (i.e. no authorisation granted) CSL would cease production. A shorter review period may see an interruption to several markets with non-acceptable impact on public health of affected markets.

4.1.3. R&D plan

CSL does not expect to perform any additional R&D during the review period.

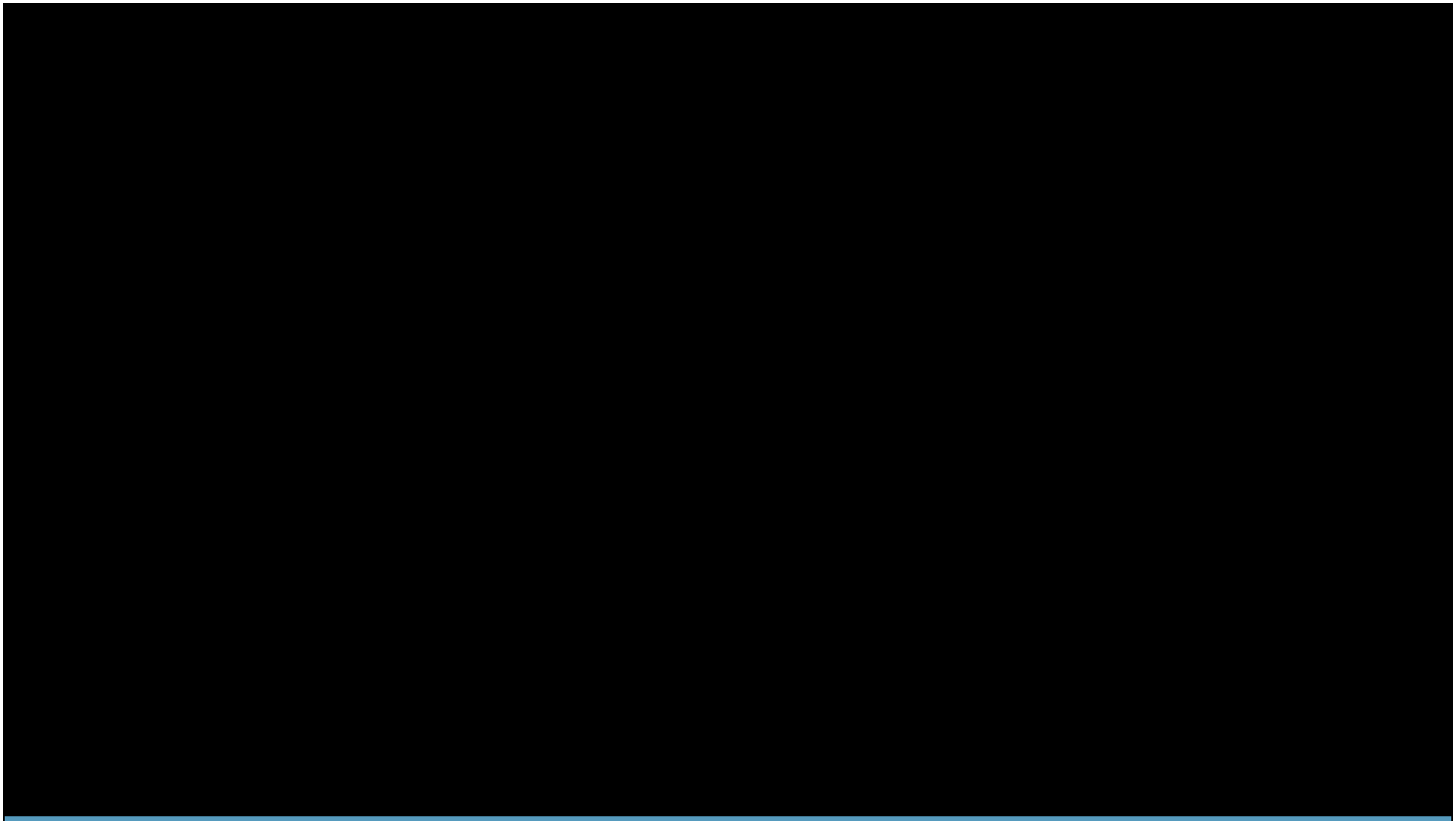

Figure 4-1: Substitution plan of the alternative and the phase out of Triton X-100 over the review period

4.2. Risks associated with continued use

The risks associated with continued use during the requested review period are discussed in the sections below. Although there will be an ongoing risk to the environment, CSL is committed to significantly reducing this risk as quickly as practicably possible. This will be achieved by installing a risk management measure that will significantly reduce the release of Triton X-100 to municipal wastewater.

4.2.1. Impacts on humans

An assessment of human exposure via the environment (HvE assessment) is not required for Triton X-100, as OPnEO was listed in Annex XIV of the REACH Regulation on the basis of endocrine disrupting properties for the environment. This interpretation is confirmed by RAC in its "Risk related considerations in applications for authorisation for endocrine disrupting substances for the environment, specifically OPnEO and NPnEO"[8] where it is stated that "risks to human health do not need to be assessed in the CSR included in an application for authorisation for OPnEO". Impacts are also described in the CSR (sections 5.6.2, 5.6.3 and 5.6.4).

Benefits of treatment with Rhophylac®

The benefits of continued use are significant and the removal of Rhophylac® for the market presents risks to healthcare providers and patients.

Rhophylac® is a medicine that contains the active substance Human anti-D Immunoglobulin. It is available as a solution for intramuscular or intravenous injection. For treatment of ITP it must be administered intravenously.

Rhophylac® is approved in 76 countries for the suppression of rhesus isoimmunization in:

- Pregnancy and obstetric conditions in rhesus (D)-negative women with an rhesus-incompatible pregnancy;
- Incompatible transfusions in rhesus (D)-negative individuals transfused with blood components containing rhesus (D)-positive red blood cells.

Rhophylac® is also approved in the US only in certain forms of chronic Immune thrombocytopenic purpura. As it is only registered in the US for ITP, ITP will not be discussed further.

Rhophylac® suppresses Rhesus (Rh)sensitization in:

- **Pregnancy and obstetrical conditions** in non-sensitized, Rh(D)-negative women with an Rh-incompatible pregnancy. In pregnancy (Rh)sensitization means triggering the Rh-negative mother's immune system to develop antibodies that may harm her newborn.

  Without administration of Rhophylac® to a Rh-negative mother a Rh-positive newborn may develop haemolytic disease of the newborn (HDN). HDN develops in the foetus when the IgG antibodies produced by the mother pass through the

[8] https://echa.europa.eu/documents/10162/17229/npneo_and_opneo_for_agreement_final_en.pdf/026cbafc-6580-1726-27f3-476d05fbeef0; accessed 14 September 2022

placenta and attack the red blood cells (RBCs) in the foetal circulation. Although HDN does not affect the mother, it can have serious consequences for her newborn, such as:

- Anaemia — red blood cells are destroyed faster than they are made
- Jaundice — a build-up of a substance in the blood that causes the skin to look yellow
- Brain damage
- Heart failure
- Death

Dramatic declines in HDN have been clearly attributed to the routine use of anti-D immunoglobulins

- **Incompatible transfusions** in Rh(D)-negative individuals transfused with blood components containing Rh(D)-positive red blood cells.

Impacts from the potential removal of Rhophylac® from the market

If Rhophylac® had to be withdrawn from the market, healthcare providers and patients would be impacted from the unavailability of a relevant product. Although alternative suppression of rhesus isoimmunization treatments are available, as described in section 2.5.4 Competition, Rhophylac® makes up almost [redacted] (range 35-60%) of the global market and in some countries, it is the only product available. The loss of Rhophylac® would likely result in significant supply constraints and it would take competitors several years to begin replacing the lost market volume of Rhophylac® as production for human plasma derived products cannot be quickly increased.

Rhophylac® is also licensed for IV and IM administration, this is a practical advantage as the majority of competitor products are licensed for IM administration only. [redacted].

Impacts of Rh Disease isoimmunisation on Newborn

As previously described, isoimmunisation occurs when a pregnant woman's blood protein is incompatible with the newborn causing her immune system to react and destroy the newborn's blood cells. There is no risk to the mother, but health impacts to the newborn can range from mild to severe and can result in long term conditions as well as death. Isoimmunisation causes Rhesus disease also known as HDN which can have devastating consequences for the newborn.

Broadly, there are 3 main outcomes because of Rh disease: death, affected and unaffected. Conditions that may develop include jaundice and anaemia which can be mild, moderate, or severe. More severe conditions of anaemia result in further health complications such as foetal hydrops and heart failure often resulting in premature death. Severe cases of jaundice lead to a further brain condition known as kernicterus which can leave some patients unaffected, or they can suffer long term and life altering health conditions such as hearing loss, developmental delay, cerebral palsy, and neurological impairments.

The two conditions that have been most documented in the literature that occur because of Rh disease are haemolytic anaemia and jaundice. Mild and moderate cases are normally easily treated and often resolve themselves, but the more severe forms of these conditions can cause additional complications. Severe haemolytic anaemia (haemolytic disease of the newborn) can result in heart failure and foetal hydrops[9].

Jaundice, in general, was estimated to occur in 80% of newborns who developed a further health condition from isoimmunisation at all levels of severity. Severe jaundice also known as extreme hyperbilirubinemia leads to Kernicterus: a condition in the brain and this was found to be more prevalent in developing countries than developed countries. This neurological condition can result in disabilities such as a hearing impairment, developmental delay, cerebral palsy, and neurological impairments (Janssens et al., 1997; Verduin et al., 2010).

These health impacts can cause disabilities that will have long lasting impacts on the newborn. Some of these impacts have significant disability weights (GHDx, 2019) and these impacts will last much of the newborns life and some may shorten their life expectancy.

Impacts of Rh(D) Ig on Mother and Newborn

Due to improvements in healthcare technology, rhesus disease is currently very uncommon. Routine antenatal (before birth) anti-D prophylaxis (RAADP) products such as Rhophylac® are offered to all women who are at risk of developing isoimmunisation and Rhesus disease. As a result of this, the prevalence of Rh disease is low in many developed countries (Hudson et al., 2020). Studies on the incidence in the population and evidence of the conditions and disabilities stemming from the disease are uncommon, with many predating the new millennium and even recent studies depend on older datasets, when Rh disease and hemolytic disease of the newborn was a much larger risk to the population because of the limits of RAADP.

Since the advent of Rh(D) Ig in 1969, the rates of *alloimmunization of the mother* have substantially decreased. Prior to the development of Rh(D) Ig, approximately 16% of Rh(D)-negative women became alloimmunized (Rh immunized) after 2 deliveries of Rh-positive infants (Bowman, 1985). In the 2000s, the risk has been documented to be as low as 0.14 to 0.2% with the addition of routine anti-D immunoglobulin administration before and after delivery (Bowman, 2003).

Since 1969, the rates of *hemolytic disease of the newborn* (HDN) have also substantially decreased. In the United States, rates of hemolytic disease of the newborn decreased from 45.1 per 10,000 total births in 1970 to 10.6 per 10,000 births in 1986 (Chávez et al., 1991). Even lower rates have been seen in other countries, such as the United Kingdom where rates dropped from 18.4 per 100,000 live births in 1977 to 1.3/ per 100,000 births in 1992 (Clarke & Hussey, 1994). These declines have been attributed to the introduction and acceptance of Rh(D) Ig use after delivery.

Based on the total live births in 2021 in all countries, where Rhophylac® is sold, the number of HDN cases without and with Rh(D) Ig treatment was estimated by CSL by multiplying the total live birth number with the US HDN rates of 45.1 per 10,000 total births and 10.6

[9] https://medlineplus.gov/ency/article/007308.htm

per 10,000 (Chávez et al., 1991), respectively. The difference between these estimated HDN cases was attributed to the availability of Rh(D) Ig treatment, from which, by multiplication with CSL's global market share of approximately [redacted] (range 35-60%), the estimated HDN cases prevented with CSL Rhophylac® in 2021 was obtained, see **Table 4-1**.

Table 4-1: Estimated number of global HDN cases prevented with CSL Rhophylac (2021)	
Births and HDN cases prevented	**Number of births/HDN prevented**
Total Live Births in 2021 in Rhophylac sales countries[1]	40,156,811
Anticipated number of HDN cases without RhD Ig in 2021 (using the 45.1/10,000 estimate from US in 1970)	181,107
HDN cases prevented with RhD Ig in 2021 (continued use)	138,541
HDN cases prevented with CSL Rhophylac® in 2021 (non-use)	[redacted] (range 50,000-100,000)
[1]live birth numbers taken from data downloaded at: https://ourworldindata.org/grapher/births-and-deaths-projected-to-2100. Birth numbers in Macedonia were not available.	

In the continued use scenario, we assume that access to Rhophylac® continues whereas in the non-use scenario there is no access to RAADP from Rhophylac®.

Per year Rhophylac® prevents [redacted] (range 50,000-100,000) cases of HDN, the number of cases prevented over the review period are provided in **Table 4-2** (2024 and 2029 values have been multiplied by 0.66 and 0.33 respectively).

Table 4-2: Estimated benefit of Rhophylac® from continued use / estimated impact from the loss of Rhophylac® in the "Non-use" Scenario	
Year	**Number of HDN cases prevent**
2024	[redacted] (range 35,000-75,000)
2025	[redacted] (range 50,000-100,000)
2026	[redacted] (range 50,000-100,000)
2027	[redacted] (range 50,000-100,000)
2028	[redacted] (range 50,000-100,000)
2029	[redacted] (range 20,000-50,000)
Total benefit/potential impact, 2024-2029	[redacted] **(range: 250,000-500,000)**

4.2.2. Impacts on environmental compartments

Conclusion from the CSR

Within the CSR, section 5.7.1.1 describes the exposure and risks for the environment. This section includes Table 20 and Table 21 presenting the exposure concentrations and risks for the environment on a local and regional scale. These tables show that the risk characterisation ratios (RCR) for freshwater, sediment (freshwater), agricultural soil, predator freshwater and predator terrestrial are all pronouncedly below one, demonstrating a low risk to these different compartments and a low risk of secondary poisoning.

4.2.3. CSL's commitment to reducing release of Triton X-100 to the environment

CSL initiated a programme to identify measures that would lead to a risk reduction from using Triton X-100 during the review period. The programme addressed several measures:

1. To bring clarity on the wastewater situation on Bern site, CSL decided to perform a feasibility study. This feasibility study should allow CSL to assess various options on possible treatment plants that could be installed on site (this cost [redacted]).
2. As part of the feasibility study, CSL investigated different technologies available on the market that would be efficient for Triton X-100 depletion.
3. After discussion with external suppliers and since every wastewater are different, CSL decided to perform treatability trials to confirm (or not) if the chosen technology would work (this cost [redacted])
4. CSL decided to test several technologies:

[redacted]

5. Parameters: CSL has a total of [redacted]/lot of wastewater coming from the chromatography column CM1 in the process.

[redacted]

6. From the various assessed options, the most important criteria for CSL were identified as being:
    a. The space available on site is significantly restricted. At Bern, [redacted]. The equipment footprint needs to fit into this room. CSL is committed to achieving a solution as soon as practicably possible. Construction of a new buildings or rooms was deemed too time consuming and complex to achieve in the short term, therefore any options not fitting in the [redacted] were out of scope.
    b. The manual operations around the new treatment system must be reduced to a minimum. The available space is [redacted].
    c. The new treatment system needs to be an energy efficient solution and if possible, it should use the existing utilities already installed on site (e.g. compressed air, water, chemicals).

Table 4-3 provides an overview of a comparison between suppliers investigated by CSL.

At this stage of the feasibility study, the technology proposed by [redacted] is the most promising one. This solution presents limited environmental impacts (from greenhouse

gas emissions, water and energy consumption) and from the lab results, a Triton X-100 reduction by at least 88% is expected.

[redacted] considering a potentially lower efficiency on full scale an overall **≥88% Triton X-100 reduction on full scale is expected**

Before installing any definitive equipment on site, CSL will perform pilot plant tests. With the help of the chosen supplier, CSL will install on site a pilot equipment and run it for at least a few months as part of internal testing. The objectives are:

- To treat a higher volume of wastewater with pilot scale equipment
- Confirm the capacity of the technology to significantly remove the Triton X-100 amount in the wastewater

If the pilot plant tests are successful, CSL is optimistic that the risk reduction measure can be implemented quickly. Planning includes a one-year lead time for procuring and installing new equipment. However, CSL is aware that the timing could take longer, for example there could still be COVID impacts and supply chain issues, or in the worst case, pilot tests could be unsuccessful. The best-case scenario is presented below in **Figure 4-2**.

At present, CSL estimate that the amount of Triton X-100 released from the process to wastewater is [redacted] kg/batch [redacted].

A 88% reduction would result in around [redacted] kg/batch [redacted] of Triton X-100 being released to wastewater from the implementation of the risk reduction measure.

Table 4-3: Supplier comparison				
Criteria	[redacted]	[redacted]	[redacted]	[redacted]
Technologies	[redacted]			
Treatability Trials				
Total CAPEX ±50% (CHF)				
Total OPEX ±50% (CHF)/year				
Comments				

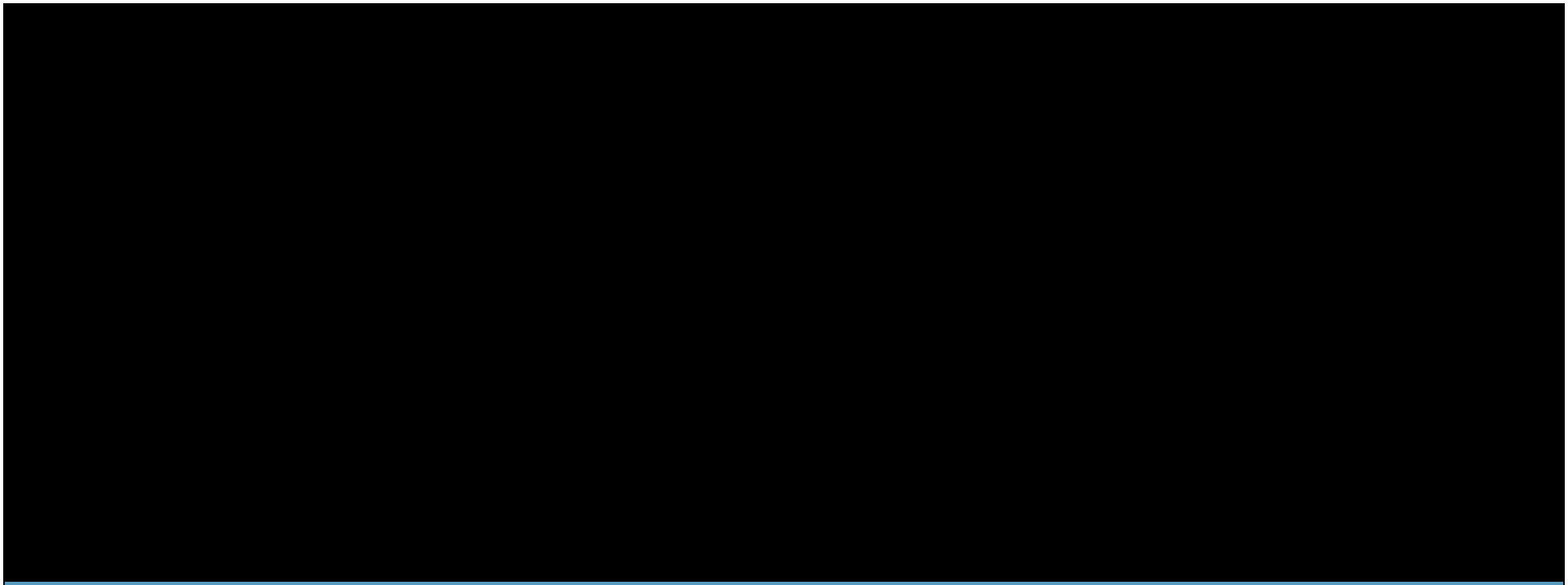

Figure 4-2: Implementation plan for the risk reduction measure

4.2.4. Compilation of human health and environmental impacts

Human health impacts are not relevant and have not been considered.

As described above, CSL's use of Triton X-100 will decrease over the review period because of the substitution of Triton X-100 by [redacted]. Furthermore, CSL is committed to reducing the releases of Triton X-100 to municipal wastewater.

If the [redacted] solution is implemented, CSL expect that releases will be significantly reduced, a summary of the emissions, considering the combined effects of Triton X-100 substitution and Triton X-100 release, is presented in **Figure 4-3** and **Table 4-4** [redacted].

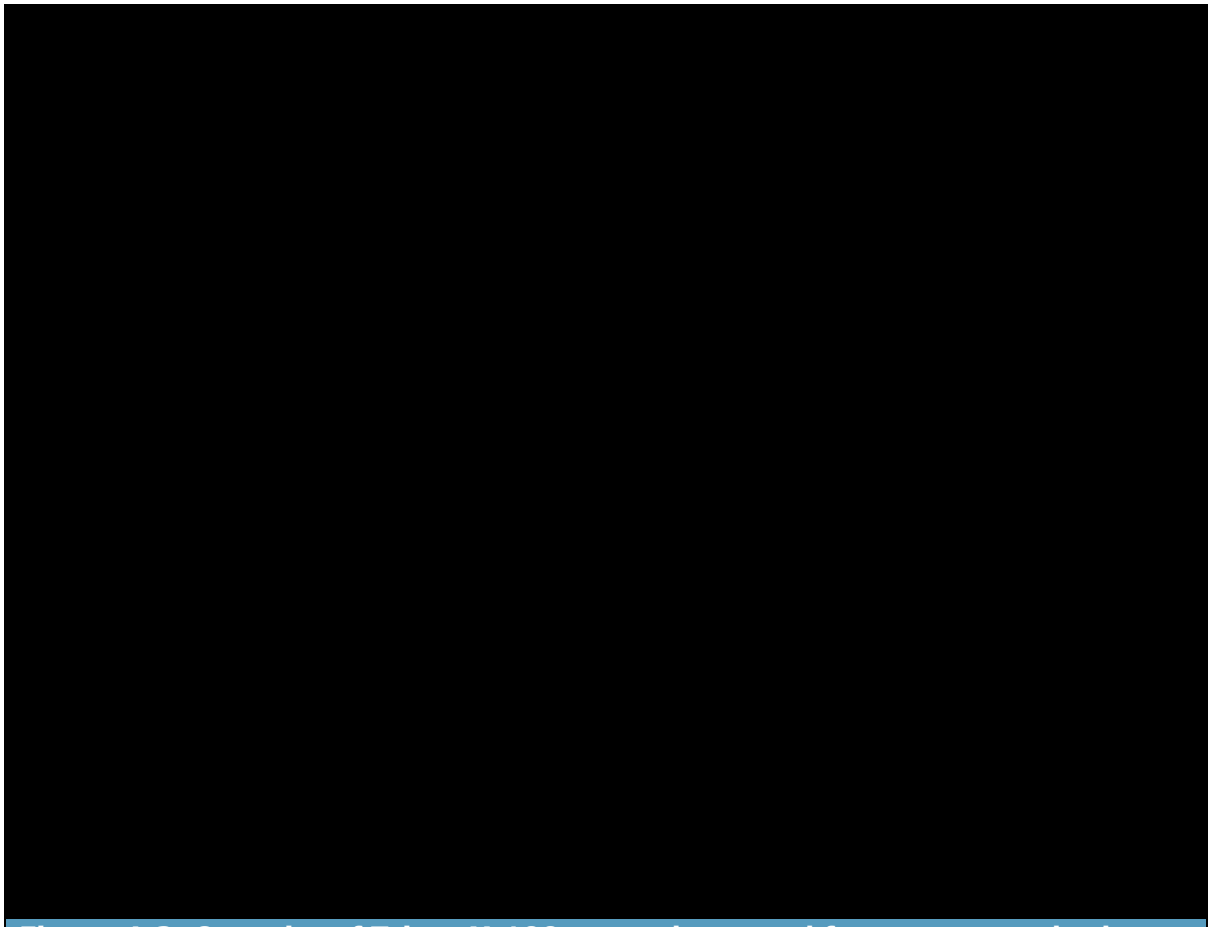

Figure 4-3: Quantity of Triton X-100 use, release and future expected release with new risk reduction treatment measure

Table 4-4: Summary of remaining releases to the environment		
Year	**Release in kg**	
	Without risk reduction measure	**Implementation of the risk reduction measure**
Year 0 - May 2023 - May 2024 (prior to risk reduction measure implementation)	[redacted]	
Year 1 - May 2024 - May 2025		
Year 2 - May 2025 - May 2026		
Year 3 - May 2026 - May 2027		
Year 4 - May 2027 - May 2028		
Year 5 - May 2028 - May 2029		
Total releases during review period		

4.3. Non-use scenario

4.3.1. Summary of the consequences of non-use

If authorisation was not granted there are likely to be significant consequences from the public health perspective. The significant socio-economic benefits from the continued use of Triton X-100 during the requested review period will be lost. Non-use will mean that patients and healthcare providers will no longer benefit from the ongoing availability of Rhophylac®. This is important as CSL is the market leader and Rhophylac® makes up almost [redacted] (range 35-60%) of the global market. Non-use will also mean that the Rhophylac® manufacturing operations will cease, jobs would be lost at CSL and within the supply chain, CSL will lose the related sales, and suppliers will also be impacted.

Although there will be limited impacts upstream on chemical suppliers (i.e. impacts to [redacted], the supplier of Triton X-100) and plasma collection[10], the downstream impact on medical facilities and their patients is much more significant from a pause or the indefinite ceasing of production. Hence, the main focus is on the downstream impact of healthcare providers and their patients.

4.3.2. Identification of plausible non-use scenarios

CSL considered five different potentially plausible non-use scenarios, these included:

1. Stop relevant Bern operations and relocate production to an existing plant outside Switzerland
2. Stop relevant Bern operations and find/build a new plant outside Switzerland
3. Stop relevant Bern operations and abandon the production of Rhophylac®
4. Stop relevant Bern operations temporarily until an alternative has been successfully developed/implemented
5. Stop relevant Bern operations temporarily for those markets that have not approved the variation with the alternative virus inactivation method at the Swiss Sunset Date.

[10] Plasma donors for the program would no longer be able to donate. High Anti-D titers are not suitable for our other products. Anti-D donors would either no longer be able to donate (which would also be an economic loss for them) or they would have to start donating plasma for competitors (if geographically possible).

Each of the non-use scenarios would have different impacts on CSL and the supply chain, and severe impact on patients not getting Anti-D prophylaxis.

4.3.3. The most likely non-use scenario

CSL considers the most realistic non-use scenario is scenario 3 (i.e. stop relevant Bern operations and abandon the production of Rhophylac®). Scenarios 1 and 2 are not realistic options for CSL as it is unable to relocate production outside of Switzerland or the EEA before May 2024. Non-use option 3 would significantly affect the supply of the medicine to patients due to CSL's significant market share. Although scenario options 4 and 5 are somewhat feasible, they would entail significant impacts on patients.

The following sections elaborate on the various costs that would arise if the requested authorisation for the continued use of Triton X-100 in the period 2024-2029 was not granted (i.e. scenario 3 - stop relevant Bern operations and abandon the production of Rhophylac®).

4.4. Impacts associated with non-use

4.4.1. Societal impacts on healthcare providers and patients

The most likely non-use scenario, ceasing production of Rhophylac®, will give rise to several societal impacts. The most significant will be the impact on healthcare providers and patients. Section 4.2.1 describes impacts avoided as part of continued use.

4.4.1.1. Swiss health related policies and international commitments

Importance of CSL's health products to the world

As previously described, CSL estimates that globally around [redacted] million persons receive Rhophylac® each year. CSL has almost [redacted] (range 35-60%) of the Rho(D) immune globulin market share. In some countries, including Switzerland, CSL's Rhophylac® is the only product available on the market. The rest of the world markets are particularly important to CSL as these make up the majority of sales by volume. The market share of Rhophylac® in other regions of the world are [redacted] (**Table 2-3**).

Isoimmunization suppression is standard of care, and medical standards prescribe antepartum (before birth) and postpartum (after birth) prophylaxis. Isoimmunisation occurs when a pregnant woman's blood contains protein that is incompatible with the newborn's, prompting her immune system to respond and destroy the newborn's blood cells. The impact of this may cause several health problems for the unborn newborn, these range from mild to severe impacts that may complicate the mother's pregnancy. Rh hemolytic illness of the newborn is a major cause of morbidity and mortality in many countries that lack prophylactic programmes. In such nations, 14 percent of affected foetuses are stillborn, and roughly 50 percent of affected new-borns suffer neonatal death or brain impairment (American College of Obstetricians and Gynecologists, 2017). The usage of Rh D immune globulin on a regular basis is responsible for the lower rate of red cell alloimmunization. After pregnancy some health problems may persist in the child, and these may lead to life altering challenges that impact the child's quality of life and result in a lower lifelong economic output.

Despite considerable proof of efficacy, there are still a large number of cases of Rh D alloimmunization (American College of Obstetricians and Gynecologists, 2017). The beneficial health impacts on persons administered Rhophylac® is significant and lack of Rhophylac® would have severe implications on morbidity and mortality and having long lasting impacts.

The importance of Rhophylac® is recognised as it is listed as an essential drug in Switzerland, see Appendix 1 of SR 531.215.32, ATC J06BB01 (Swiss Federal Council, 2015).

The loss of Rhophylac® from the market is expected to be significant in RoW markets that are less developed. CSL's Rhophylac® directly support the Swiss Health Foreign Policy which is built on two important foundations. Firstly, the foreign policy advocates for advancing a country's healthcare infrastructure and population's overall health. Secondly, it is a mechanism of Swiss foreign policy and, as such, serves to further its goals, namely, the strategic defence of Swiss interests and the successful promotion of global health. It is concentrated on protecting one's right to health as well as other human rights connected to health.

Swiss/UN - 2030 Agenda for Sustainable Development

The Swiss 2030 Agenda for Sustainable Development[11] (Swiss Confederation, 2018) aligns with the UN's sustainable development goals (SDG) and it makes several references to ensuring health lives:

> *"**Ensure healthy lives and promote well-being for all at all ages.** In its Health 2020 strategy, the Federal Council set out the following goals for the Swiss healthcare system: maintain quality of life, increase equal opportunities, raise the quality of healthcare and improve transparency. Mandatory health insurance guarantees all Swiss residents access to medical services and products. Life expectancy in Switzerland is very high at 81.5 for men and 85.3 for women in 2016. However, according to Eurostat, in terms of the healthy life expectancy (HLE), Switzerland was below the EU average in 2015."*
>
> *"International level: Geneva has a special role in international health policy since it is the seat of relevant international organisations, NGOs and many global initiatives. Moreover, Switzerland is also important as a centre for innovation and research in health. The pharmaceutical, biotechnology and medtech industries are among the most significant Swiss export sectors. Switzerland is involved in multilateral forums and/or projects with partner countries and focuses on (i) combating communicable diseases[12]; (ii) sustainably improving access to medical products without undermining intellectual property rights; (iii) combating non-communicable diseases and promoting a health and human rights-based addiction policy; (iv) enhancing health systems; **(v) improving the health of mothers, newborns and children, and strengthening sexual and reproductive health and rights."***

Rhophylac® also support other sustainable development goals (SDG) in the long term by helping to ensure a healthy pregnancies and child development, such as UN SDG 3.2 on

[11] https://www.eda.admin.ch/dam/agenda2030/en/documents/laenderbericht-der-schweiz-2018_EN.pdf

[12] As well as non-communicable diseases, like chronic care diseases

newborn and child mortality[13]. Indirectly, Rhophylac® also support other such goals such as SDG 8, this is to promote sustained, inclusive and sustainable economic growth, full and productive employment and decent work for all. CSL substituting Triton X-100 also contributes to SDG 15 (to protect, restore and promote sustainable use of terrestrial ecosystems, sustainably manage forests, combat desertification, and halt and reverse land degradation and halt biodiversity loss) whereas competitors currenting using Triton X-100 may continue to use it.

Switzerland's International Cooperation Strategy

Within Switzerland's International Cooperation Strategy[14] (Swiss Confederation, 2020), the Federal Council sets objectives for its international cooperation strategy. For the period 2021–24, one of the objectives is:

- Saving lives, ensuring quality basic services, **especially in relation to** education and **healthcare**, and reducing the causes of forced displacement and irregular migration (human development)

The International Cooperation Strategy also identifies:

> ***"Cross-sectoral approaches.*** *In order to effectively meet the challenges of sustainable development, such as migration and climate change, international cooperation will make greater use of cross-sectoral approaches, particularly in urban contexts. Actions targeting multiple SDGs and sectors boost efficiency and will be stepped up. For example, improving health is about more than the quality of healthcare systems: it also entails working on food quality (pesticides), air pollution, water quality and a healthy living environment.*
>
> *The Global Programme Health will focus on the quality and viable financing of health systems and services so that they are better equipped to respond to the needs of disadvantaged communities. It will* ***promote health, reproductive and sexual rights, maternal and child health, and the fight against the main communicable and noncommunicable diseases that affect developing countries****.* ***It works closely with the private sector and the academic community, particularly in relation to research on, development of and better access to new high-quality medicines****. It also addresses other health-related factors such as water quality and air pollution."*

The continued availability of Rhophylac® complements the objectives of Switzerland's International Cooperation Strategy and its removal from the market will be damaging to child and patient health.

[13] https://www.who.int/data/gho/data/themes/topics/indicator-groups/indicator-group-details/GHO/sdg-target-3.2-newborn-and-child-mortality

[14] https://www.eda.admin.ch/dam/deza/en/documents/publikationen/Diverses/Broschuere_Strategie_IZA_Web_EN.pdf

Swiss Health Foreign Policy 2019–2024

The Swiss Health Foreign Policy 2019–2024[15] (Swiss Confederation, 2019) describes how:

> *"**Access to medicines is both a human right and a complex global challenge** at the nexus of health, business, politics and development. According to the World Health Organisation (WHO), despite international efforts, approximately two billion people around the world have no access to life-saving medicines – whether generics or patented products. The question of access also affects high-income countries such as Switzerland, especially where certain high-priced medicines are concerned."*

The pharmaceutical sector is also recognised as being by far Switzerland's biggest exporter. Access to available medicines is important and relevant as this helps to fulfil Goal 3.B of the 2030 Agenda for Sustainable Development. The international community set itself the objective of further improving access to safe, effective, quality, affordable medicines and vaccines around the world by 2030. This access is vital to achieving the higher-level goal of universal health coverage. The ongoing access to Rhophylac® compliments this goal.

4.4.2. Economic impacts on CSL

Lost sales following the withdraw of Rhophylac® from the market

Introduction

The loss of sales that would continue as part of the continued use scenario would arise only in the event of non-Authorisation. Although CSL believe that the market might be growing, this market growth is not included in the estimation of lost sales.

Estimate of lost sales for CSL under the non-use scenario

Table 3-1 provided an overview of Global Rho(D) Immune Globulin market, including CSL's past Rhophylac® sales. CSL's current Rhophylac® sales were budgeted as being [redacted] million in Financial Year 2021/2022. These sales are assumed to be unchanged in future. The table below (**Table 4-5**) shows CSL's sales that would be lost in the future as a result of a refused authorisation. Neglecting growth of sales over the five years requested review period, a cumulated global sale of [redacted] (range: $100-1,000 million) are estimated to be lost for the period between May 2024 and May 2029.

[15] https://www.bag.admin.ch/dam/bag/en/dokumente/int/Swiss%20Health%20Foreign%20Policy%202019%E2%80%932024.pdf

Table 4-5: Estimated lost sales for CSL under the non-use scenario (2022: year 0)				
Year	Year #	Discounting factor	Gross sales losses in Bern (US$ millions)	
			Estimate	Discounted value
2024	2	0.925	[redacted]	[redacted]*
2025	3	0.889	[redacted]	[redacted]
2026	4	0.855	[redacted]	[redacted]
2027	5	0.822	[redacted]	[redacted]
2028	6	0.790	[redacted]	[redacted]
2029	7	0.760	[redacted]	[redacted]*
Total sales loss, 2024-2029, US$ millions				**[redacted] (range: 100-1,000)**
Total sales loss, 2024-2029, CHF millions				**[redacted] (range: 100-1,000)**
*2024 and 2029 values have been multiplied by 0.66 and 0.33 respectively				

Summary of economic impacts

Table 4-6 summarises the economic impacts of non-authorisation.

Table 4-6: Summary of economic costs associated with the implementation of [redacted] as a substitute for Triton X-100 - Assessment period: 2024-2029			
Cost category	Cost element	Cost estimate (costs incurred post May 2024)	
		"Non-use" Scenario	"Applied for Use" Scenario
Investment and stoppage costs	Additional R&D costs	Nil	Nil
	Cost of capital investment in new equipment and its installation	Nil	Nil*
	Cost of preparing and submitting applications for variations to Marketing Authorisations	Uncertain, but equal to costs under the "Applied for Use" Scenario	Uncertain, depends on health authorities' requirements
	Lost sales from stopping production and exiting markets	CHF [redacted] (range: CHF 100-1,000 million)	Nil
Changes to operating costs	Cost of using the new S/D	Nil	Negligible
Other costs	Opportunity costs	Some investment in other projects potentially delayed or abandoned	Nil
Difference in costs between the two Scenarios		**CHF [redacted] (range: CHF 100-1,000 million)**	
*As previously described, although there will be some costs for the risk reduction measure, these are excluded from the summary of economic costs			

4.4.3. Economic impacts on the supply chain

Upstream supply chain

Upstream supply chain losses, including those to the existing suppliers of Triton X-100 [redacted] and costs to suppliers of consumables, services, utilities, etc. have not been calculated. These costs are expected to be negligible compared to the costs from the loss of the product for use by healthcare providers and patients as well as other costs.

Downstream supply chain

These costs are primarily described in section 4.4.1.

4.4.4. Economic impacts on competitors

CSL's competitors are included in **Table 3-1**. The lost market accrued by CSL under the non-use scenario would in part be counter-balanced by gains by EEA and non-EEA-based competitors, although it would take several years to replace the lost market volume of Rhophylac®. In other words, CSL (in Switzerland) would lose out to EEA and non-EEA companies and these sales would eventually move from Switzerland to EEA and non-EEA countries. The sales gains for competitors of CSL have not been estimated.

4.4.5. Wider socio-economic impacts

4.4.5.1. Social impacts

Employment impacts avoided under the applied for use Scenario

The continued use of Triton X-100 in Bern would allow the retention of jobs at CSL. It is estimated that [redacted] (range 10-50) workers would lose their jobs under the non-use scenario. These are the directly impacted jobs in the Rhophylac® bulk facility in Bern and is a conservative estimate as it does not include any support functions at the Bern site (e.g. quality control, quality assurance, maintenance) nor any lost FTEs at the CSL Marburg site responsible for filling and packaging Rhophylac® and no job losses in other supporting departments including administration, sales, marketing or regulatory. These job losses are not monetized, and no indirect job losses are developed here, as the predominant impact of any Rhophylac® manufacture discontinuation is on public health.

4.5. Combined impact assessment

The following table summarises the impacts described in the previous sections and sets out the differences between the Applied-for Use scenario and the most likely selected non-use Scenario over the five-year review period applied for. Whenever a quantification of benefits and costs was not possible, a qualitative assessment is provided instead.

Table 4-7: Summary of socio-economic benefits and risks of continued use		
Economic actor	**Indicator**	**Monetised value – lower bound of calculated range**
Socio-economic benefits of continued use		
Impacts on healthcare providers and patients	Rhophylac® will continue to be supplied to patients that are treated. The secure supply of market leading products like Rhophylac® is important to healthcare providers. Main Indication: The medicinal products prevent harmful effects during pregnancy that may impact the life of the unborn child during pregnancy and once born. The prevention of these harmful effects results in very significant benefits to	Healthcare provider and patient benefits are not monetised. HDN cases prevented are estimated as being [redacted] (range 50,000-100,000) per year and [redacted] (range: 250,000-

Table 4-7: Summary of socio-economic benefits and risks of continued use		
Economic actor	**Indicator**	**Monetised value – lower bound of calculated range**
	society as described in section 4.2.1	500,000) over the five-year review period
Impacts on CSL	Net present value sale losses avoided from the market loss of Rhophylac®	CHF [redacted] million (range: CHF 100-1,000 million)
	Costs of manufacturing changes at CSL	Negligible change, other costs are not included
	R&D into alternatives	Not monetised, R&D complete, alternative already identified
Social benefits linked to continued employment	Direct employment - [redacted] (range 10-50) jobs (Indirect and induced domestic and interregional employment - not estimated)	Not monetised
Impacts on suppliers	Net present value of losses avoided on the supply of raw materials	Not monetised
Excess risks associated with continued use		
Human health impacts by use of Triton X-100	Not relevant	Not monetised
Environmental impacts	1.Highest annual release for the year 2024 2.Total estimated release over the reviewed period	1. [redacted] kg 2. [redacted] kg
Impacts on CSL	Costs of manufacturing changes at CSL	Not monetised
	R&D into alternatives	Not monetised

Overall, the benefits of the continued use of Triton X-100 in the production of Rhophylac®, during a time where CSL is obtaining Marketing Authorisation and implementing the alternative ([redacted]) in the Rhophylac manufacturing process, significantly outweigh the residual risks from continued use.

Comparison of the benefits and risks for Bern

Table 4-7 summarises the socio-economic benefits of continued use of Triton X-100 in Bern that were presented in Section 4.

The total emissions of Triton X-100 to the environment under the applied for use scenario were discussed in section 4.2.4. CSL is committed to reducing release of Triton X-100 to wastewater and have undertaken an investigation of different technologies that will result in a significant risk reduction to the environment (see section 4.2.3). **Table 4-4** presents the estimated releases to wastewater that will occur once CSL implement the risk reduction measure, and the stepwise reduction in the release of Triton X-100 that will take place over the review period as CSL implement the alternative after manufacturing change will be approved by health authorities. These releases represent a total of ca. [redacted] kg (range 5-50 kg) over five years.

Over the same five-year review period Rhophylac® will prevent [redacted] (range: 250,000-500,000) cases of HDN.

4.6. Justification for the requested review period

This AfA is essentially a 'bridging' application which is requesting an Authorisation for the continued use of Triton X-100 to allow a smooth transition to an already selected technically feasible but currently not implemented alternative. The implementation of the selected alternative would be accompanied by a modest cost under the applied for use scenario, whereas a non-authorisation would result in significant detrimental impacts on Rhophylac® users. In several markets Rhophylac® is the only product available and users would therefore not have easy access to any alternative product. Rhophylac® also offers advantages over similar products in terms of licensed route of administration. Non-authorisation would incur sales losses for CSL, job losses and CSL may potentially leave the market indefinitely. The loss of Rhophylac® may lead to supply chain issues due to increased demands for alternatives, and alternative products are unlikely to be able to fill the gap in the market left by Rhophylac® for several years. The Federal Office of Public Health (FOPH) recognises the issue of supply disruptions of human medicines that are growing worldwide, including in Switzerland. The FOPH also recognises that the European Association of Hospital Pharmacists (EAHP) states that the medicine shortages in European hospitals are increasingly jeopardising the adequate treatment of patients (Federal Office of Public Health, 2022).

The driving force behind the length of the requested review period are the regulatory requirements that the change to virus inactivation by S/D treatment will imply as well as the operational needs of the Bern site. Four parameters play a key role:

- The need to generate long-term stability data for Rhophylac® using the alternative S/D treatment. These stability data need to be included in the variation data package to be submitted for approval to the relevant national health authorities;
- The time required by authorities to decide upon and approve variations to Marketing Authorisations. Variable data requirements and durations are expected for granting approval, in some countries this may take up to 2 years;
- The implementation strategy of the new S/D treatment for manufacturing Rhophylac® at the Bern site, starting after regulatory approvals of individual markets rather than after approval by all markets. This will imply manufacturing in campaigns, i.e. manufacturing using the Triton X-100 process will be performed alternating to manufacturing using the new process; and
- Ultimately, the need to minimise the disruption to the supply of important medications to all users in Switzerland, the EEA market and beyond.

The implementation plans for [redacted] are presented in **Figure 4-1**. CSL has the intention to implement [redacted] fully at Bern before May 2029 (the end of the requested review period).

Although there may be delays for the successful implementation of the alternative, CSL expects that these can be managed:

- CSL will constantly review substitution plan timelines; and
- Although CSL will crucially depend on regulatory authorities across many countries to promptly issue their approvals to variations, by March 2026, approximately [redacted]

of the market volume is expected to be approved under the best-case scenario. The remaining time until the end of the applied for review period (May 2029) is needed for implementing the alternative on the remaining markets and contingency for any delays to be resolved.

For these reasons, the May 2029 is considered an appropriate and justified time for implementing the alternative S/D treatment without suffering loss of market and without removing an important medicine from global markets.

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